ŠAFÁRIK UNIVERSITY KOŠICE
FACULTY OF MEDICINE

COMPENDIUM OF GENERAL PATHOLOGICAL PHYSIOLOGY

Vol. 1

Oliver Rácz - Jozef Kolenič - Rudolf Korec - František Ništiar
Anna Šipulová - Anna Šofranková - Zoltán Tomori

Košice 1995

Autori: doc. MUDr. Oliver Rácz, CSc., MUDr. Jozef Kolenič, CSc.,
prof. MUDr. Rudolf Korec, DrSc., MVDr. František Ništiar, CSc.,
RNDr. Anna Šipulová, doc. MUDr. Anna Šofranková, CSc.,
prof. MUDr. Zoltán Tomori, DrSc.

Hlavná odborná recenzentka: MUDr. Ružena Tkáčová, CSc.

Recenzenti: MUDr. Mária Kovářová, CSc., RNDr. Ján Sabo, CSc.,
doc. MUDr. Ivan Tkáč, CSc., Ing. Ivan Kron, CSc.

Jazyková recenzentka: PhDr. Brigita Wallová

Ilustrácie: Noémi Ráczová (5)

Technický redaktor: MUDr. Peter Dombrovský

dtp: Martin Kurpas

1. THE BASIC PRINCIPLES OF PATHOLOGICAL AND CLINICAL PHYSIOLOGY

1.1. THE ORIGINS OF THE PATHOLOGICAL PHYSIOLOGY AND ITS DEFINITION

Pathological physiology is a relative young subject - it was detached from pathological anatomy (which is a morphological discipline) only in the 19th century. The basic principles of the new discipline were laid down by the father of the modern experimental medicine, Claude Bernard (1813-1872) who characterized the new discipline in such way:

Experimental medicine, the synonymum of the scientific medicine should develop only if its scientific spirit will more and more penetrate into medical circles. The only thing necessary to achieve this aim is to provide the youth with thorough education in experimental physiology. I will not maintain that physiology is the basis of medicine, I should only say that experimental physiology is the most scientific part of medicine and young physicians through its study can attain scientific habits which they later can apply in research of pathology and therapy.*

Pathological physiology in current opinion is the medical discipline, which deals with the **functional changes of human body in disease**. In addition pathological physiology in contrast to pathological anatomy is an **experimental discipline.** It is neither a clinical subject (as internal medicine or surgery) nor a theoretical one (as biochemistry or molecular biology) but forms a bridge between the theoretical and cli-

*The term "pathological physiology" was coined later. The new discipline was first called experimental medicine, experimental pathology and experimental physiology.

nical subjects. It tries to summarize and synthesize the molecular, biochemical and cellular aspects of medical science in order to help understand the hidden background of diseases at the level of organs, systems and the whole organism.

The main objectives of pathological physiology are as follows:

Pathological physiology :

* Studies the causes and the conditions of development of the pathological processes and diseases (**etiology**).

* Studies the interrelationships between the causes of diseases and the regulatory, defensive, adaptive and compensatory processes (**pathogenesis**).

* Studies the pathways leading to recovery from illness or to death (**sanogenesis, thanatogenesis**).

* Employs models (mostly in the form of experiments on animals) to gain better insight into the essence of diseases and pathological processes.

* Analyzes the results of experiments and clinical observations and confronts the theoretical knowledge with observation from practice.

* Elaborates hypotheses and theories about the general laws of pathological processes and disease as a whole.

1.2. PATHOLOGICAL PHYSIOLOGY AS A PART OF MEDICAL SCIENCE AND PROFESSION

Medicine is a unique and very old human activity with a lot of interactions with almost all aspects of human life. According a nice definition of Walsh McDermott : **Medicine is not a science but a learned profession, deeply rooted in**

a number of sciences and charged with the obligation to apply them for man's benefit.

At this point one should not forget that the bioscientific character of recent medicine is a relatively new development. Thorough history, medicine was anything but scientific, being dominated by empiricism. For example the old proverb *ubi pus, ibi evaqua* did not ask anything about the cause and the essence of the purulent process, but advised to evacuate it. Of course this alleviated the symptoms and often helped the body's own forces to override the disease. Diagnoses were inexact, causes of disease poorly understood, and therapies frivolous and haphazard. The contribution of the basic sciences in this century (microbiology, biochemistry, molecular biology and genetics) to medicine is tremendous. However the list of human diseases for which there are as yet no measures for prevention or causal cure remains formidable.

A very important problem arising from modern scientific approach to medicine is the relationship of the **part** and the **whole**. The modern medicine goes down to the level of molecules and electrons. The results achieved in the field of molecular biology, genetics, biochemistry are of enormous significance for curing hitherto fatal diseases but they also carry the danger of losing ourselves in the details. However, this reductionist approach is the prerequisite of synthetic endeavors. A good physician should know a lot of these details but always should assemble an entire picture from the pieces. Pathological physiology, which in the second half of our century penetrated deeply into all branches of clinical medicine is the subject which enables to put together the pieces of the jig-saw puzzle arising as a result of advance in

basic medical sciences (Fig. 1.1).

In the course of medical curriculum pathological physiology follows the basic morphological and functional disciplines, runs parallel with pathological anatomy and precedes clinical subjects.

The relationship between the morphological and functional disciplines is the relationship of **form and function**. If one looks at the four chambers of the heart and the valves within (anatomy), he can easily understand its function as a pump (physiology). At molecular level this distinction between shape and performance disappears and we describe the structure and the function of nucleic acids, enzymes in the frames of the same discipline (molecular biology, biochemistry). Pathological physiology is unambiguosly a functional discipline but it loses its sense without pathological anatomy - its morphological counterpart.

A further very tight connection exists between physiology and pathological physiology. First one has to get acquainted with the **norm** (physiology) and only thereafter is possible to study the **abnormal** or **pathological** state (pathological physiology).

In the first years of medical study the future physicians do not examine and cure patients. They are mainly sitting in lecture halls and working in labs. In the everyday clinical practice they will use only a small part of the vast amount of knowledge required at exams of anatomy, histology, biochemistry or physiology. But the **theoretical knowledge** acquired in the first years is the bedrock of the physician's future **practical competence.**

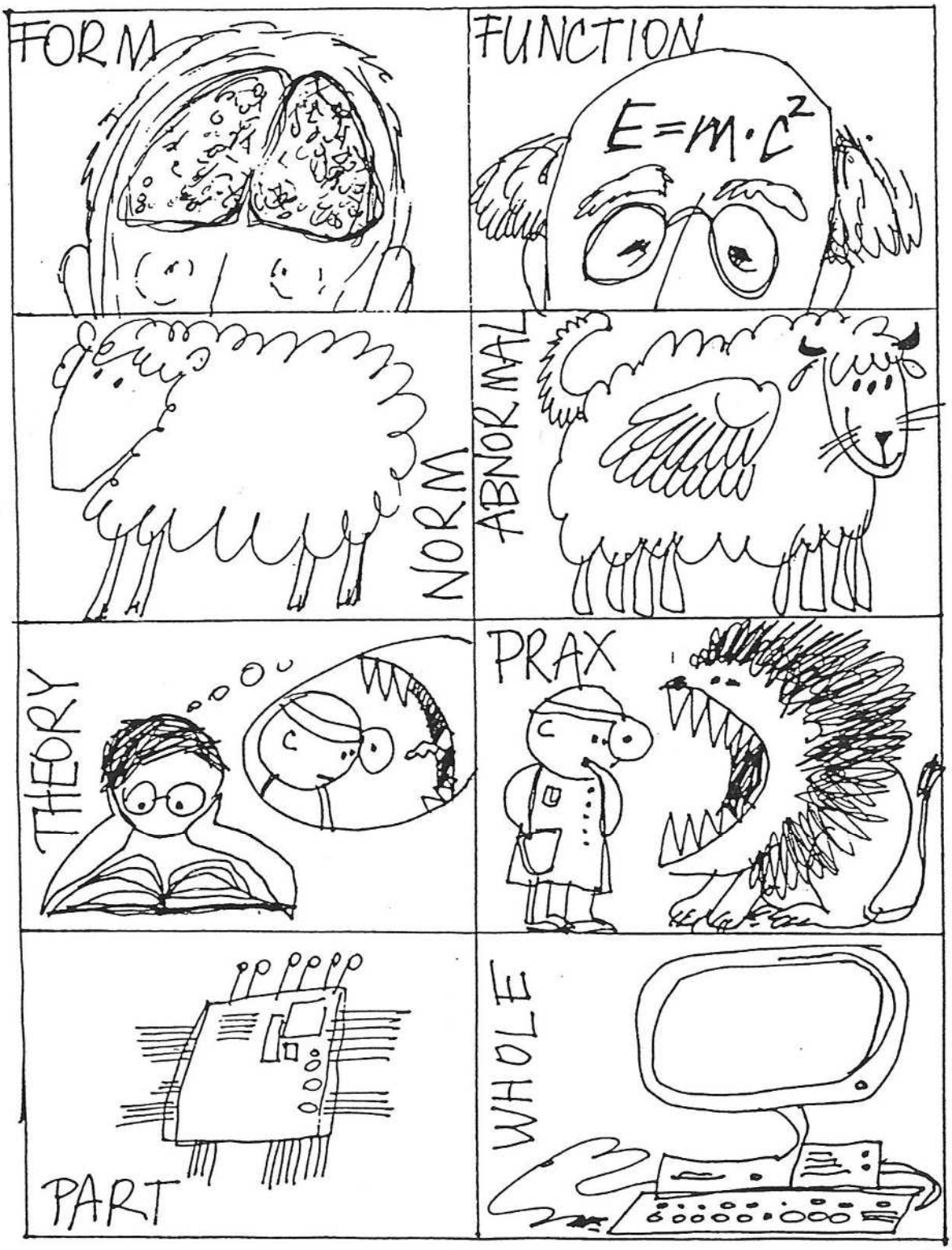


Fig. 1.1. Analytic and synthetic thinking in medicine.

The frontiers of modern scientific medical disciplines are not clear-cut and they frequently use common methods or study the same problem from slightly different point of view. In this context the nearest relatives of pathological physiology are **experimental pathology** and **clinical physiology**. The first subject puts more emphasis on experimental methods, the second on clinical studies but there is a considerable overlap between them and pathological physiology.

1.3. GENERAL AND SPECIAL PATHOLOGICAL PHYSIOLOGY

Pathological physiology is divided into two parts - into **general and special pathological physiology**.

The main chapters of **general pathological physiology** are as follows:

* **Nosology** - deals with the general laws of disease as a whole and the classification of diseases.

* **Etiology** - studies the causes of the diseases and the conditions of their development

* **Pathogenesis** - deals with the laws of development of pathological processes, disease symptoms and diseases. (The difference between the etiology and pathogenesis of a given disease can make some difficulties. Etiology asks the question **why** is this disease occuring and pathogenesis studies **how** it develops.) Nevertheless, in clinical medicine one often uses the term "**etiopathogenesis**" which involves both the cause and the development of the given disease.

* **Sanogenesis and thanatogenesis** - chapters closely related to pathogenesis. They study the mechanisms leading to recovery from disease or to death, respectively.

From practical point of view we include into the general part of pathological physiology also chapters on **typical pathological processes** as aging, hypoxia, inflammation, disturbances of water and mineral metabolism and acid-base balance.

The special part of pathological physiology is divided according to systems and organs: Pathological physiology of cardiovascular system, blood, nervous system, etc.

1.4. BASIC PRINCIPLES OF EXPERIMENTAL WORK AND THE ETHICS OF SCIENCE

METHODS OF RESEARCH IN PATHOLOGICAL PHYSIOLOGY

The oldest method of scientific research is the **empirical method**, - the observation of phenomena occurring spontaneously in the nature. Physiologically observation is an active perception of stimuli coming from various receptors. These receptors send signals to the central nervous system, where their time sequence, quality and intensity is registered in conscious man and animal as memory engrams. Although phylogenetically the oldest receptors are chemoreceptors functioning already at cellular level, their higher developmental stages are taste and olfactory receptors. Very important for discrimination of physiological and pathological stimuli are pain receptors. For man the majority of informations from external world comes from visual receptors.

By repeated observations registered by memory man and animal gain experience what in the observed phenomenon is primary and what is secondary or tertiary, what is regular and stable, and what is changing and rare - the quantitative and qualitative, time sequence and spatial characteristics of

perception of the observed phenomena.

The principal characteristic of a thinking homo sapiens is to pose the question: Why and how the phenomenon occurred? The man may, thank to deductive properties of his brain and mind answer correctly also question "why" and "how" on the basis of observation only, as did Galilei, Kepler and Copernicus for examples. The history of science and above all the history of medicine teach us, however, that sole observation is often insufficient for explication of phenomena and of their causes and that simple or repeated observations led to their incorrect explanation and interpretation. For example, the pathomorphologist on the basis of the observed change/s/ in the cadaver cannot say either which is the cause of the observed change, nor that this change is the cause of death. Every scientist has to verify or reject the conclusion: *Cum post hoc - ergo propter hoc* (if something occurs after that, then it is because of that). The first observation should be a stimulus for further observations and only in the case when the observed phenomenon repeats regularly after the first can one assume causal relationship between these two phenomena.

The sole observation of naturally occurring phenomena is an insufficient scientific method also therefore that some events occur very rarely and last for very short time making their profound analysis impossible (e.g. sudden death or a strike of a meteorite on the earth). Therefore even in sciences in which phenomena and conditions under which they occur are not so complex as in biological sciences and systems, there wew necessary long-term, up to generations lasting observations to settle the essence and laws of these phenomena - e.g.thelaws the heliocentric system or the heart activity

and blood circulation.

In pathological conditions the sole observation is insufficient to settle their laws, because some of them (e.g. congential malformations, inborn errors of metabolism and other disorders) occur not only infrequently but also with considerable variability. This is due to variability of causes of these diseases but also upon internal (e.g. psychic) and many external condition under which the noxious agents are pathogenic and also upon individual susceptibility and species differences.

On the basis of these experiences and the acquired knowledge scientist began to interfere actively with natural phemomena and to study them by **experimental method**, of which characteristic tool is experiment.

THE BASIC RULES OF THE EXPERIMENTAL WORK

Experiment is an artificial, conscious and aimful production of a phenomenon under defined conditions established ususally by the experimenter. The immediate aim of the experiment is to establish the cause of the phenomenon and further to clear the quantitative and qualitative relationships between the supposed or known cause and its consequences in time and space and then also the relations of the event under study to other phenomena.

Scientific disciplines which exploit the experimental method are called **experimental sciences**. Since 1850 when Claude Bernard introduced experiment as the main tool into physiology and medicine, nearly all branches of medicine accepted this method and by its use reached not only larger amount of knowledge - the principal aim of scientific research, - but also achieved greater practical, diagnostic and

therapeutic results and preventive aims, than did physicians during the previous more than three thousand years of empirical medicine. Also the great Russian physiologist, I.P. Pavlov (1849 - 1936), the founder of gastric and cerebral physiology, emphasized correctly the importance of new methods for the progress of natural sciences.

Today, experimental physiology with the help of experiment enriches our knowledge about normal body function, experimental pathology and pathophysiology and clinical physiology experimentally produce, study and try to cure and reverse morphological and functional changes, experimental morphology produces and studies changes at organ, tissue, cellular down to molecular level etc.

The starting point for an experiment is observation, e.g. clinical or mediated information or a new, even phantastic idea, which in the mind of the experimenter evokes a supposed relation between two or more phenomena - a **hypothesis.** The experimenter faces now the task to prove or disprove this hypothesis through experiment.

The principal access of the experimenter to the examined phenomenon or idea, hypothesis, should be analytical: The experimenter, above all in the area of biological phenomena should be aware, that the phenomenon is a complex of causes and their consequences, not only in horizontal, vertical but also in relations of time and space. Therefore, he has to select from the complex whole a part of the phenomenon and study the cause and consequence of this part only. For example from the whole complex of symptoms of heart failure he can select for his study only dyspnoe. By doing this he simplifies the complex of questions, disconnects the whole in its

parts and temporarily renders the dynamism of the process quasi static.

The second task of the experimeter is to create strictly defined conditions of the experiment. For example, the experiment is to be carried out at well defined and constant temperature, pH, concentration of components of the administered solution, with defined type and depth of anesthesia. The proper choice of nutritional state, species, age and gender of experimental animal are very important as well. The experimenter should know that the species of animal or type of anesthesia is acceptable for the study of the given phenomenon, mainly when he tries to apply the results of his experiments to other species or man. He has to respect also the diurnal or seasonnal variations of the function and form studied.

Strictly defined and appropriate conditions are *conditio sine qua non* (indispensable condition) for establishment of cause-consequence relations, for formulation of laws of the phenomenon and for the possibility of verification of results by repetition of the experiment by himself or another scientists who are far from him in space or time, when applying the same cause under the same conditions.

The third task of experimenter is the objective observation of the phenomenon produced by the experiment without the influence of his original hypothesis. The experimenter has to subordinate his original hypothesis to the results of his repeated experiments and if they disagree he should abandon, reject his own hypothesis.

The fourth task of the experimenter is to doubt about the unique cause of results observed, in accordance with his hy-

hypothesis. Thus, he has to perform *experimentum crucis*, the control experiment, in which under the same conditions omits one of the supposed causes. In accordance with principal axioma: *Cessante causa cessat effectus*, (ceasing the cause ceases the effect) he will declare as the cause of results and of the phenomenon that condition only after elimination of which he does not get the results.

The experimenter in such way verifies or rejects the original hypothesis. In both cases, he goes ahead with a new, more elaborated hypothesis, continues in the experiments and examines the second, third part of the studied complex phenomenon.

The final task of the experimenter is the synthesis of various parts of the complex phenomenon, **creating a theory based on results of experiments.** The author of this chapter, in contrary to some other sicentists, regards a theory, not supported and verified by results and experiments only as a hypothesis.

The succession of ideas and working activity of a experimenter from observation to theory is outlined in Fig. 1.2.

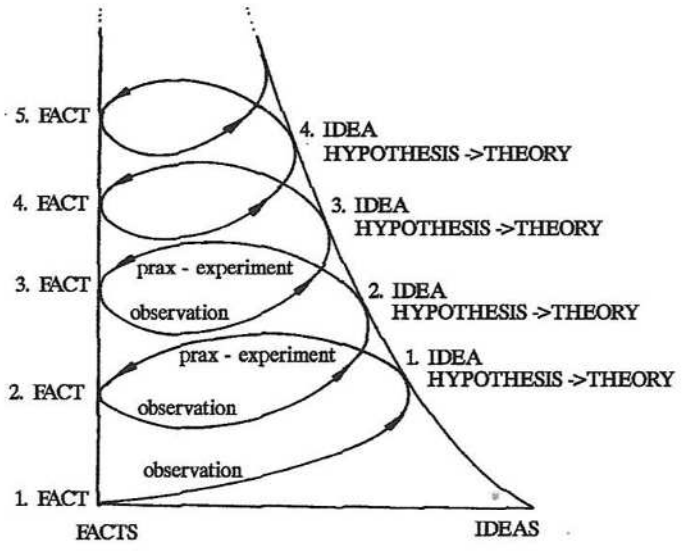


Fig. 1.2. The route from ideas to theory. (R. Korec)

The progressive approach of science and of scientist to the objective reality and eternal truth from observation to ideas, hypotheses and facts reached by experiments to theories of higher ranks is presented also by the scheme of perfectioning scientific knowledge of man.

The scheme emphasizes the primary analytical approach of the scientist to any question. The scientific knowledge goes from the part to the wholeness, from partial to general, from analysis to synthesis. From synthesis reached at certain level of thinking of individual man or his society, we move on to deeper analysis of phenomena: From completed knowledge of human macroscopical anatomy medicine progressed to histological and physiological and biochemical knowledge, now reaching cellular, subcellular and molecular level, their form and functions, from cells to cytoplasm, nuclei, chromosomes, DNA, RNA, genes, their isolation, synthesis, manipulation, transfection, which are helpful but may be also dangerous for Mankind if agreed ethical principles will not be adhered.

TYPES OF EXPERIMENTS IN MEDICINE

There are two main types of experiments in medicine: **Acute and chronic experiment.**

Acute experiments last few minutes up to few hours. Acute experiment is e.g. measurement of various cardiovascular parameters after injection of cardiovasoactive agents, changes of glycemia after insulin and surgical intervention, operation. In chronic experiment the changes after experimental intervention are measured or observed during following days, weeks, months up to years. Classical types of chronic experiments were Pavlov s fistulas of stomach, of salivary glands for the study of secretion of gastric juice or saliva in dogs

after repeated chemical or stimuli, of conditioned reflexes. I have produced and studied for years chronic alloxan, streptozotocin or postpancreatectomy diabetes in rats.

Generally one can declare the acute experiment as more prone to errors due to drastic influence to regulatory mechanisms of body functions e.g. by anesthesia which is often necessary for acute experiments modeling acute emergency state in man. On the other side, the chronic experiment allows often not only the repetition of the same experiment in the same animal or man but also often without anesthesia.

The current medicine tends with much success to substitute the previous invasive, bloody methods of research by non-invasive, non bloody methods, as e.g. two-three dimensional sonography, computerized colour tomography or infrared and magnetic imaging of biochemical parameters and reactions in the body without the necessity of taking blood samples.

ELABORATION AND EVALUATION OF EXPERIMENTAL RESULTS

Every, even miscarried or badly performed experiment, brings some results. Experiments carried out under right and correctly defined criteria are characterized by equal results achieved by the same or other research worker when repeated, about all from qualitative standpoint. Apart from intra- and interindividual variability it is extremely difficult to keep the same condition of experiment even when repeated by the same experimenter, e.g.influences of weather, endocrine and psychical cycles influencing both the experimenter as well as the living object of the experiment, the results of repeated experiment show some variation and therefore they have to be evaluated statistically to prove, whether the observed values of examined parameters are caused by chance or they are regu-

lar and significant changes due to stimuli which were applied or withdrawn. If the measured changes, calculated and evaluated by various appropriate statistical methods, the most frequently used are Student s t-test. F-test, Lord s L-test - have a certain quantitative difference of the means which exceeds the probability of of their occurence by 5% chance, $P < 0.05$, such differences are accepted as statistically significant for the stimulus applied or withdrawn.

The author of this chapter, although using statistical methods for evaluation of his own results for decades is expressing some criticism about the misuse and interpretation of statistical significance at change 5% for biological phenomena and cautiously recommends differences higher than 10% as biologically significant. As far as the philosophy of statistical methods is concerned, they do not solve the problem of individuality which exists and is often the starting point for a new discovery. If for example insulin, for over seventy years well known hypoglycemizing hormone produces in 100 animals the decrease in glycemia but not repeatedly in one animal, this non-effect is not statistically significant, although there is the discovery of a new quality - of insulin resistance. Simlarly, if I administer, inject a diabetogenic dose of alloxan to ten rats, and due to resistance of five animals five have normal glycemia of 5 mmol/l and the other five only become to be diabetic with fasting glycemia e.g. 20 mmol/l, I cannot declare all rats as diabetic with mean glycemia of 12.5 mmol.

PRINCIPAL AIMS OF SCIENCE AND EXPERIMENT

The primary aim of a scientist s work and of the experimenter is to establish the knowledge and truth about the stu-

died phenomenon, to discover its laws, its succesion of causes and consequences which bring him satisfaction or even joy expressed by the word "heureka".

The secondary aim of scientific research, regrettably now predominant is utilitarian - and should aim at the benefit and good of Mankind. It is well known that every thing has its inherent dual quality the possibility to be used for good or bad. Many results of basic research aiming primarily at the knowledge of truth have no immediate practical applicability, The astronomical discoveries of Galilei, Kepler and Copernicus had to wait many hundred years to be practically used in cosmo- and astronautic, similarly as the description of diabetic symptoms by egyptian Ebers papyrus or by Aretaeus over two or three thousand years. If the research is primarily directed for practical exploitation it should be always at the good of Mankind and the scientist who is working consciously on a project whose effect will be mainly or clearly detrimental to humnas and the living nature is working unethically such as scientists working on development of nuclear or similar mass-destructive military weapons.

From philosophical standpoint there are some unanswered questions such as if the science and experiment are elucidating only the question: How? or also the question: Why? My opinion is that science should answer the question: How? and the principal question: Why? is answered partially, continuously during each experiment, but it will be never answered completely. Convinced of necessity of scientific research for the benefit and progress of Mankind, I am against scientific research aiming at the destruction of human life - e.g. by genetic and abortional procedures, production of toxins and

arms, above all those of mass destruction.

ETHICS OF THE EXPERIMENTER AND OF EXPERIMENTAL MEDICINE

Ethics of the experimenter is reflected:

1/ In aims of his experiment

2/ In methods and attitude toward the experimental object, above all when he performs experiments on man, monkeys, higher mammals dogs and laboratory animals.

3/ In evaluation and presentation of his results.

Ethics of experimental aim and target. As said before the primary aim of the experiment is to discover the truth about the phenomenon studied, to know its cause and its consequences, its laws. This aim is highly ethical and natural and it reflects a special expression of the general desire of man in all fields of his activities. The second aim or target of the experiment is its exploitation, which is also ethical, when results of experiments serve to indisputable benefit not for the experimenter alone, but for his environment, his neighbours, society or all Mankind. When experimenter performs an experiment, the results of which will be detrimental to the enviroment, to human and higher animal beings or even protected plants, his experimental activity is unethical, should be abandonned or even prohibited. The autor of this chapter is of different attitude toward ethical principles and hierarchy of ethical values among scientists and experimenters defending their rights to perform experiments without respect to the of their results saying that every result or discovery has inherent dual value: To be used for the good or benefit of Mankind or for misuse or abuse. In medicine we have to defend the highest ethical, Hippocratico-christian and islamic (Ibn Siná - Avicenna, 980 - 1037) values, aims and task: To

protect human life at every stage of its development, to prevent and to cure, not to cause disease: *Primum nil nocere et Salus aegroti suprema lex!* (Above all do not harm and the health of the patient is the highest law.)

As far as the methods and attitude of the experimenter toward his object are concerned, he has to perform his experiments on animals with minimum necessary stress, pain and suffering, in appropriate type and stage of anesthesia, caring also for the animal in postoperative period. When results of the experiment have to be used for human beings and diseases, he has to use appropriate species with transferable results, e.g. monkey for AIDS, dog, swine, rats for diabetes. When suffering and killing of the animal is inevitable, he has to get permission of a committee evaluating the importance of the problem studied for human denefit. The experimenter does not perform unnecessary number of experiments when results are unequivocal. A well planned project prevents multa /experimenta / and yields multum. Experiments to show known facts are allowed for pedagogic purposes only. Even though fundaments of physiology and of medicine were build up on results of experiments carried out on animals, some experiments on both healthy and ill men are necessary for the progress of human medicine. Acknowledging the enormous species differences between highest mammals including monkeys and man in the brain and psychic activity, it is clear that we cannot elucidate the higher mental function of human brain, of feelings and of intellectual activity, of physical work, of specific human metabolic or infectious diseases through experiments on animals and that experiments on both healthy and ill men are necessary under conditions formulated by experts of world Me-

dical Association in Helsinki 1964 and Tokyo in 1974 as well as by WHO. The chief preconditions for experiments on healthy men are:

1/ To be instructed about the aim, the method and possible danger of the experiment and has to give his voluntary non-inforced written consent, which he can revocate at any time.

2/ The personnel of doctors and other scientists performing the experiment have to obtain written permission of an independent ethical scientific comission, which should assure that there is no danger to the health of the volunteer and if any sign of danger appears during the experiment it should be interrupted.

There are similar preconditions for experiments on diseased people, on patients. The written conset for self-non responsible patients as children or psychiatric patient may be given by their parents or responsible patron.

In the case of emergency and life danger doctor/s/ may use a new non approved method or treatment, if the usual method or medicament is ineffective and the new method according to scientific - medical reports offers hope or help to the patient.

In the course of last decade the number of experiments on patients show an increasing tendency and although medical journals request and publish that experiment on patient fulfill the conditions of Declaration from Helsinki and Tokyo, the autor is convinced that the prescriptions are not strictly adhered, because money is distorting ethical principles both on patients and doctors side, above all when a new medicament has to gain popularity. Moreover, ethical principles

are not sanctioned in each country legally and medically non indicated abortions, even euthanasia and non ethical genome manipulations and cloning of fertilized human ova continue and some "liberal" scientists carry out fascist racial expe-rimets.

The third criterion of ethics for an experimenter says that he should precisely and correctly elaborate and evaluate his results logically, statistically and confront them with pertinent results of others. Every author - experimenter has the desire of early publication of his results in a renowned journal or book, the desire for acknowledgment of his origi-nality but some reviewers are not fully competent or strict in accepting or rejecting the submitted paper. Even at such high level as awarding Nobel prize sometimes big errors are made, e.g. for the discovery of insulin to MacLeod and Ban-ting, omitting the priority of Paulesco and contribution of Best. During the last century Claude Bernard was the sole author of original discoveries and of papers and books, simi-larly Minkowski the discoverer of postpancreactectomic diabe-tes and of enormous work in many species on this problem, si-milarly J.E.Purkyne alone discovered the Purkynje bundle of the heart and Purkynje cells of cerebellum, to-day papers are mostly collective with unknown responsability for partial re-sults of the paper and the results obtained in vitro are in-correctly applied to whole organism, because highly analyti-cal approach at subcellular or even molecular level neglect the higher physiological levels of regulation. The recent progress in biochemistry and immunology is characterized by discoveries of hundreds new active molecules with unpredic-table dialectic interactions, leading to hypothetic conclusi-

ons to which the words of W.Harvey, the discoverer of heart function and blood circulation in animal body are ethically valid: *Omnes itam studiosi, boni honestique - nec putant mutare sententiam si veritas suadetet aperta demostratio.*

2. HEALTH AND DISEASE, GENERAL NOZOLOGY AND ETIOLOGY

2.1. AN ATTEMPT TO DEFINE HEALTH AND DISEASE

If we want to define disease, first we should define health. In the ancient and modern medicine one can find a lot of definitions of these two essential concepts but none of them is perfect and what is more important, none of them is generally used in the everyday practice.

One of the most cited definition is that accepted by the World Health Organisation (WHO) which in shortened version states:

Health is the state of complete physical, mental and social well-being and not merely the lack of disease or physical defects.

Accepting this definition we inevitably should run into difficulties because:

* It is almost impossible to find a person in the world who fulfills all its requirements completely.

* This definiton surpasses the scopes of medicine.

On the other hand this second point is principially correct, because health is not only a matter of health care providers (doctors, nurses, chemists, etc.) The relationships between socioeconomical and professional aspects of health care were fully recognized and formulated in a detailed way (as a set of 38 targets) by the member states of WHO in 1984 and updated in 1991. The aim of this policy, what is a *blend of today's reality and tomorrow's dream* (J. E. Aswall, WHO Regional Director for Europe, 1991) is clear:

The main social target of goverments and WHO in the co-

ming decades should be the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life. (This statement eludes the problem of the unattainable complete health - it speaks about **level of health**).

The idealized WHO definition of health is a useful tool to investigate the different aspects of the health, namely to realize the strong ties among the medical, psychical and social aspects of health and disease.

1. Sick people are rarely in the state of good temper and the disease often has a negative influence on their social status.

2. People under psychic stress complain frequently on heart, gastric and other symptoms and sometimes develop real organic disease.

3. People with low income (and poor communities) cannot afford proper medical care, cannot ensure healthy food and water and are not educated enough to protect themselves from disease. The poverty influences profoundly their state of mind and body and their health.

In search of a generally acceptable definition of health and disease one should also realize that these concepts have different meanings from different points of view. Different sense of health and disease have lay people, general practitioners, medical specialists, people engaged in medical research, insurance agents, employers and politicians.

From the point of view of pathological physiology a usable definition is as follows:

Health is the sum of abilities of the organism enabling to counterbalance the environmental effects without disinteg-

ration of the homeostasis.

If these abilities are overriden, death can ensue or the life continues with various functional and morphological changes at various levels of the organism. The dynamic steady-state of the body and the unity of its various functions are disturbed - this is disease.

2.2. THE PRINCIPAL FORMS OF PATHOLOGICAL PROCESSES

Despite the difficulties to agree on an exact definition of disease in most cases the distinction between healthy and ill people is quite easy. However, not every deviation from physiological values is disease.

PATHOLOGICAL FINDING

Abnormal biochemical findings. Although excellent handbooks deal with the physiological ranges of biochemical values of blood, urine and other body fluids, (considering the differences due to age, gender and other biological variables), every result should be evaluated and interpreted only in context with the results of general basic (anamnesis, physical examination) and auxilliary (laboratory, functional, X-ray, etc.) examinations. Isolated high or low value of a single assay without clinical signs may but need not denote disease. For example a single glucose value about 8 mmol/l in an otherwise healthy man is not a proof of diabetes mellitus. Other tests should be performed to confirm or exclude the presence of disease. But if the value is 15 mmol/l and technical failure in the laboratory can be excluded (even the highly sophisticated modern laboratory equipment is not fully foolproof), the diagnosis of diabetes is almost sure.

In general, unexpected abnormal results of laboratory investigations not in agreement with the clinical picture should be repeated before conclusions were drawn from them. because

Abnormal morphological findings. A century ago the discovery of X-rays revolutionized the diagnostic process in medicine. In former times only the surgeon and the pathologist had some insight into the inner parts of the body. Everybody else was forced to find out anything about the functions of the organs by using indirect methods such as palpation, percussion and auscultation or through observations of body excrements.

In the past 20 years another technical revolution is under way. Myriad, for human mind unarrangable bits of information (gained through reflection of ultrasound, absorption of X-rays, resonance of atomic nuclei in magnetic field) are gathered in computers and arranged in a split second yielding images as clear as in a picture textbook of anatomy.

The new **noninvasive imaging** techniques, (ultrasonography, CT, NMR, PET)* although some of them are extremely expensive, speed up the diagnostic process, make the doctors' decisions safer and mean less inconvenience, pain and danger to the patient. On the other side the convenient survey of the inner parts of the body often reveals **asymptomatic pathological findings.** Their interpretation should be made in a similar way as the interpretation of random abnormal biochemical values - always in context with the whole health state.

---

* CT - computerized tomography, NMR - nuclear magnetic resonance, PET - positron emission tomography

Abnormalities of human genome. The human genome obtains about 50 000 - 100 000 genes and its structure and function is far more complex than anybody would anticipate some years ago.

The number of known inborn (genetic) errors of metabolism is raising steadily. In many common diseases stronger or weaker genetic background was found or anticipated. New techniques are introduced into research and clinical practice which enable quick analysis of the genes. The objective of the Human Genome Project is to map the entire human genome in the course of a couple of years.

It is impossible to imagine that anybody on the earth has a genome without some hidden faults. They might lead to disease but they need not. One of the future tasks of the medical sicence will be the elaboration of evaluation and interpretation schemes for a given individual genetic blueprint enabling efficient counselling.

PATHOLOGICAL REACTIONS AND REFLEXES

A pathological reaction is a short-term nonphysiological and often inadequate response of the organism to various stimuli (exaggerated rise of blood pressure to negative emotions, local hyperreactivity to chemical substances, hyperglycemia after burns, etc.) They might be isolated, single events or can indicate the presence of pathological processes or latent diseases.

Abnormal reflexes of the nervous system indicate the dysfunction or damage of various parts of central or peripheral nervous system in (e.g. the presence of Babinski reflex in adults).

PATHOLOGICAL PROCESSES

Pathological processes are complex responses of the body to various pathogenic factors which include adaptive and defensive reactions as well. There is no sharp dividing line between physiologic reactions and pathological processes. For example the response of thrombocytes and coagulation system to an injury of the vessel wall is clearly a physiologic event - **blood clotting**. The same event taking place on vessel wall coated with atherosclerotic plaques (although there is no danger of exsanguination) is a dangerous pathological process - **thrombosis**. Another example is **fever** which mobilizes the defensive forces of the organism against the invading bacteria or viruses but the high body temperature can overload and damage the circulatory system.

Pathological processes are not identical with individual diseases, but they usually arise form a part of many different diseases (inflammation, hypoxia, oedema, fever, etc. - they are treated in the 2nd volume of this textbook).

STATIC PATHOLOGICAL CONDITIONS

Pathological processes and diseases are always dynamic. There are, however, static conditions (congenital malformations, loss of limbs or parts of organs, scars of skin after wounds or of stomach after healing of ulcer, etc.) which are clearly nonphysiologic but do not correspond to the common medical conception of "disease".

2.3. STAGES OF DISEASE AND ITS POSSIBLE OUTCOMES

Every disease has its own individual course but in most cases four consecutive stages (**latent, prodromal, manifest stages and the stage of healing**) can be distinguished. According the duration of the manifest stage **acute** and **chronic** diseases can be distinguished (with such transitional forms as **subacute** and **subchronic** diseases) - Tab. 2.1.

Tab. 2.1. Acute and chronic diseases

DISEASE	DURATION	EXAMPLE
PERACUTE	minutes - hours	anafylactic shock
ACUTE	days - 3 weeks	myocardial infarct flu pneumonia
SUBACUTE (SUBCHRONIC)	3 - 6 weeks	glomerulonefritis myocarditis
CHRONIC	months, years or the whole life	tuberculosis epilepsy diabetes mellitus

There are, however many exceptions from this pattern. Some diseases do not have latent and prodromal stages and in other cases certain diseases do not heal despite all efforts of the adaptive and defensive forces of the body and despite available medical care. From acute events lifelong chronic diseases or steady pathological conditions can develop or they can deteriorate at a slower or quicker pace and after a period of **end-stage disease** the patient dies.

LATENT STAGE

This stage begins in the moment of attack of the pathogenic factor on the body. In this stage no complaints or clinical symptoms are present and the results of basic laboratory

investigations (biochemical and hematological assays, X-ray photographs) are mainly in the physiological range. On the other hand the new, sophisticated scientific methods enable to recognize some diseases already in the latent stage. (As an example, the polymerase chain reaction discloses the presence of viruses causing AIDS and other agents already some days after infection.)

If the defensive forces of the body are strong enough, diseases (mainly infections) can be stopped at this stage and the other stages do not manifest.

Time of incubation. The latent stage of infectious diseases, called as **time of incubation** has usually a well-established duration and provides important information for the differential diagnostic decision.

Diseases without latent stage. In some cases (cyanide intoxication, injury by electric current or lightning) the latent stage is so short that from practical point of view it is virtually nonexisting. Of course it is meaningless to speak about latent stage in congenital malformations, inborn errors of metabolism, etc.

Clinically asymptomatic chronic disases. In many primarily chronic diseases (e.g. coronary heart disease, non-insulin dependent diabetes mellitus and many others) it is difficult to decide, when the disease actually begins. These diseases develop lurking for a long time without subjective complaints and without apparent clinical signs. As far this period can be considered as a long, but typical latent stage.

A very simple investigation of the **risk factors**, namely anamnesis (smoking, early cardiovascular death in the family,

etc.) and laboratory investigation (high cholesterol, low HDL-cholesterol,) can reveal the high probability of existence of a serious disease. A positive coronarographic finding provides the ultimate proof of the **coronary heart disease.**

From this point of view the clinically asymptomatic stage before the investigation cannot be further considered as "latent" according to the original definition (i.e. the beginning of a disease), because the disease is already fully developed but **unrecognized.** The sudden death of many people from unrecognized asymptomatic coronary heart disease furnishes the best evidence that the asymptomatic or silent period of a disease is not always denotes its beginning.

PRODROMAL STAGE

This stage (present in most infectious but absent in many other diseases) is characterized by nonspecific symptoms such as fatigue, headache, pain, loss of appetite, etc. which do not enable to make a clinical diagnosis. In some diseases (e.g. viral hepatitis) the results of basic biochemical, serological, immunological and other auxilliary methods can already disclose enough specific information to make a diagnostic decision with high probability of correctness. This enables to start appropriate therapy before the outbreak of the disease.

MANIFEST STAGE

In the manifest stage the subjective and objective signs of the particular disease are clearly expressed. The pathogenous factor has transiently overcome the defensive forces of the body.

The manifest stage is characterized by subjective and objective signs and abnormal values of laboratory investigati-

ons. These signs are termed **symptoms**. To make a diagnosis it is necessary to arrange the symptoms in a logical way. Such sets of arranged symptoms, which reveal the presence of a particular disease are **syndromes** (Tab. 2.2).

Tab. 2.2. Symptoms and syndromes

SYMPTOMS	SYNDROME
Thirst, polyuria, glycosuria, hyperglycemia, ketones in the urine, weight loss	DIABETES MELLITUS
Fatigability, diarrhoea, periodic weakness of muscles, paresthesia, hypertension, poly- and albuminuria, high losses of potassium in urine	PRIMARY HYPERALDOSTERONISM CONN'S SYNDROME
Hypodynamia, fatigability, hyperpigmentation of the skin, nausea, vomitus and diarrhoea, bradycardia, hypotension, loss of sodium in urine	HYPOCORTICALISMUS ADDISON'S DISEASE
Spastic paresis on the one side of the body with disturbance of the deep sensitivity; disturbed pain and thermal sensitivity on the other side	UNILATERAL TRANSVERSE LESION OF THE SPINAL CORD SYNDROME BROWN-SÉQUARD
Limp, pain in the leg after a short walk, pale, cold and cyanotic skin of the foot	CHARCOT'S SYNDROME
Obesity, hypoventilation, sleep disturbances with snoring and apnoea, hypertension, daytime drowsiness	PICKWICK'S SYNDROME
Cyanosis and dyspnoea from the first days of life, growth retardation, dextroposition of the aorta, defect of the ventricular septum, pulmonal stenosis and hypertophy of the right ventricle	FALLOT'S TETRALOGY

The symptoms during the manifest stage of a disease are not pronounced at a constant intensity even in the same subject and even without treatment. In **remission** the intensity of symptoms (and the whole pathologic process) diminish, but if they appear again this is called an **exacerbation** or **relapse**.

In some patients despite proper treatment **complications** occur which might but need not be connected with the primary disease. They usually worsen the prognosis of the patient. If a disease is complicated with another disease, it is called **intercurrent** disease.

Very interesting in this sense is AIDS because its main feature, the killing of T lymphocytes in itself has no symptoms and therefore almost every clinical sign of the disease is attributable to intercurrent infections and other pathological processes due to diminished immunity.

THE OUTCOMES OF DISEASES

Under favourable conditions and with proper treatment and medical care the body overrides the damaging forces. The symptoms gradually disappear, the pathological processes regress and the stage of **reconvalescence** begins. In classical medical textbooks two forms of transition between the manifest and reconvalescent stage are mentioned. Some diseases (e.g.lobar pneumonia) ended suddenly (**crisis**) in others the recovery was gradual (**lysis**). This classic pattern of disease termination is now rarely seen because medication and treatment profoundly affects the course of diseases.

In the stage of recovery the body is on his way to the normal state but its adaptability and ability to compensate various damaging environmental factors is often compromised for some time.

In the optimal case the recovery after disease is full - **sanatio ad integrum**. Moreover the immunity after some infectious disease can last for many years. Some diseases leave behind some irreversible tissue or organ damage. This damage is usually compensated by the reserve forces of the same or

other systems - **sanatio per compensationem**. The patient feels well, the results of examinations are within the normal range but his reserves are diminished and in the case of extra burden the damaged system can break down.

In other cases acute diseases do not heal completely - they transform into **chronic disease** or **static pathologic conditions**. In the worst case nor the defense forces of the body neither the treatment are able to conquer the diseases and after a shorter or longer period of **end-stage** disease death, **exitus lethalis** ensues.

2.4. GENERAL ETIOLOGY - THE POSSIBLE CAUSES OF DISEASE

At the first approach the division of the possible causes of disease is quite simple. Diseases and injuries can be caused by **external** agents (bacteria, toxins, electric current) or something goes wrong in the body itself - diseases with **internal** causes (e.g. hypertension, inborn errors of metabolism, endocrine diseases or mental illness).

Further investigation confuses in this simple concept. What is the cause of diabetes mellitus in an obese person? Excess food or the (probably inherited) internal weakness of his insulin producing cells residing in islets of Langerhans? Everybody knows that smoking can "cause" lung cancer but from other point of view and according to textbooks malingnancies are "caused" by the loss of control of the cell proliferation. Mental illness often appears after negative life events. Was the stress the cause of the disease or was it only its triggering factor? These and many other similar questions arise seeking the causes of diseases and the answers are not

simple.

Every disease has its cause but it could be extremely difficult to find it in the complex network of various conditions and mutual connections in time and space. The cause is **necessary** for the development of a disease but often not **sufficient**. Often the various **conditions** decide wether a disease will develop or not. Mycobacterium tuberculosis is the unambiguous cause of tuberculosis but in people with proper function of the immune system the infection is conquered at a very early stage and the disease does not develop. (Of course no tuberculosis appears in subjects sensitive to disease if they are not infected with the bacteria.)

Further difficulties in search after causes of diseases arise considering the various levels of life. For a lay person hypertension is caused by stress at work **(social level)**. His physicians knows that it is true to some extent but he considers high blood pressure for a disturbance of cardiovascular regulation **(system or organ level)**. Research workers are seeking the clues of hypertension at deeper, **cellular, subcellular and molecular** levels. Every explanation is partly true and to treat hypertension effectively, one should be aware of every its aspect.

Despite these difficulties the first mentioned division is useful if one keeps in mind that it is a didactic oversimplifications and does not forget the complexity of the topic. The next three chapters deal with the external causes of the diseases. They are divided according to the division of the natural sciences to physical, chemical and biological causes. Again, this division (Tab. 2.3) is not without some contradictions.

Tab. 2.3. The external etiological factors of disease

FACTOR	EXAMPLE
PHYSICAL	
MECHANICAL ENERGY	Injuries, wounds, blast and crush syndrome
ACCELERATION AND GRAVITATION	Acceleration, weightless state, kinetosis
HYPOBARIA AND HYPERBARIA	Mountain sickness[1], decompression sickness, hyperbaria
HIGH AND LOW TEMPERATURE	Burns and chilblain, hyper-, hypotermia, sunstroke
ELECTRICAL CURRENT	Electrical injury
ELECTROMAGNETIC FIELD	Damage by IR, visible and UV light
IONIZING RADIATION	Damage by X and gamma rays, neutrons, etc.
CHEMICAL	
TOXICANTS	Anorganic, organic, biological toxins, pollutants, carcinogens nicotine, alcohol[2]
BIOLOGICAL	
MICROBIOLOGICAL[3]	Viruses, bacteria, fungi, protozoa
NUTRITIONAL	Undernourishment, vitamin and trace element deficiency, obesity[4]

[1]Treated under heading Hypoxia in Vol. 2
[2]Nicotine and alcohol are harmful exogeneous chemical substances, but smoking and alcoholism are social phenomena
[3]Treated in microbiology
[4]Not caused by exogeneous factors

Mechanical energy, electrical current, ionizing radiation are clearly physical agents, carbon monoxide and cyanides chemical causes of disease. On the other side ethanol, nicotine and cocaine are chemical substances, too, but smoking, alcohol and drug abuse, (included in chapter on chemical causes) are above all social and psychological problems and nor simple intoxications. The chapter which should deal with the main external biological causes (bacteria, viruses, etc.) is omitted because it is the whole topic of microbiology. Instead a chapter on disturbances of nutrition is included despite obvious doubts that famine in poor countries and obesity in a third of the rich world's population is merely a biological problem.

3. PHYSICAL FACTORS AS CAUSES OF DISEASES AND HEALTH DAMAGE

3.1. THE EFFECT OF MECHANICAL ENERGY

INJURIES AND WOUNDS

If the human body collides with another (human, living or nonliving) body, the kinetic energy of the collision can cause different **injuries (trauma), wounds (vulnus)** and in the worst case **sudden death.**

Injuries are the most important cause of premature death and disability in young people in developed countries. One third of all deaths from injury are due to motor vehicle crashes, one third to other unintended causes (especially falls) and one third to intentional violence (suicide and homicide). As an example in the USA more than 150 000 injury caused deaths are recorded each year and the consequences of nonfatal injuries causing permanent disability pose an even larger medical problem.

The main forms of wounds are listed in Tab. 3.1. The consequences of these wounds vary considerable from negligible inconvience to permanent disability and even death.

Tab. 3.1. The main forms of wounds

Contusio	bruise
Abrasio	graze
Laceratio	tear
Vulnus sectum	cut wound
Vulnus punctum	stabbed wound
Vulnus morsum	bited wound
Vulnus sclopetarium	bullett wound
Fractura	broken bone
Luxatio	dislocation of a joint

The most common symptom of wounds is **pain** caused by irritations of extero- and interoreceptors, products of tissue destruction and later by inflammation.

Almost every injury leads to some **blood loss**. If considerable amount (10 - 30 % of the total volume, that is 0.5 - 1.5 l in average adults) is lost, arterial hypotension develops which in turn can contribute to the development of **traumatic shock** (described in the Pathophysiology of Circulation).

Into damaged blood vessels bubbles of air or droplets of fat from the surrounding tissues can get causing **air or fat embolism**, respectively. These bubbles and droplets obture the small capillaries in remote organs and deteriorate their oxygen supply.

Open wounds are **locus minoris resistentiae** where infection can enter the body. The most dangerous possibilities arise if the wounds are contaminated with anaerobic bacteria (mostly from soil) and not treated properly in time. In such cases life-threatening **gas gangrene** (necrosis of affected limbs with development of gas and sepsis) can develop. Gas gangrene was common in the pre-antibiotic era, namely in the wounded soldiers of World War I. In necrotic tissues around (even very small) wounds germs of Clostridium tetani can produce tetanotoxin - a protein of M_r about 150 kD which is one of the most potent toxic substances. **Tetanus** is characterized by generalized painful muscle contractions. Vaccination and revaccination every 5 years completely prevent the danger of tetanus.

Every major injury triggers also the nonspecific adaptive reactions of the organism (**stress reaction**, Vol. 2).

Blows of the head (even without fractures of the bones) often lead to brief loss of consciousnes - **commotio cerebri** with consequences ranging from some hours or days (amnesia, vegetative symptoms as nausea and vomitus, nystagmus) up to such chronic complications as **posttraumatic epilepsy**. Repeated small injuries of the brain are characteristic features of boxing. The blows probably cause microscopical haemorrhages in the brain or lead to transient depression of neuronal and synaptic metabolism. Years after leaving the sport career the damage of the brain usually manifest as **extrapyramidal motor disturbance** and in some cases as serious deterioration of mental abilities - **dementia pugilica**.

BLAST SYNDROME

This syndrome is caused by the shock wave of explosions. In fact after explosions several waves of increased and decreased pressure arise in very short time. These shock waves can damage the tympanic membrane and the tiny structures of the middle ear, disrupt the alveoles in the lung leading to lung haemorrhage and air embolism and compress the abdominal organs containing air (stomach, guts).

Blast syndrome is usually combined with other types of injury (pushing the body against wall, splits of projectiles, flying objects, etc).

Properly targeted and focused underwater shock waves of appropriate energy are used to destroy gallstones and stones in the urinary tract (**extracorporeal litothripsy**, Fig. 3.1).

CRUSH SYNDROME

In people buried or partly buried under avalanches, in destroyed buildings (earthquakes) or crashed vehicles and similar situations the compression of soft tissues leads to

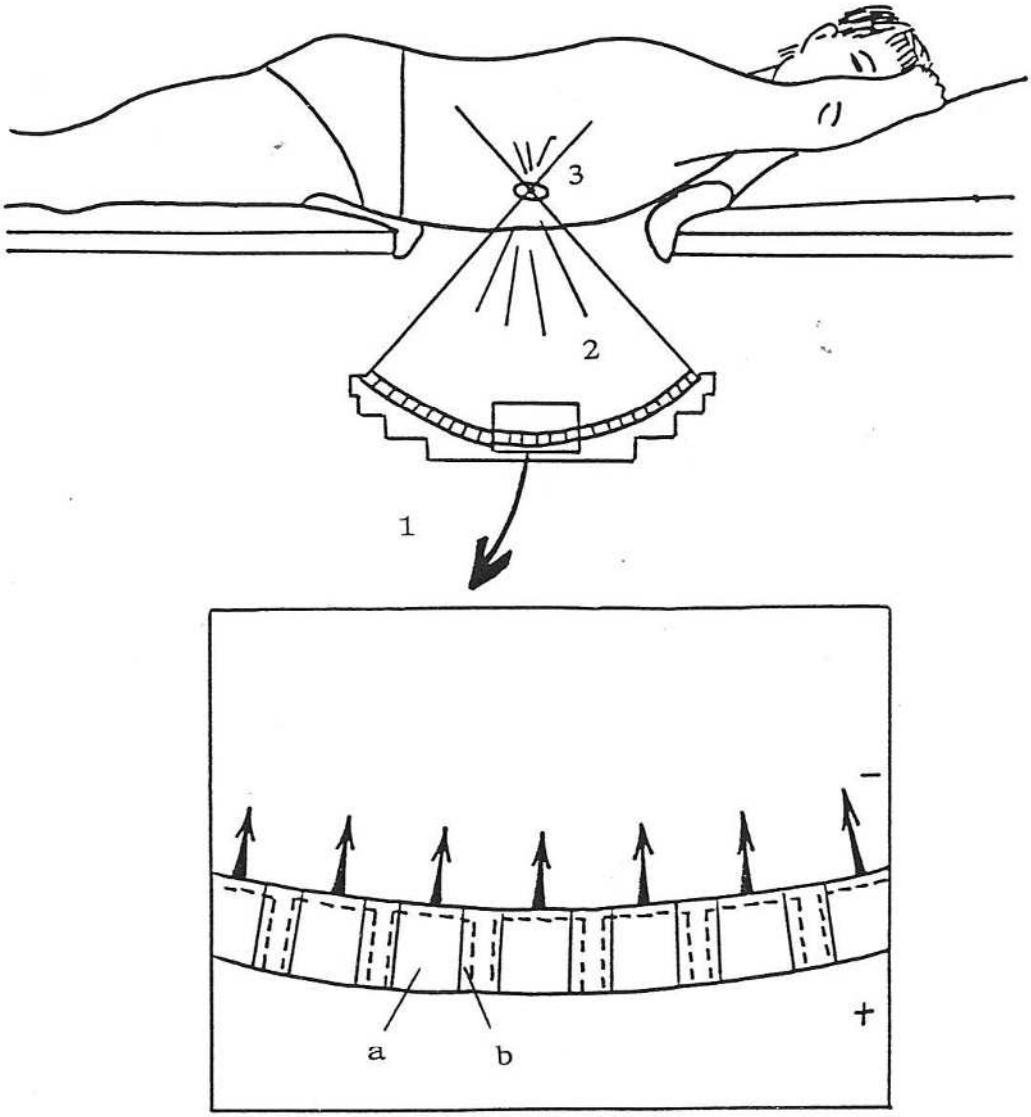


Fig. 3.1. Extracorporeal piezoelectric litothripsy

1-piezoelectric ceramic crystals which under electric impuls change their shape
2-focused shock wave propagating in fluid medium
3-gallstone
Insert a,b - the shape change of piezoelectric crystals

The litothriptor is equipped with ultrasonographic scanner (not shown on the scheme) which help to locate the stones and controls their destruction. The duration of the shock waves is in the mikrosecond range and they are repeated with frequency 1 - 2.5 Hz. Usually 500 - 3000 impulses are necessary to destruct stones in the gallbladder and urinary tract.

their ischemisation. After rescue and decompression the perfusion is restored but mostly too late. If the endothel and the vessel wall is already irreversibly damaged, water and small molecules escape from the intravasal space and the fluid accumulates in extravasal space (**oedema**). This additional layer of fluid between vessels and cells further deteriorates the diffusion of oxygen to cells. Due to the fluid loss from the vessels the density and viscosity of blood increases and hypovolemia develops. Breakdown products of muscle and other substances released from the anoxic tissues (e.g. histamin) further worsen the circulation. If the compression is not released in time hypovolemic shock develops whith prerenal kidney insufficiency resulting in oliguria or anuria. Crush syndrome may lead to death due to shock or uremia even without serious external injury and blood loss. In renal tubuli of the victims cylindres of precipitated myoglobin are present and according to an older theory this is the cause of the renal insufficiency. In fact the cylindre formation in crush syndrome is only a consequence of the renal failure.

VIBRATIONS, NOISE AND ULTRASOUND

Man perceives vibration in the range of 25 - 8200 Hz. People exposed repeatedly to vibrations (mostly as occupational damage) complain after months or years of exposure on pain of the spine and extremities. X-ray investigation can disclose severe osteoporosis. The regulation of the tone of small vessels of fingers is deficient, vasospasms and the damaged local circulation lead to increased sensitivity of the fingers to cold and later to trophic changes of the skin and muscles. The symptoms are similar to those in Raynaud's syndrome which is a congenital disturbance of the vasomotor tone.

Vibrations, in addition may damage the ear, can foster the development of neuroses and high blood pressure.

Vibrations between 16 - 20 000 Hz are perceived by the human ear as sound. Chronic exposure to noise (noise is every sound which is percieved as disturbing and of intensity above 50 dB*) leads to hearing loss and deafness and disturb the activity of the vegetative and central nervous system.

Ultrasound - frequency above 20 kHz, not perceived by human ear - of high intensity can lead to the same damage as vibration and noise and in addition it has also a thermal effect. The intensities employed in the diagnostic and therapeutic ultrasound devices are well below the dangerous threshold.

3.2. THE EFFECTS OF ACCELERATION AND GRAVITATION

ACCELERATION AND DECELERATION**

Acceleration is the **change of movement** (characterized by its speed and direction). (Fig. 3.2). Moving at constant speed in one direction itself has no effect on the body (without visual control it is even impossible to perceive it) but if the speed or the direction of the movement changes the various parts of the body behave according the law of inertia - they tend to retain their original speed in the original

---

*The relationship between the physical energy of acoustic vibrations and their perceiving as sounds or noises is logarithmical. The threshold of perceiving a sound is 0 dB and the physical energy of a 10 dB sound is 100 times more. The energy value of the 0 dB threshold varies with the frequency of the sound, its minimum is in the range of 2 - 3 kHz.

** deceleration (slowing down) and negative acceleration are the same.

Fig. 3.2. Examples of acceleration and deceleration.

direction. The vestibular apparatus of the inner ear works on this very principle and enables perceiving acceleration and deceleration. It is very important to recognize, that the forces arising from the change of movement act always in the opposite direction as compared with the acceleration.

The change of speed can occur in various directions, be of various intensity and duration. (Tab. 3.2).

Tab. 3.2. The effects of acceleration on human body

ACCELERATION G	TOLERANCE	EFFECTS
+2	> 10 min.	The weight of the body is increased, the body is pushed into the seat
+2.5	minutes	Impossible to stand up from the seat, breathing is difficult
+3	seconds	Pale, distorted face, sight disturbance (grey shield)
+4	seconds	black shield, tachycardia, dyspnoe, loss of consciousness
-1	minutes	Discomfort
-1.5	minutes	Pressure in the head, red face
-2	10 seconds	Strong pressure in the head, eyes lacrimation, dizzines
-2.5	seconds	pulsating pressure in the head, dyspnoe, red shield
-4	< 1 second	Acute pain in the head and eyes, red shield, disturbances of brain function similar to commotio, loss of consciousness

Let us consider some common examples:

Acceleration and deceleration in traffic vehicles. A racing car after start achieves in some seconds speed over 200 km/h. It is a strong positive acceleration in ventrodorsal

direction, but this is relatively well tolerated. The pilot is pushed into his seat. Before the curves he needs to brake (negative acceleration or deceleration) and his body is held in the cockpit with the help of the safety belts. In the curves there are two possibilities: If the track is flat, the acceleration is lateral (the car and the pilot's body tend to proceed in the original direction). Some very fast tracks have tilted curves enabling the racers to take them with high speed. In this case the main force (arising from the combination of the vectors) is upward down and this in fact has the same effect as positive acceleration in craniocaudal direction.

The worst case of deceleration occurs in a crash, when in a very short period of time extreme negative acceleration takes place. Proper construction of cars, their bumpers together with the safety belts and air bags help to absorb most of the kinetic energy of the crash and can avoid serious injuries and death in accidents (see also Chapter 3.1).

Acceleration in aviation and astronautics. If a plane accelerates upward (looping) the blood accumulates in the lower parts of the body. If the force of acceleration overrides the compensatory mechanism of the circulatory system, the brain (and the retina) are suddenly deprived of blood supply - the pilot's sight is disturbed due to a **"black shield"** and even unconsciousness can occur. The same process occur after launching a rocket.

If the pilot dives the nose of the plane downward (looping forward) the blood accumulates in his head and causing hyperemia of the retina and sight disturbance termed as **"red shield"**. Special suits designed for pilots of warplanes dimi-

nish the dangerous effects of sudden changes of speed and direction.

Acceleration and deceleration in an elevator. In an elevator starting upward a short period of positive acceleration occurs (the weight of the body is perceived heavier than usual). After the start we do not feel anything strange - the speed is constant. At arrival at the top floor the change of speed is negative (deceleration) and the body becomes lighter than normal. On the way down the events occur in opposite direction (first acceleration downward, then slowing down the downward movement) and the feelings correspond to that.

Angular acceleration. If a body rotates at constant speed, (e.g. the rotor of a centrifuge or a figure skater making a piruette, Fig. 3.3) acceleration arises from the change of the direction of the movement (centrifugal force). The particles in the test tubes in the centrifuge sediment and the skater should use force to pull his arms to his trump.

GRAVITATION AND WEIGHTLESS STATE

The forces of acceleration and deceleration have the same effect on the body as the gravitational force. (According to Einstein's theory of relativity it is impossible to decide between these two types of forces.) Our body (and every thing on the earth) is pulled to the earth with force equivalent to an acceleration 9.81 $m*s^{-2}$ = 1 G. Our mind and cardiovascular regulatory mechanism perceive this force as normal in upright, sitting or horizontal position. The gravitational force does not change if we are standing on the head but our body perceives it as a negative acceleration of -1 G (the overall change from +1 G to -1 G is -2 G). On other planets the gravitational force may be much higher than on the Earth

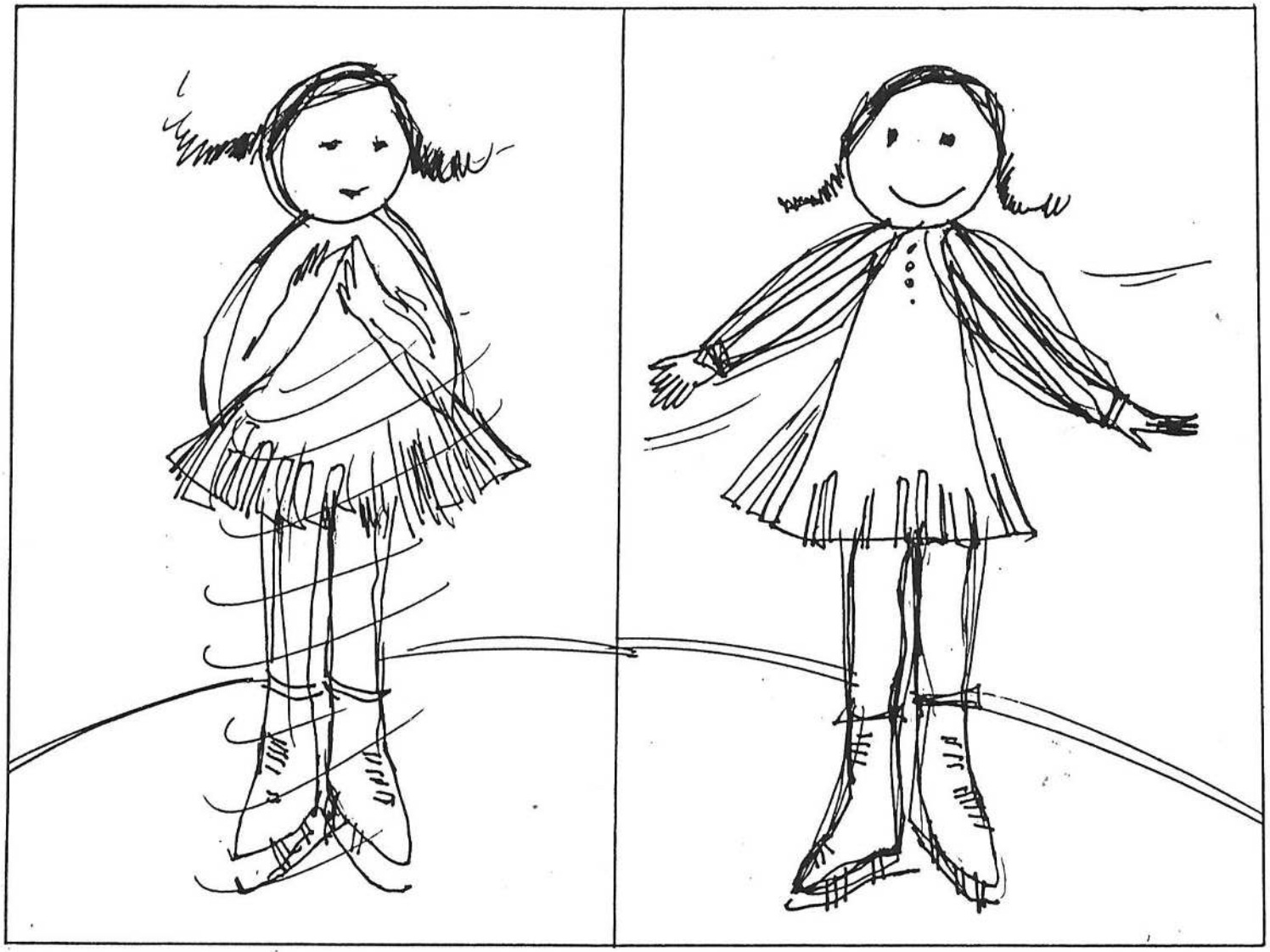


Fig. 3.3. Angular acceleration.

and on the Moon is only a sixth of it.

Weightless state is present in the case when the gravitational forces are counterweighted with acceleration. The most common case is the free fall (e.g. that of a parachutist before opening the parachute). Weightless state of long duration occur in astronautics. If a space ship moves on an orbital trajectory round the earth, the gravitational force and the radial acceleration are in balance. The same is true for voyages between planets where the acceleration of the space ship is given by the gravitational forces of the surrounding celestial bodies and therefore its passengers are in weightless state. This is changed only when the rockets of the space ship are working or when the whole space ship is rotating around his axis (artificial gravitation).

The effects of the space flights* on the human body are diverse. During launch strong acceleration occurs but the forces are far less intense than those imagined by the early science-fiction authors. On the orbit the weightless state disturbes first the function of the vestibular organ and symptoms similar to kinetosis can occur. The orientation in space is more difficult, the movements are less coordinated and precise than on the earth but in well-trained persons these changes are transient.

The lack of gravitation (or more precisely the **microgravitation)** leads to a shift of blood volume from legs to the upper part of the body, to changes of the heart rate (first to tachycardia, later to bradycardia) and to fluctuations of blood pressure. Interstingly, a similar shift in the distri-

---

*The data of this part were provided by courtesy of profs. Eva and Ivan Ahlers, Faculty of Sciences, Šafárik University

bution of blood does not occur in the lungs. The excretion of water and sodium is increased due to hormonal interactions - mainly those of antidiuretic hormone and atrial natriuretic factor.

In the course of long-term flights demineralization of the skeleton with concomitant rise of blood calcium and atrophy of postural muscles (mainly those of leg) develop. The muscular atrophy in the course of the longest flights (about 1 year) can reach as much as 40 %. The loss of calcium may be a limiting factor of the long-term space flights because administration of calcitonin and D vitamin are ineffective measures against the steady calciuria. Fortunately, in the course of long flights the calcium loss stopped at 20 % of total body calcium but the occurence of more profound losses during flights lasting more years are not excluded. With regular physical training and specially designed suits these changes are partially preventable.

An interesting feature of the space flights is the **cosmic anemia** - due to the decreased production of young red cells without apparent reason. The lifespan of the red cells is normal. During space flights the immune system is affected, too: the proliferative activity of lymphocytes and the activity of T-lymphoctes is decreased.

Space flights desynchronize the normal biorythms of the human body and therefore the "day" and "night" of cosmonauts is timed from the space center on the earth.

The construction of the spacecrafts provide a good shield against the cosmic rays. However, the burden of ionizing radiation in long-term flights is near the upper limit of hygienic norms. Work in scafanders outside the spacecraft is li-

mited from the same reason. Serious danger of radiation will be a problem in the future voyages planned to reach Mars and other planets.

The body adapts quite well to the conditions of the weightless state but transient (mainly cardiovascular and postural) difficulties arise after landing because the regulatory systems are disaccustomed to the normal gravitational force of 1 G.

SEA SICKNESS (KINETOSIS)

Short changes of speed of different direction irritate the otolith apparatus of the inner ear. The chaotic signals from the utriculus are conveyed to the vegetative centers of medulla oblongata and the cerebellum together with signals from muscle spindle and tendon receptors. These parts of the nervous system are responsible for the symptoms of the sea sickness, namely nausea, hypersalivation, vomitus, changes of heart rate, pallor, faint and others. The sensitivity to kinetosis is indvidual. Some people do not suffer from travel on rough sea, others become sick during every trip by car or plane. Forced slow and deep breathing and visual control of the motion may be of some help against kinetosis.

3.3. HYPOBARIA AND HYPERBARIA

The atmospheric pressure on the surface of Earth is 101.3 kPa (760 torr or Hgmm or 1 ATA). Small fluctuations (± 3 - 4 kPa) of this pressure occur in connection with meteorological events and these exert certain influence on the physiological functions and health state. The study of meteorological and climatic effects on health and disease is the topic of **bioclimatology** and **meteoropathology**.

The atmospheric pressure decreases parallel with the altitude (Tab. 3.3) and above 3 km **mountain disease** can develop due to the decreased partial pressure of oxygen. The main etiologic factor of mountain disease and other similar conditions is the lack of oxygen. All forms of **hypoxia** are treated in the 2nd volume of this textbook.

Tab. 3.3. The relationship between altitude and air pressure

ALTITUDE km	PRESSURE kPa	torr
0	101.3	760
0.5	95.4	716
1	89.4	671
2	78.9	592
3	69.6	522
4	61.5	461
5	54.3	407
8	35.6	267
10	26.4	198

In addition to lack of oxygen hypobaria threatens the body with damage due to distension of gases in hollow organs. Pain from middle ear and paranasal cavities can occur during flight in high altitudes in non-pressurized cabins if the communication of these cavities with the surrounding atmosphere is blocked. Gas pockets in carious or improperly filled teeth can also manifest with acute toothache in hypobaric conditions. The gases normally present in gastrointestinal tract expend, stimulate the stretch receptors in the intestinal wall, the peristalsis becomes more active and gut cramps may occur.

The ultimate limit of human tolerance to hypobaria is about 6.25 kPa which corresponds to an altitude of 20 km.

This is the vapor pressure of water at 37 °C, and at this pressure the body fluids boil at body temperature causing death within a couple of seconds.

DECOMPRESSION SICKNESS (CAISSON OR DIVER'S DISEASE)

The pressure increases during diving by 101 kPa at every 10.3 meters of depth. The solubility of gases in fluids is pressure dependent and therefore in hyperbaric conditions more oxygen and nitrogen is dissolved in the blood, body fluids and cytosol of cells than at the surface of the earth. It is a physical phenomenon and the amount of oxygen bound to haemoglobin does not change. In addition to underwater diving hyperbaric conditions occur in diving-bells (caissons) and during building of underground constructions (in this case the increased pressure is achieved by compressors).

If sudden decrease of pressure occurs, the dissolved gases are released as bubbles which in turn damage cells and obture small capillaries (**gas embolism**) deteriorating the perfusion of the organs. The damage is caused more by nitrogen than oxygen because it is readily dissolved in lipids and its diffusion and elimination from the fat is slow. The main symptoms are:

- joint and periarticular pain
- itching and localized paresthesias (bubbles in the skin)
- mottles on the skin, resembling cyanosis
- tachypnoe, substernal pain, dry cough (bubbles in pulmonary capillaries cause pulmonary hypertension)
- variable signs of CNS dysfunction up to delirium and loss of consciousness (bubbles in the brain capillaries, brain vasospasms)

After years of diving and repeated decompression sickness

irreversible diffuse brain damage can develop.

The prevention of this disease is simple - slow decompression leaves enough time for the released gases to be eliminated without bubble formation. The first aid is based on the same principle: recompression in a pressure chamber and slow decompression thereafter.

Principially the same process takes place when the decompression occurs at high altitudes, for example if the pressurized cabin of a high flying plane is damaged. The pressure falls in a split of second from normal to very low value (27 kPa at 10 km), **explosive decompression** occurs with air embolism, distension or rupture of the hollow organs combined with acute hypoxia.

HYPERBARIA

Elevated pressure in itself does not damage the body but physical work in these conditions is very exhausting. Well-trained healthy humans can live and work at pressures up to 50 ATA - 5000 kPa, equivalent to 500 m underwater depth. Nitrogen from 400 kPa partial pressure exerts narcotic effect on the nervous systems and therefore in such conditions a mixture of helium and oxygen is employed instead of air. In helium atmosphere the forming of voice is distorted - a shift towards higher frequencies occurs making the human speech virtually unintelligible.

Artificial hyperbaria with **hyperoxia** (Vol. 2) is used in the treatment of carbon monoxide poisoning and other conditions but in these cases increased oxygen concentration is the primary objective and not the increased pressure.

3.4. THERMAL INJURY

Most enzymes function optimally at 37 °C and at temperatures above 42 °C they inactivate quickly (with the exception of the enzymes of thermophil bacteria living in hot springs). At 50 °C the cytosol of the cells coagulates. Low temperatures (above 0 °C) do not affect the structure of proteins but they simply stop working. At temperatures below 0 °C (and during subsequent melting) crystals of ice can damage the subcellular structures.

The effects of local high or very low temperatures on the body lead to **burns** or to **chilblains**, respectively.

Man survives at elevated or low ambient temperatures in a limited range by means of his thermoregulatory processes. If these are overriden, **hyperthermia and hypothermia** develop. **Sunstroke** is a special case of hyperthermia. On the other side **fever** (->) is not a disturbance of thermoregulation, because in this case not external influences change the body temperature but the thermoregulatory center is set to a higher value.

BURNS (COMBUSTIO)

Local effect of temperature over 50 °C causes burn injury whith overall effects on the organism according to its degree and area of damaged body surface (Tabs. 3.4 - 3.6). Small burns or scalds cause pain, leukocytosis and transient elevated body temperature. Burns of large area of body surface trigger the stress reaction (-> Vol. 2). Through denuded body surface pathogen microorganism can enter the body and beacuse the immune function is deteriorated, **sepsis** can develop.

Severe burn injury threats with **burn shock**, which is a special form of **hypovolemic shock** (-> pathophysiology of

Tab. 3.4. Scalding with hot water

Temperature of water °C	Time of action leading to serious injury
49	> 5 min
53	≈ 1 min
56	≈ 15 sec
60	≈ 5 sec
65	≈ 2 sec
69	≈ 1 sec

Tab. 3.5. Features of burn injuries according to their degree

1st DEGREE - COMBUSTIO ERYTHEMATOSA
Only the epidermis is damaged. Characterised by necrosis of keratinocytes, vasodilatation in the dermis, red and aching skin. Heals without scars.
2nd DEGREE - COMBUSTIO VESICULOSA **a/ Superficial - only the epidermis is affected** **b/ Deep - both the epidermis and the dermis are damaged** Necrosis of the epidermal and (b) the dermal cells, intra- and extracellular oedema, subepidermal blisters and perivascular lymphocyte and neutrophil infiltration. Usually heals without scars but hyperpigmentation can be left over.
3rd DEGREE - COMBUSTIO ESCHAROTICA **a/ Dermal - affecting only the skin** **b/ Subdermal - affecting the tissues under the skin (muscles, bones)** Devastation of the skin and its adnexes, necrosis and damage of subepidermal structures, blisters, scabs, oedema, inflammatory infiltratation. Heals with scars. Skin transplantation and plastic surgery is usually necessary to prevent the forming of deforming hyperplastic scars.
4th DEGREE - CARBONISATIO Complete destroying, charring of tissues.

Tab. 3.6. Classification of burn injuries according to severity and range

CLINICAL RATING	% TBSA[1]	
	TOTAL	DEEP
1 - **SMALL**[2]	< 20*	no
2 - **MIDDLE HEAVY**	20 - 25	< 10
3 - **HEAVY**	25 - 40	10 - 20
4 - **CRITICAL**[3]	> 40	> 20

NOTES:
[1]TBSA % - Percentage of total body surface area affected.
[2]Only if injury of face, hands feet and perineum is absent.
[3]Every burns in children under age 3 years and in people older than 60 years should be considered as critical. The same holds for burns cobined with trauma, smoke intoxications and other aggravating conditions.

* In children the values are always lower by 5 - 10 %

circulation). The damaged skin allows uncontrolled loss of extracellular fluid and in addition the capillary permeability is increased due to direct damage of the capillary wall in the burned area, massive histamine and prostaglandin release and presence of toxic breakdown products of burned tissues in the circulation. The chemical mediators and toxins act not only in the site of injury, but in distant organs as well. The fluid loss and its translocation from the vessels into the extravasal space leads to decreased plasma volume, increased hematocrit and bood viscosity. If the fluid replacement is not sufficient, acute praerenal kidney failure can develop.

The metabolic response to severe burns is characterised by increased basal metabolic rate, protein catabolism with loss of lean body mass and raised core temperature. In addi-

tion hyperdynamic circulation, mild haemolysis and compromised immune function are usually present. Warm ambient temperature (32 °C) and pain relief are effective means of limiting the hypermetabolic state which otherwise can last some weeks.

Smoke inhalation is an important determinant of mortality in patients with burns. It can cause acute carbon monoxide and cyanide (from burning plastic materials) intoxication, upper airway obstruction, pulmonary oedema and pneumonia with subsequent pulmonary fibrosis.

The mortality after burn injury depends on percentage of total body surface area burned (% TBSA), on the age and general health state of the injuried and on the presence of complicating factors (trauma, smoke inhalation, infection, etc.). In the past 40 years considerable progress in treatment of burns took place. Now even patients with 70 - 90 % TBSA burned have good chances to survive the injury which is in striking contrast with the older data about high mortality after 33 - 50 % TBSA damage. The improvement is due to adequate fluid and electrolyte replacement, early excision of the damaged tissues, subsequent coating the wounds with natural or artificial skin preparations, auto- and allotransplantation of skin and appropriate antimicrobial pharmacotherapy.

CHILBLAIN (CONGELATIO)

Depending on the temperature and the time of action the skin is first pale (vasoconstriction) and aching, later cyanotic (vasodilatation), the pain ceases and parestheses or total anestesia develop. In the worst cases blisters, skin oedema and necrosis can occur with subsequent wet gangrena. The cold injury develops more rapidly and at relative higher

temperatures if the circulation of the affected limb was deteriorated before the injury.

HYPERTHERMIA

There are four ways to lose excess heat produced by the body or absorbed from the environment:

1. **Radiation** is a simple physical phenomenon. Every object radiates energy according to its absolute temperature.
2. **Conduction** of heat to cooler things. A cold shover, contact with cold things or a cold drink cools the body in such way.
3. A breeze cools through **convection.**
4. The last but most important way of thermoregulation is connected with sweating. The **evaporation** of every gram water brought to the surface of skin by the sweat glands needs 2.4 kJ of energy. If the ambient temperature is higher than the temperature of the body, this is the only way to lose heat.

In warm and dry environment (e.g. in sauna, in ironworks and other similar workplaces) the blood perfusion of the skin and the excretion of sweat increases, and heat is lost through evaporation. This type of thermal burden is tolerated well until adequate replacement of lost fluid (which is slightly hypotonic) is maintained. Without fluid supply dehydratation develops with hypovolemia, blood hyperviscosity, low blood pressure with fainting. The first symptoms are muscle cramps and exhaustion (**heat cramps, heat exhaustion**). Inappropriate fluid replacement (pure water without electrolytes) can lead to dangerous hypokaliemia.

In warm humid environment, or if the evaporation of sweat is hampered by tight suit, this last thermoregulatory system is unable to function and hyperthermia develops. The body

temperature rises together with the heart and respiration rate and the blood pressure falls. In this stage collapse can occur. As the core temperature reaches 40 °C fatigue, headache, buzzing in the ears and later vomitus and muscle seizures appear. (**heat stroke**). At 43 °C loss of consciousness ensues with subsequent failure of the circulation and irreversible damage of the nervous system.

SUNSTROKE (INSOLATIO)

If the thermal burden due to sunshine is concentrated on the uncovered, sometimes hairless head, (small children, old people) similar symptoms similar to hyperthermia can develop without dehydratation and without failure of the thermoregulatory systems. The symptoms are probably caused by local overheating of the nervous system and by meningeal and brain vasodilatation and hyperemia.

HYPOTHERMIA

The body temperature of **poikilotherm** animals varies with the ambient temperature, whereas **homoiotherm** creatures maintain their core temperature within narrow range. Some mammals, called **hibernates** survive winter in a dormant state with decreased core temperature, metabolism, respiration and heart rate (e.g. bear, hedgehog, marmot). **Hypothermia in humans** is a pathological condition defined as core temperature of the human body below 35 °C.

In cold environment the perfusion of blood in the skin is diminished and piloerection appears (gouse pimples). The skin and the immobilized layer of air on its surface act as thermal insulators. Man has lost his fur in the process of evolution and therefore he is forced to wear suit as additional thermal insulator.

In addition to the decreased heat loss in cold environment the production of the heat is increased by muscle work or by shivering. Fat has a dual role in thermoregulation. It acts as an insulator and can also produce heat through fat catabolism. This process is regulated by hormones (e.g. catecholamines and thyroid hormones).

The adaptability to cold varies with age, health status and other conditions.

People living in cold climate (Eskimos) have better developed thermoregulatory adaptation against cold than people living in warmer parts of the Earth and individual adaptation to cold through inure is also possible.

Newborns babies posses some brown body fat which safeguards them from hypothermia. The brown fat is used up in the first days of life and premature infants whose thermoreguratory system is not completely matured are prone to hypothermia. On the other hand newborns tolerate the consequences of hypothermia better than the adults.

Thermoregulation and cold adaptability is deteriorated in the **elderly** (-> Chapter 7). Fat is one of the best heat insulators and therefore obese people better bear cold than lean persons. People with strong muscles and vast energy reserves can produce more heat than their weak and undernourished counterparts.

Patients with insufficient circulation, muscle weakness, diminished function of the thyroid gland and those suffering from Addison's disease are especially prone to hypothermia.

Striated muscles, the main producents of energy are able to produce enough heat only some hours because of fatigue and glycogen depletion. **Exhaustion** (e.g. in mountain-climbers

without appropriate training and acclimatisation) therefore leads to rapid development of hypothermia. **Alcohol** and some drugs acting on the nervous system paralyze the thermoregulatory center. Alcohol in addition causes vasodilatation and a false feeling of warmth. This is the explanation of the well-known fact, that drunk unconsciouss people can die from hypothermia even at moderate ambient temperatures.

If the adaptability range of the thermoregulatory system is overriden, the core temperature of the body begins to fall. At core temperature of 33 °C one becomes stuporous and muscular rigidity sets in. The heart and respiratory rate declines. At 30 C the shivering ceases and at 27 °C the muscles become flaccid and consciousness is lost. At this temperature fibrillation of the heart chambers can lead to sudden death. At lower temperature death due to circulation and respiration arrest ensues although individual cases of survival have been reported after core temperatures as low as 18 °C.

Immersion cooling is a special case of hypothermia. The skin is quickly cooled to the ambient water temperature and survival depends on the thickness of subcutaneous fat layer. Exercise (swimming) in cold water increases the heat loss. Death in very cold water can ensue within hours.

In cold weather the probability of viral and bacterial infections of the respiratory tract is increased for various reasons (the decreased blood flow deteriorates the defensive functions of skin and mucous membranes of the upper airways) and although bad weather is not the true etiologic agent of these diseases (it is probably only their triggering condition) the term **"common cold"** is widely used to date.

Hypothermia reduces the metabolic rate and the oxygen de-

mand of the tissues. During controlled hypothermia or **artificial hibernation** the blood supply of the brain may be interrupted or the heart may be stopped for a few minutes without causing irreversible damage of brain cells. This technique was employed in the past in cardiac surgery but was already replaced by modern artificial heart and lung devices.

3.5. THE EFFECT OF ELECTRICAL CURRENT ON HUMAN BODY

The effect of electrical current on human body depends on various factors:

* **the intensity and voltage of the current;**
* **the time of its action;**
* **the type of the current (alternating - A.C. or direct - D.C.);**
* **the frequency, if the current is A.C.;**
* **the resistance of the body;**
* **the path of the current within the body.**

As a rule of thumb one should remember that every current above intensity 0.1 A and voltage 50 V and of duration more than 1 second threatens the life. Alternating current is more dangerous than direct and the most dangerous frequencies are between 30 - 150 Hz.

The dry human skin is a good insulator but moisture decreases its resistance considerably. Ohm's law holds also in this case* and therefore the intensity of the current flowing

---

* $I = \frac{U}{R}$ Ohm' s law: The higher is the voltage (U), the higher is the intensity (I). The lower is the resistance (R), the higher is the intensity.

through the body will be much greater if one shuts the electric circuit with moist hands than if his skin is dry.

Within the body the current follows a path corresponding to the least resistance. Body fluids, muscles and nerves are the best conductors because they contain ions in high concentration. Putting two fingers into a current outlet leads therefore only to painful experience but if the current crosses the heart, sudden death can follow.

The electric current depolarizes the membranes of the cells. This is the cause of **muscle cramps, general seizures, respiratory arrest, loss of consciousness with amnesia and fibrillation of the heart chambers**. Heart fibrillation ensues when the electrical impulse crosses the chambers in the **vulnerable period**, that is during the T wave (Fig. 3.4). Ventricular fibrillation is the most serious consequence of electrical injuries because it is hemodynamically equivalent to cardiac arrest and without reanimation leads to death.

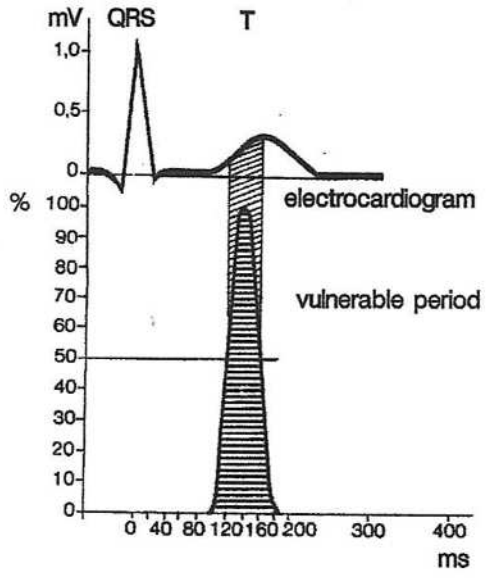


Fig. 3.4. The vulnerable period.

Within the cells the electrical current tranlocates the ions and disturbes the function of intracellular organelles.

The energy of the electrical current transforms into heat and may cause burns. The production of the heat depends on the resistance of the tissue and therefore burns affect mostly the skin in the places where the current enters and leaves the body. The heat formed along the path of the current within the body coagulates the cytosol of the cells and can damage the vessel wall causing thromboses. High voltage electrical injury or injury by lightning can cause serious and large 3rd degree burns.

The effect of the electrical current on the central nervous system is employed in the treatment of certain psychoses as electroshocks. Alternating currents of several hundred mA are applied transversely across the cerebrum causing immediate loss of consciousness and seizures but after recovery the symptoms of the diseases are attenuated.

Electrical current can cause heart fibrillation but on the other hand cardiac arrest can be succesfully treated with short impulses of direct current - **defibrillation**. The energy of impulses is between 200 - 360 Joule for adults. The same principle is employed in treatment of atrial fibrillation, but in this case (**cardioversion**) the electric impulse is very carefully timed not to reach the ventriculi in the vulnerable period. In **cardiac pacemakers** properly timed weak electrical impulses substitute for the missing function of the heart's own pacemakers. Weak A.C. currents are employed also in various procedures of **physical therapy** and **electroacupuncture**.

3.6. THE EFFECTS OF THE ELECTROMAGNETIC FIELD ON THE BODY

Between two electrically charged objects of opposite sign electric field and between two poles of a magnet magnetic field exists. Fluctuations of the intensity of either magnetic or electric field create electromagnetic waves. They are characterized by the frequency of the fluctuations and by the intensity of the electromagnetic field. All these waves propagate in vacuum with the speed of light ($\approx 3*10^8$ ms^{-1}) and this value divided by the frequency (waves in one second, Hz) gives the wavelenght of the radiation (Tab. 3.7).

Tab. 3.7. The electromagnetic waves

SOURCE	FREQUENCY*	VAVELENGTH
Alternating electrical current	16 - 50 Hz	18000 km - 6000 km
Radio and TV		
long	150 - 300 kHz	2 km - 1 km
middle	500 - 2000 kHz	600 m - 150 m
short	6 - 20 MHz	50 m - 15 m
FM radio	66 - 108 MHz	5 m - 3 m
TV bands	49 - 12500 MHz	6 m - 24 mm
Microwaves and radar	0.3 - 1000 GHz	1 m - 300 µm
Light		
infrared	10^{12} - $3.9*10^{14}$ Hz	300 µm - 760 nm
visible	$3.9*10^{14}$ - $7.8*10^{14}$ Hz	760 nm - 380 nm
ultraviolet	$7.8*10^{14}$ - $3.0*10^{16}$ Hz	380 nm - 10 nm
X, gamma and cosmic rays	> $3*10^{16}$ Hz	< 10 nm

*The energy of the radiation is directly related to its frequency according the equation E = hn, where "n" is the frequency of the radiation and "h" is the Planck's constant:

$$h = 6.623*10^{-34} \text{ Js.}$$

One photon of a 100 MHz UHF radio signal carries therefore $\approx 6.62*10^{-26}$ J energy; a "red" photon of 760 nm wavelength $\approx 2.6*10^{-19}$ J (0.26 aJ) and a 10 nm X-ray photon $\approx 2*10^{-17}$ J (20 aJ).

To warm 1 g water by 1 °C ≈ 4.2 J is necessary, that is $\approx 1.6*10^{19}$ photons of red light or $\approx 2.1*10^{17}$ photons of absorbed X-ray radiation.

According to the quantum physics electromagnetic waves are at the same times small particles - photons. The energy of the radiation is in linear relationship with the frequency of the waves.

The range of the electromagnetic waves is extremely wide. Alternating electrical current (50 Hz) creates waves 6000 km long. The waves employed in broadcasting and television begin at kilometer (or kHz) and end somewhere in the centimeter (hundreds of MHz) range. Man and animal see waves between 760 nm and 380 nm as colors and green plants use the energy of this radiation to produce organic material and oxygen from water and carbon dioxide (photosynthesis). The artificially generated waves in X-ray devices, the gamma rays emitted from radioactive materials and arriving from the cosmos have wavelengt below nanometer range and frequencies between 10^{16} - 10^{24} Hz and are carriers of dangerous amount of energy.

All these waves generated by natural (cosmos, sun, radioactive background radiation) or artificial (fire, light, radio, TV stations, electrical circuits) sources constantly bathes the earth and surrounds every object or living creature. Considering the biological and health effects of electromagnetic waves the basic but often neglected law is very simple: **Only the absorbed radiation can exert an effect.**

RADIO FREQENCIES

The human body is relatively transparent for these short waves. The absorbed portion of radiation has some heat effect which correponds to the absorbed amount of energy. It is employed in physical therapy to treat painful muscles and joints (**short wave diathermy** - 40.68, 27.12 and 13.56 MHz).

In the history of medicine mystical beneficial (or harm-

ful) effects were assigned to magnetic and electromagnetic fields and much pseudomedical quackery was based on these misbeliefs. Serious research of this topics started only in the recent years.

People living in the neighborhood of radio, TV or radar stations or working close to emitters often complain on different diffuse symptoms (headache, psychic fatigability, etc.) and the results of some reports do not exclude the possibility that strong magnetic or radio frequency electromagnetic field can promote the proliferation of malignant cells and exert influence on the secretion of hormones and on the metabolism of calcium in the cell. Future research is necessary to give unambiguous answers on these open questions.

MICROWAVE AND INFRARED WAVES

Every warm object radiates infrared waves and recently special kitchen aplliances (microwave owens) became widely used in households.

Biological structures absorb this type of radiation and therefore they have thermal effect. This pose certain danger because much of the radiation passes the skin and is absorbed only in the deep structures lacking thermoreceptors. Overheating with concomitant tissue damage can occur because the the nervous system is not alarmed through pain.

Chronic exposure to infrared radiation can cause cataract of the eye lens (**glass-blower's cataract**).

VISIBLE LIGHT

The eye is an optical device which focuses the light on the retina. Visible light of high intensity (sun observed through telescope, the light of lasers and nuclear blasts) can cause retinal burns with blind spots as a consequence. On

the other side laser treatment in ophtalmology can save the sight of many patients with diabetic retinopathy, glaucoma or retinal tears.

ULTRAVIOLET LIGHT

The range of the ultraviolet (UV) light is divided into three components:

* **UV-C : 100 - 280 nm;**
* **UV-B : 280 - 315 nm and**
* **UV-A : 315 - 380 nm.**

This high-energy radiation coming from the sun is invisible but it is absorbed well in biological structures. It can disrupt (UV-C) even covalent chemical bonds - damage nucleic acids, proteins and other macromolecules. Oxygen absorbs waves shorter than 240 nm and the ozone layer in the ionosphere those shorter than 290 nm. Vapors of water and dust in the various layers of athmosphere absorb a great part of the remaining UV light. The surpassing small amount of UV-A and UV-B is sufficient to convert provitamin to vitamin D in the skin and irritate the skin to produce melanin and attain a healthy suntan.

Too much sunshine (the sensibility depends on the color of the skin) can cause **sunburn** which begins with painful erythema and discomfort lasting 8 - 24 hours. Sometimes vesiculation (actually it is a 2nd degree superficial burn) and massive desquamation occur. Gradually increasing doses of UV light enable adaptation of the skin and do not cause such problems. Repeated sunburns or too much sun-bathing after many years lead to degeneration of the skin, to its accelerated aging and can foster the development of skin cancer.

All these dangers became augmented in the past few years.

Due to the continuing ozone depletion more short-wavelength UV radiation reaches the surface of the earth (the most at the poles, in spring and summer and at noon). The situation threatens with increasing number of skin cancer and cataract not only in humans (who are able to defend themselves) but mainly in the animal kingdom. The first reports on blind sheep and kangaroos from Australia are alarming. Other possible effects may arise in the future, e.g. disturbances of the immune system in humans and animals or the increased number of mutations in plants if the destruction of the ozone will continue.

3.7. THE INFLUENCE OF IONIZING RADIATION ON HUMAN BODY

From physical point of view the important forms of radiation are divided into corpuscular and electromagnetic radiation (Tab. 3.8). Radiation penetrating either living or non-living matter is partly absorbed and the radiation energy is delivered mainly by means of ionization of atoms and molecules and free radical formation*. The basic units of radioactivity and those employed in radiobiology are given in Tab. 3.9.

---

* From physical point of view free radical formation and ionization can arise as a result of collision of the accelerated particles with electrons (e.g. alfa and beta particles) or with atomic nuclei (e.g. neutrons). Photons can also hit and excite electrons of atomic or molecular orbits or interact with nuclei of heavy atoms and give rise to electron-positron pairs. The excited particles are sources of secondary, mostly gamma radiation.

Tab.3.8. The main forms of ionizing radiation

ELECTROMAGNETIC WAVES - INDIRECT IONIZING EFFECT*
X-rays Electromagnetic waves (photons) from X-ray tubes. Penetrate soft tissues, absorb well in bones gamma rays Electromagnetic waves (photons), a part of cosmic radiation or from decay of radioactive elements
CORPUSCULAR RADIATION CHARGED PARTICLES - DIRECT IONIZING EFFECT
protons (p^+) Exist in great amount in the Van Allen belts surrounding the earth and are produced by solar flares. Absorbed in the highest layers of atmosphere, may be dangerous for space travellers alpha particles (α^{2+}) Identical with nuclei of helium - two protons and two neutrons. Produced spontaneously in the process of radioactive decay of heavy elements. Enormous ionizing power but short tange of action and low penetrating ability. beta particles (β^-, β^+) High energy electrons or positrons produced by nuclear transformation or in accelerating devices. When decelerated can produce high energy electromagnetic waves (electrons in X-ray tube). The only difference between electrons and positrons is in their charge. Positrons interacting with electrons annihilate and release great amount of gamma rays
WITHOUT CHARGE - INDIRECT IONIZING EFFECT
neutrons (n^0) Neutrons can interact with matter only when collide with it. Ionization is an indirect consequence of these colisions (

*The other types (light, thermal radiation, radiowaves) of electromagnetic radiation are nonionizing.

Tab. 3.9. Basic units of radiobiology

UNIT	SYMBOL	DEFINITION	EXPLANATION, OLD UNITS
ACTIVITY	BECQUEREL, Bq	s^{-1}	1 Bq = 1 radioactive decay in 1 second Old unit: Curie, Ci 1 Bq = $2.7*10^{-11}$ Ci
RADIATION DOSE		C/kg	Coulomb/kg The dose of radiation which in 1 kg of air forms 1 coloumb of negative and 1 C of positively charged particles Old unit: Röntgen, R 1 C/kg = 3876 R
ENERGY	JOULE, J	m^2*kg*s^{-2}	See Table 3.7 Unit often used in radioactivity: eV (electronvolt) or MeV 1 J = $6.242*10^{12}$ MeV
ABSORBED DOSE	GRAY, Gy	J/kg	Old unit: rad 1 Gy = 100 rad
EQUIVALENT DOSE	SIEVERT, Sv	J/kg*RBE	RBE = relative biological effectivity. Its value for some common types of radiation: X, gamma and beta rays = 1 alpha particles = 20 neutrons = 2 - 10 Old unit: rem 1 Sv = 100 rem

THE RADIATION BACKGROUND, PROFESSIONAL AND OTHER EXPOSURE

It is important to take into consideration that we live in an environment with a certain natural radiation level **(radiation background)** which penetrates here both from the space **(cosmic radiation)** and from the soil **(terrestrial radiation)**. To this natural radiation in this century man-made sources of ionizing radiation were added. The average dose of natural background radiation is about 0.5 - $1*10^{-3}$ Gy yearly. However, there is a great geographic variability in the value of the terrestrial radiation. For an example in the inland of

state Denver (USA) the mean value of absorbed radiation is more than 10^{-3} Gy/year but on the coastal area of Cape Kennedy only a tenth of it. Furthermore different building materials have different level of natural radioactivity. Persons living in stone buildings are exposed to a higher risk of cumulative radiation damage (due to radon emission) than inhabitants in wooden buildings.

A further source of ionizing radiation in the living organism is the **potassium isotope ^{40}K, an emittor of β radiation.** ^{40}K constitutes 0.0012 % of potassium in the nature and has a half-time of $1.3*10^{9}$ years. From ^{40}K our body receives approximately a dose of another 10^{-3} Gy per year. In a lifetime of 70 years it presents 0.07 Gy of cumulated radiation dose.

For different professions it is necessary to add further radiation doses to the background radiation. It concerns namely health workers dealing with diagnostic or curative X-ray and other radiation sources. The introduction of effective safety measurements and modern equipment with low radiation level led to substantial reduction of this type of radiation exposure. It exceeds now the yearly dose of 0.01 Gy only exceptionally. Principially the same is true for patients undergoing X-ray investigations.

In some cases the radiation exposure can exceed the background level considerably. Atomic bombs (thrown to Hiroshima and Nagasaki in 1945), tests of atomic and hydrogen bombs, accidents in nuclear plants (Tchernobyl, 1986) exert twofold effects: Near the epicentre of the blast or the accident the radiation dose usually reach deadly levels, and in remote regions the radioactive fallout and the elevated background ra-

diation can do harm to large number of people. Elevated radiation exposure restricted to individuals occur furthermore in uran mines, during nuclear laboratory accidents and in patients undergoing tumor radiotherapy. The handling and storage of radioactive waste materials (especially those with long half-life) poses a very important ecological problem.

THE EFFECTS OF IONIZING RADIATION ON LIVING MATTER

The biological effects of ionizing radiation are extensive. There is no part of the body not affected by it but it is evident that there are different functional changes in every tissue originating from absorption of radiation energy. From biological point of view it is significant that the slower is the movement of the radioactive particle, the bigger is its ionization effect. (A single alfa particle can give rise to 20 - 60 thousand ion pairs while penetrating a 1 cm layer of water, whereas the energetically more powerful gamma radiation is far less effective from this pont of view.) This property of radiation is expressed in the factor termed "Relative Biological Effectivity (RBE)" and in the sievert (Sv) unit (Tab. 3.9).

The effect of ionizing radiation on living organism is at present explained by two theories which are not mutually exclusive:

* **The shot theory (direct effect)** states that radiation damages sensitive parts of biomolecules directly while handing over energy to the target molecule.

* According to **the radical theory (indirect effect)** radiation penetrates into the molecules of water, causing radiolysis of water and creating highly reactive free radicals which enter into reactions with biologically important macro-

molecules. (These free radicals are usually ions at the same time but the two terms are not synonyms - for details see Chapter 6.1.)

Free radicals have a high affinity to biologically significant molecules and can damage nucleic acids, proteins, lipids and polysaccharides. On the other side due their high reactivity they are soon inactivated by the surrounding molecules with redox ability or neutralized by the different mechanims of **antioxidant defense system** present in all cells, tissues and in the body fluids.

For better understanding the effects of radiation can be divided into four stages depicted in Fig. 3.5:

* **physical** - the radiation hits an atom or molecule;
* **physicochemical** - free radical formation and ionization;
* **chemical** - reactions of free radicals, damage of biological macromolecules and
* **biological** - subcellular, cellular and tissue damage, radiation disease or late genetic consequences (carcinogenesis, mutations).

CELL AND TISSUE DAMAGE CAUSED BY RADIATION

At the **cell level** radiation leads to functional and structural alterations of biological membranes, proteins and nucleic acids. From lysosomes hydrolytic enzymes are released and the ATP synthesis in mitochondria is decreased. The cells are, however, able to repair this type of damage during relatively short time

One of the crucial effects of ionizing radiation is the damage of the genetic code, particularly of chromosomes during the mitotic cycle with successive suppression of cell mitotic activity and other consequences. Single-strand breaks

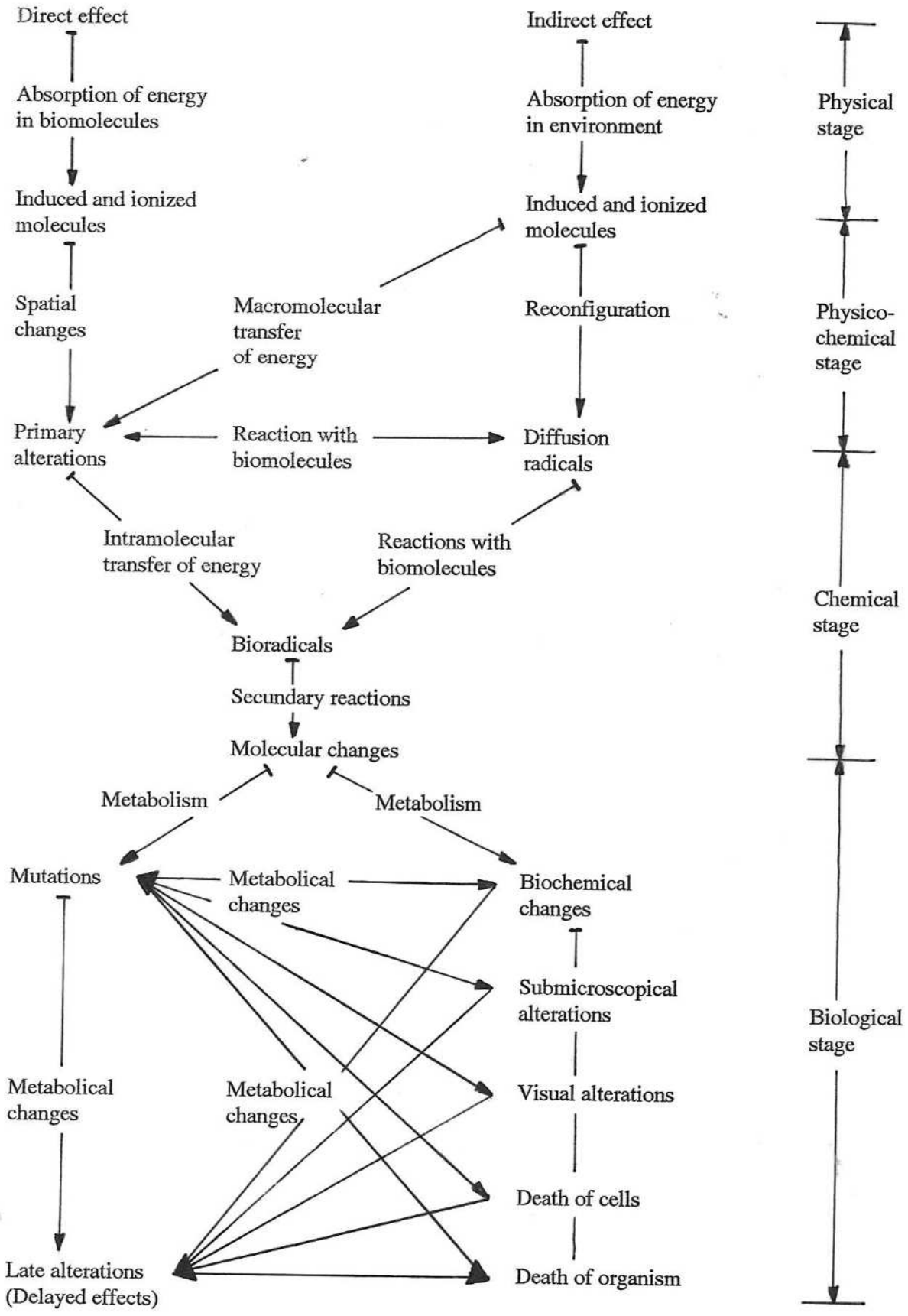


Fig. 3.5. Effects of radiation in biological system.

can be repaired but double-strand damage leads usually to irreperable chromosome damage.

According to its consequences the damage can be divided into three types:

* **pure somatic damage** (at cell level loss of mitotic capacity, membrane, mitochondrial and other organelle damage)

* **genetic damage restricted to the somatic cells** of the given individual (possible consequence: carcinogenesis)

* **genetic damage of the gametes** witch can be handed over to the next generations (new mutations manifesting in the next generations).

The first type of injury requires relatively high doses of radiation (above 2 Gy) whereas a few, otherwise harmless quantums of absorbed energy can change the genetic information (2nd and 3rd type of damage) with the possibility of severe late consequences.

The range of tissue damage caused by ionizing radiation depends on the kind and dose of radiation, on the total condition of the organism and on the length of radiation. A given dose divided into small portions exerts lesser somatic effects than the same dose absorbed at once because less cells are killed and the others have time to regenerate. On the other side, the probability of genetic damage is higher in the case of repeated doses. The effect of radiation is furthermore different depending on the fact whether the radiation is local or affects the whole body.

Single tissues and organs have different sensitivity to ionizing radiation. In general cells with high mitotic rate are very sensitive to radiation whereas postmitotic cells are usually resistant. The sensitivity of tissues furthermore de-

pends on their metabolic intensity and grade of differentiation. According to this aspect we divide the tissues of human body into:

* **radiosensitive** (bone marrow, lymphatic tissue, mucosa of small intestine, bone marrow, gonads)

* **radioresistant** (muscle, kidney, liver, endocrine organs except gonads).

A specific case of extreme sensitivity towards radiation injury is the **developing fetus** especially in the first weeks of intrauterine life.

In addition to external radiation injury the body can be contaminated with radioactive materials through inhalation, ingestion or directly (through injuries or in the case of surgical implantation of radioactive sources). The affinity of radioactive isotopes towards particular organs is shown in Fig. 3.6.

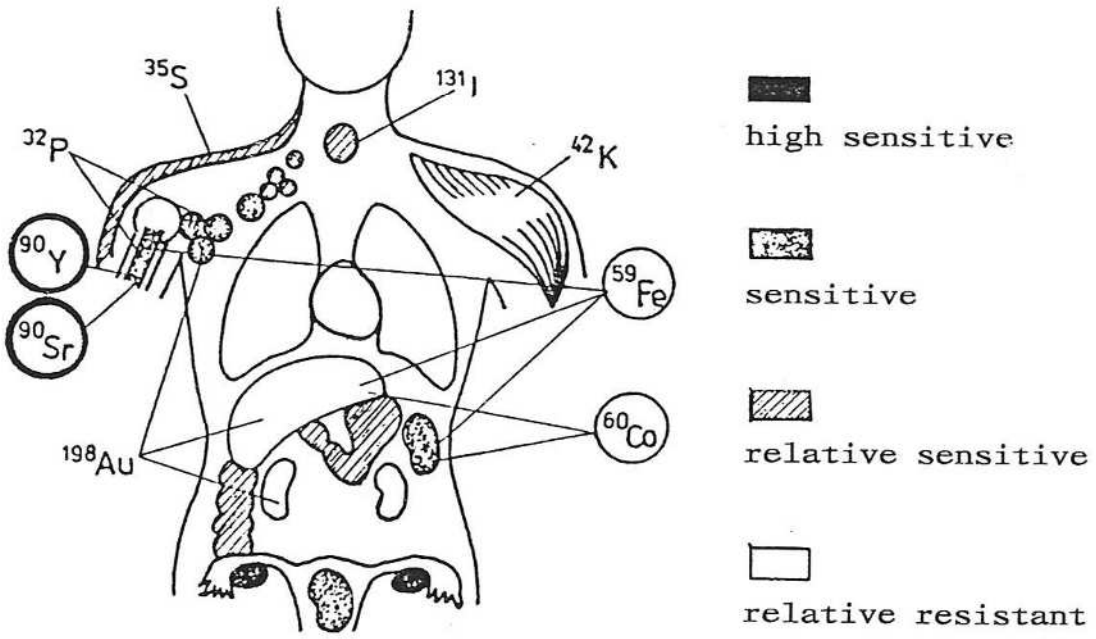


Fig. 3.6. Radiosensitivity of human body and predilection localization of selected radioisotopes (by King).

DOSE-RESPONSE RELATIONSHIP

Despite intensive research discussion is going on about the problem whether the effect of ionizing radiation has got a quantitatively determinable threshold or any small dose of ionizing radiation has its own harmful, though tiny effect. In such case it would mean a non-threshold effect. The problem is probably unresolved because small doses cumulate during a lifetime and their effect manifest only after a long latency.

There might be another possibility, namely that very low doses of ionizing radiation may have a stimulating effect on some biological functions. In such cases one cannot speak about a direct relation of the dose and its effect which could be rather expressed by a **"J" shaped curve.** The plausibility of this model seems to be supported by experiments and the results of a study, which states that employees of nuclear laboratories live longer than the comparable controls. In this study a significant difference was found between qualified staff exposed to higher doses of radiation and manual workers with lower expositions. In the second group an inverse correlation of tumour occurence and absorbed doses was found. It shows a controversial situation, where the radiation apparently stimulates the biological resistance of organism.

RADIATION DISEASE

Radiation disease (morbus ex irradiatione) can be initiated either by external radiation or by internal contamination of organism and according its course can manifest as acute or chronic form.

Acute disease from radiation develops after a single

irradiation of the whole body with high doses of ionizing radiation. We distinguish four stages of acute radiation disease and three types according to the main symptoms:

1. The stage - primary reaction

Nausea and vomiting (after dose 2-3 Gy these may be the only symptoms), lassitude, irritability, higher temperature, accelerated breathing.

2. Latent stage

No clinical symptoms but apparent changes of blood count as a result of hemopoiesis inhibition (leukopenia, thrombocytopenia, reticulopenia)

3. Stage of evident clinical symptoms

Manifestation of hemorrhagic diathesis, further inhibition of hemopoiesis, increased permeability of cell membranes, decreased immunity with bacteremia or sepsis - for further details see the description of the radiation syndromes.

4. stage - reconvalescence or transition into the chronic form of the disease or death.

According the main clinical symptomes three forms of radiation disease can occur:

1. Bone marrow (or hematological) syndrome

It occurs after radiation with doses in the range of about 2-10 Gy. The symptoms of the primary stage subside after one day but 2 - 3 weeks later purpura, petechiae and signs of deteriorated immunity (infections) manifest. The symptoms correlate well with the changes in red and white cell count (Fig 3.7).

2. Gastrointestinal syndrome

If the dose of absorbed radiation is between 10 - 30 Gy the intestinal mucosa gets rid of its epithelial cells, stops

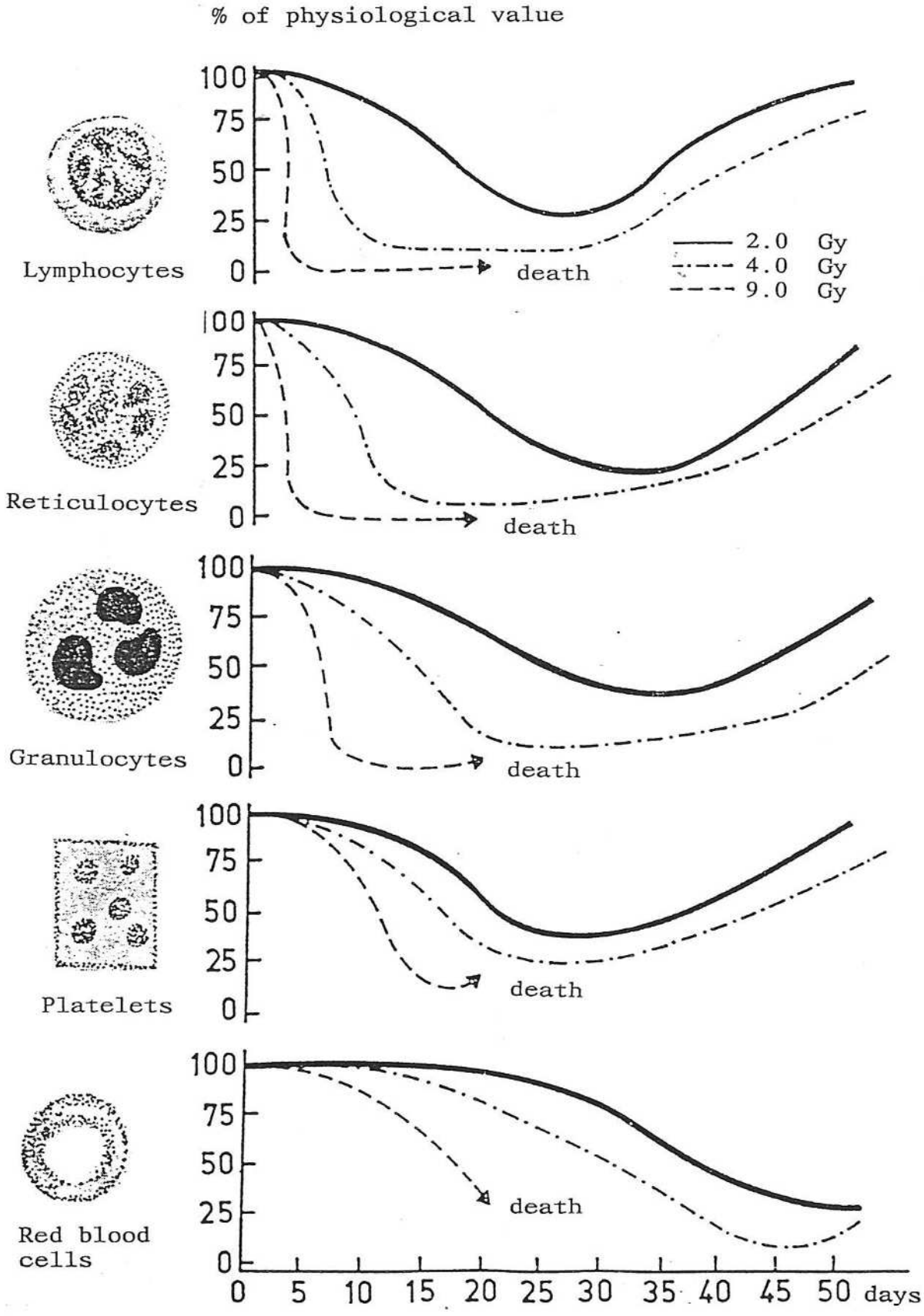


Fig. 3.7. Hematological changes in acute postirradiation (radiation) disease (by King).

absorbing nutrients and water. From clinical point of view after a short asymptomatic period severe diarrhea and fluid loss occur together with hematological symptoms and infection. Doses around 100 Gy lead to immediate manifestation of gastrointestinal symptoms. This type of radiation disease is usually fatal despite modern treatment techniques (bone marrow transplantation).

3. central nervous syndrome

After 20 - 50 Gy the immediate gastrointestinal symptoms are followed with ataxia, sweating, prostration and shock. Huge doses (300 - 500 Gy) can cause immediate death due to CNS dysfunction.

Chronic disease from radiation originates either after a single radiaction with subletal dose or after repeated radiation with low doses or after internal contamination by radionucleids. Clinical symptoms include weakness, exhaustion and irritability. Significant are changes in blood count - permanent leukopenia, thrombocytopenia, anemia and hypoplasia of bone marrow. Months or years after irradiation hepatopathy with portal hypertension, renal injury with proteinuria, headache and decrease of mental abilities can occur. Repeated intermediate doses of radiation lead to premature aging.

The symptoms after **local or regional irradiation** are in general less pronounced and depend largely on the sensitivity and properties of the affected organs.

Late effects of low-leve ionizing radiation manifest with genetic and carcinogenic consequences. The estimated risk of carcinogenesis and birth defects is around 1000 events in million people after 1 Sv of exposure per year.

The average time of latency between radiation exposure

and tumor manifestation is about 10 - 15 years. This fact, however, can be modified by various other circumstances favouring carcinogenesis. In actual fact in the surroundings of nuclear experimental centres in Semipalatinsk (Kazahstan) and Lop Nor (China) there is an extraordinarily high occurence of malignant tumours (in all age groups) and also of birth defects and inborn diseases in children.

4. EXOGENEOUS CHEMICAL FACTORS AS CAUSES OF DISEASE

The human body interacts permanently with a number of chemical substances. Some are essential for life (water, oxygen, mineral salts, foodstuffs, vitamins and trace elements), others can damage biological macromolecules and cause health disturbances. This division into "good" and "bad" chemical substances is, however, a didactic simplification. In many cases the same substance in appropriate (mostly minute) amount is essential for health but its overdose can cause disease (e.g. selenium or chromium, see Chapter 5). The same is true for almost every drug used in medicine.

Substances which are alien to human body are called **xenobiotics**. Those which cause serious health problems in minute amounts are **poisons** or **toxins** (**toxicants**). In addition to acute intoxications, manifesting themselves usually through dramatic clinical symptoms in the past few years the danger of accumulation of many non- or slow metabolizing chemical substances in the body has been graudally recognized. Chemical substances play an important role in the **carcinogenesis**, as well. Air, water and soil **pollution** has become one of the crucial problems of 20th century influencing the health of whole groups of population and the mankind as a whole. Sometimes the effect of these polluting chemical compunds is indirect. Chlorofluorocarbons (CFCs or freons, e.g. dichlordifluormethan, CCl_2F_2) used as stable and nontoxic gases in sprays, refrigerators and in the plastic material industry) deplete the ozone layer of the stratosphere. As a consequence more short-wave ultraviolet light reaches the surface of the earth with possible deleterious effects on humans, animals

and plants. Carbon dioxide, CO_2 is a normal constituent of the air (with important physiologic function in respiration and acid-base balance). The slow rise (by 12 % from 1960) of its concentration in the athmosphere does not exert any short- or long-term health effect on humans and animals but it probably contributes considerably to the **greenhouse effect** - a change in heat radiation balance of the atmosphere and to its consequence, the global warming of the biosphere observed in the past few years. The climatic change due to accumulation of this nontoxic gas threatens the mankind with unpredictable ecological and economical dangers.

In this chapter it is impossible to deal with the whole range of **toxicology, occupational medicine and ecology** which are now independent medical resp. scientific subjects. In addition to a short and incomplete survey of the most common poisonings chapters are devoted to the health disorders caused by **smoking** and **alcohol**. These problems differ from common accidental or intentional poisonings. The clue to their understanding lies partly in genes guiding the human behavior, partly in the social environment of modern life.

Not only excess of chemicals but also their deficiency can cause health problems. The problems arising from trace element and vitamin deficiencies are treated in the next chapter.

4.1. COMMON POISONINGS

CLASSIFICATION OF TOXIC SUBSTANCES

The toxic substances can be classified according to various aspects. The quantitative classification is given in Tab. 4.1. The most plausible qualitative classification is according to the chemical nature of the toxins: **anorganic, organic**

Tab. 4.1. Toxicity rating

Probable Lethal Dose	Rating
> 15 g/kg	1 - Practically nontoxic
5 - 15 g/kg	2 - Slightly toxic
0.5 - 5 g/kg	3 - Moderately toxic
50 - 500 mg/kg	4 - Very toxic
5 - 50 mg/kg	5 - Extremely toxic
< 5 mg/kg	6 - Super toxic

and biological toxins with various subgroups in each group. (Tab. 4.2). Some toxins (anorganic and biological) occur **naturally**, others (the vast majority of toxic organic compounds) are **synthetic**. The occurence of toxic substances is usually restricted to special locations such as laboratories, factories, workplaces, etc., where strict rules govern their handling, but there are also toxic substances occuring widely in the environment (air, water, food) and households. Medical drugs are unique in this respect, because they are widely used in treating diseases but their accidental or deliberate overdose is the most frequent cause of poisoning in western countries.

The poisonings may be divided according to the timing and of exposure and dose to **acute** (one big dose) and **chronic** (repeated small doses) intoxications and to **accidental** or **voluntary** ones.

ENTRY OF TOXINS INTO THE BODY

Toxins can enter the body through airways, through the gastrointestinal system, through skin and sometimes directly through injuries. A special but very important possibility is the transplacental transport of toxicants.

Each portal of entry permits a different rate of penetration and may also enable different metabolic pattern of the

Tab. 4.2. The most important toxic substances

ANORGANIC TOXINS

METALS AND METAL COMPOUNDS

Lead (Pb)
Mercury (Hg)
Chromium (Cr)
Cadmium (Cd)
Beryllium (Be)
Arsen (As)
Cobalt (Co)
Bismuth (Bi)
Silver (Ag)
Gold (Au)
Cuprum (Cu)
Iron (Fe)
Mangan (Mn)
Baryum (Ba)

TOXIC GASES
Carbon monoxide (CO)
Hydrogen sulfide (H_2S)
Carbon disulfide (CS_2)
Phosgene ($COCl_2$) and chlorgas (Cl_2)

CYANIDES
Hydrogen cyanide (HCN) and the cyanides (e.g. KCN)

NITRITES AND NITROCOPOUNDS

STRONG ACIDS AND BASES (CAUSTIC AGENTS)
HCl, H_2SO_4, NaOH

ORGANIC TOXINS

ORGANOPHOSPHATES
CHLORINATED ORGANOCOMPOUNDS (DDT)
HALOGENATED HYDROCARBONS (CCl_4, trichlorethylen)
HERBICIDES, FUNGICIDES AND RODENTICIDES OF OTHER TYPES (Paraquat, warfarin, etc.)
ORGANIC SOLVENTS
Aromatic compounds (benzol, xylol, toluol)
Methylalcohol
Glycols (ethylenglycol)
ORGANIC DYES (anilin)
AROMATIC NITRODERIVATIVES (nitrobenzol, trinitrotoluol)
ORGANIC METALLOCOMPOUNDS
Tetraethyl lead, methyl mercury
ALKALOIDS[1]

BIOLOGICAL TOXINS

ANIMAL TOXINS
Venoms of snakes, spiders, scorpions
PLANT TOXINS, MYCOTOXINS
Hemlock, mushroom toxins, aflatoxin (moulds)
BACTERIAL EXOTOXINS
Botulotoxin, tetanotoxin, diphteric toxin, cholera toxin, toxins from staphyllococci and streptococci

[1]Their ranging into the group of biological (plant) toxins is also plausible

given compound. In general, the respiratory system offers the most rapid (apart from the rare direct entry) and the dermal the least rapid route of entry.

Toxicants pass a number of further barriers on their route into tissues and cells. Biologic membranes are in general much less permeable to compounds in the ionized state than to those in the nonionized form. A second parameter influencing penetration is the lipid solubility of the potential toxicant. The mechanism of the movement of toxicants across membranes include all possibilities known from physiologic membrane transport: passive, facilitated and active transport, endocytosis (liquids) and phagocytosis (solid particles).

Respiratory penetration

Airborne toxicants are divided in two general types. Compounds that are subjects to gas laws include gases and vapors. These are easily carried to the alveolar areas. The rate of entry of vapor-phase toxicants is controlled by the alveolar ventillation rate.

The compounds of the second group are in particular form and include aerosols, clouds, fumes, etc. Particles of 5 μm and greater are usually deposited in the nasopharyngeal region. Particles down to 2 μm are deposited in the tracheobronchial region and are cleared upward by the mucus blanket that covers the backward-beating cilia. In addition to upper pathway clearance, phagocytosis in the lung is very active. If not phagocyted, particles 1 μm and smaller may penetrate to the alveolar portion of the lung. They are absorbed in the alveolar region, similarly to gases and vapors.

Gastrointestinal penetration

As gastrointestinal tract is specially designed to enable the ingestion of food and resorbtion of chemical compounds, this is the most common route of accidental or deliberate intoxications.

For toxicants with structural similarities to compounds normally taken up by active transport, the entry is greatly enhanced. As an example, cobalt is absorbed by the same active transport mechanism that normally transports iron.

Every compound absorbed from the stomach or the intestines must cross the liver, where most of them are further transformed. An important aspect of gastrointestinal route is the enterohepatic circulation. In the first step the absorbed compounds are transported to the liver where they undergo different chemical reactions. Following secretion of conjugated metabolites from the liver through the bile duct into the intestine, a water-soluble metabolite may be altered to a less polar compound, reabsorbed through the intestine, and returned to the body in this, altered form.

Skin penetration

The skin is a complex barrier relatively impermeable to most ions as well as compounds in aqueous solutions. It is permeable to a large number of toxicants in the solid, liquid, or gaseous phase, however. Many examples of poisonong by the dermal route have been reported - organophosphate pesticides in agricultural works, chlorophenol in domestic and wild animals, etc. In general compounds mixed into unguents and ointments readily cross the skin.

DISTRIBUTION OF TOXICANTS IN THE BODY

After a chemical subtance enters the body, it is trans-

ported mostly in the blood. Toxicants interact with the blood proteins in various ways (simple nonspecific adsorption, use of specific transport proteins, formation of complexes or covalent bonds) according to their chemical nature. Some toxins enter the red cell and can interact with enzymes (e.g. Pb) or with hemoglobin (e.g. CO).

In the tissues the toxicants may be sequestered either physically, such as solubilization of lipophilic chemicals in fat or chemically by binding to tissue components, such as proteins.

METABOLISM OF TOXICANTS

Some toxicants do not undergo metabolic changes, they only interact in some way with enzymes, membranes, nucleic acids or other physiologically important molecules and damage the cells and tissues (e.g. heavy metals, CO, cyanides). The others undergo metabolic changes (mainly in the liver) as follows:

Phase-one reactions (nonsynthetic reactions)

Phase-one reactions include microsomal monooxygenations, cytosolic and mitochondrial oxidations, reductions, hydrolysis, and epoxide hydration. All of these reactions introduce a polar group which, in most cases, can be conjugated during phase-two metabolism.

Phase-two reactions (synthetic reactions)

Metabolits of phase-one products and other xenobiotics containing functional groups such as hydroxyl, amino, carboxyl, epoxide, or halogen can undergo conjugation reactions with endogenous metabolites, these conjugation being collectively termed phase-two reactions. The endogenous metabolites in question include sugars, amino acids, glutathione, sulfa-

te, etc. Conjugation products are more polar, less toxic, and more readily excreted than are their parent compouds.

THE MOST IMPORTANT INTOXICATIONS DUE TO TOXIC METALS

Lead (Plumbum, Pb)

Lead is used in typography, storage batteries, and is a component of paints, solder, pottery glaze, rubber products, etc. Tetraethyl lead was widely used as a gasoline additive and until introduction of lead-free gasoline led to substantial pollution in regions with high intensity of automobile traffic.

The fatal dose of absorbed lead has been estimated to be 0.5 g. Approximately 50 % of lead deposition in the lung is absorbed, whereas usually only 10 % of ingested lead passes into the circulation. Lead interferes in the biosynthesis of porphyrins and heme (Fig. 4.1), and several screening tests

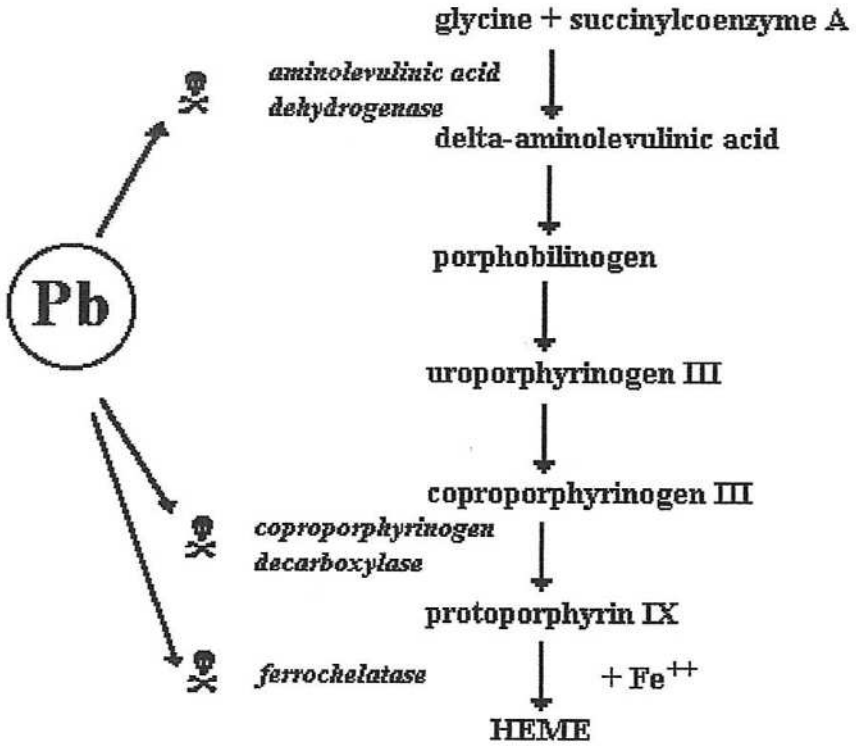


Fig. 4.1. The interaction of lead with heme biosynthesis.

for lead poisoning make use of this by monitoring either inhibition of the affected enzyme - aminolevulinic acid dehydratase (ALAD) or appearance in the urine of aminolevulinic acid and coproporphyrin. The metabolism of inorganic lead is closely related to that of calcium and excess lead can be deposited in the bone.

In acute poisoning (from ingestion or injection of soluble compounds of lead), pathologic findings include inflammation of the gastrointestinal mucosa (abdominal pain, vomiting, diarrhea) and renal tubular degeneration (oliguria).

In chronic lead poisoning (from ingestion, skin absorption, or inhalation of particulatae or organic lead), cerebral edema and degeneration of nerve and muscle cells occur. Clinical findings are: fatigue, sleep disturbances, anemia, colic, and a gray line (**lead line**) on the gums.

Organic lead has an affinity for brain tissue. Mild poisoning may cause insomnia, restlessness, and gastrointestinal symptoms, whereas severe poisoning results in delirium, hallucinations, convulsions, coma (encephalopathia saturnina), and even death.

Mercury (Hydrargyrum, Hg)

Mercury and its salts are used in the manufacture of thermometers, felt, paints, explosives, electrical apparatures and batteries. The diethyl and dimethyl mercury compounds are used in treating seeds. Mercury blocks cellular enzymatic mechanisms by interacting with sulfhydryl (-SH) groups and for this reason, soluble mercuric salts (e.g. $HgCl_2$, sublimate) are toxic to all cells. Inorganic and organic mercury differ in their routes of entry and absorption. Inhalation is the principal route of uptake of metallic mercury (Hg^0) in

industry, with approximately 80 % of the mercury inhaled as vapor being absorbed. Metallic mercury is less readily absorbed by the gastrointestinal route. Organic mercury compounds are readily absorbed by all routes. In fatalities from mercury poisoning, the pathologic findings are acute tubular and glomerular degeneration. Ingestion of mercuric salts causes inflammation, congestion and corrosion of the gastrointestinal tract. Symptoms of acute poisoning include abdominal pain, vomiting, bloody diarrhea. One day to 2 weeks after ingestion, urine output diminishes or stops. Inhalation of mercury vapor, dusts, or organic vapors, or skin absorption of mercury over a long period causes chronic intoxication - **mercurialism**. Findings are extremely variable and include tremor, anxiety, psychic irritation, inflammation of the mouth, blue line on the gums, and nephrotic syndrome characterized by proteinuria.

In Minamata Bay (Japan) mercury released from a factory into the sea water was transformed by bacteria to organic mercury compounds, then ingested by fish. Consuming of contaminated fish caused an epidemic of serious CNS injury including birth defects in newborns born to mothers in the region.

Recently the safety of **amalgames** (alloys of mercury with other metals) widely used in dentistry was questioned, too.

Cadmium (Cd)

Cadmium is used for plating metals and in the manufacture of bearing alloys and silver solders. Cadmium plating is soluble in acid foods such as fruit juices and vinegar. Cadmium is a very cumulative toxicant, accumulation occurs mainly in the kidney and the liver, where it is bound to metallothionein. The critical target organ after long-term exposure to

cadmium is the kidney, with the first detectable symptom of kidney toxicity being an increased excretion of specific proteins. Others symptoms of chronic poisoning include anemia, severe bone and mineral loss.

Beryllium (Be)

Soluble beryllium salts are directly irritating to skin and mucous membranes and induce acute pneumonitis with pulmonary edema. At least part of the changes present in acute pneumonitis and chronic pulmonary granulomatosis develop as a result of hypersensitivity to the beryllium in the tissues.

Arsen (As)

White arsenic - As_2O_3 is historically the most common poison used for criminal purposes. It produces inflammation of the gastrointestinal tract, violent purging and vomiting, hemolysis with jaundice, hematuria, anuria. If death does not ensue in the early stage, sensory changes in the peripheral nerves cause pain, and paresthesias follow. Later there may be motor paralysis, loss of hair, deformities of the nails, skin lesions, and symptoms of upper respiratory tract irritation. Arsenic presumably interacts with sulfhydryl groups of enzymes interfering with cellular metabolism. An excellemt description of arsene poisoning is found in Flaubert's Madame Bovary.

TOXIC GASES

Carbon monoxide (CO)

Carbon monoxide is produced by the incomplete combustion of carbon or carbonaceous materials. CO combines with hemoglobin and forms carboxyhemoglobin, which is incapable of carrying oxygen and therefore tissue anoxia follows. The affinity of hemoglobin towards carbon monoxide is 210 times

greater than for oxygen and therefore serious intoxication can occur at relatively low concentration of CO in the air. The presence of CO reduce the availability of oxygen to the tissues in 2 ways:

* **by direct combination with hemoglobin** to reduce the amount of hemoglobin available to carry oxygen and

* **by preventing the release of the oxygen** at the low oxygen pressure present in tissues.

CO also combines with the myoglobin of muscles and with certain enzymes. The absorption of CO and the resulting symptoms are closely dependent on the concentration of CO in the inspired air, the time of exposure, and the state of activity of the person exposed. Due to its high affinity towards hemoglobin low concentration of CO in the inspired air can cause serious intoxication. At 0.01 % CO in the air 44 % of the Hb is blocked, at 0.1 % the concentration of HbCO is already 62 % (HbCO concentration > 20 % causes cerebral symptoms.) A person who inhales smoke from 20 cigarettes during one day will have at least 6 % of hemoglobin saturated with carbon monoxide.

Hydrogen sulfide (H_2S) and carbon disulfide (CS_2)

Hydrogen sulfide is released spontaneously by the decomposition of sulfur compounds and is found in petroleum refineries, tanneries, mines, and rayon factories. Carbon disulfide is a liquid which boils at 46 ^{o}C. Hydrogen sulfide causes both anoxic effects and damage to the cells of the CNS by direct action. Carbon disulfide damages chiefly the CNS, the peripheral nerves, and the hemopoietic system.

Phosgene and chlorgas ($COCl_2$, Cl_2)

Phosgene is used in chemical synthesis. It is hydrolyzed

to hydrochloric acid in the body and thus irritates and damages cells. The principal manifestations in acute poisoning with phosgene are respiratory and circulatory failure. Chlorgas acts in similar way.

CYANIDE INTOXICATION

Hydrogen cyanide, (H-C≡N, a blue-colored liquid) is used as a fumigant and in chemical synthesis, other cyanides (e.g. KCN, a solid substance) in chemical industry. Cyanides, the most potent inorganic toxicants act by inhibiting the cytochrome oxidase system responsible for oxygen utilization in cells. They interrupt the electron transport in the mitochondrial cytochrome chain at the cytochrome A step. Other enzyme systems are also inhibited, but to a lesser degree. Cyanide first causes a marked increase in respiration by affecting chemoreceptors in the carotid body and respiratory center and then quickly paralyzes all cells. The principal manifestations of poisoning with these compounds are rapid respiration, blood pressure fall, convulsions, and coma.

Stones of certain fruits (e.g. bitter almonds, apricots) contain glycosides (e.g. amygdalin) which upon acid hydrolysis release cyanide. Eating large amount of stones of bitter almonds can lead to serious intoxication. More dangerous are the cyanogenic glycosides of cassava and manioca roots, which are important foodstuffs in some parts of Africa and South America.

Cyanates and isocyanates (e.g. HO-C≡N resp. H-N=C=O) from chemical point of view are derivatives of carbonic acid (H_2CO_3). In 1984 large amount of a toxic compound, **methyl isocyanate** ($CH_3N=C=O$) seeped from an insecticide plant in Bhopal, India killing more than 2000 and causing serious

health damage to 150 000 persons.

THE MOST COMMON ORGANIC TOXIC COMPOUNDS

Organophosphates

Organophosphates (cholinesterase inhibitors, e.g. parathion - Fig. 4.2a) are mostly used in agriculture as insecticides. Organophosphate derivatives act by inactivating the enzyme acetylcholinesterase (AChE). The inactivation of cholinesterase by organophosphates allows the accumulation of large amounts of acetylcholine, with resultant widespread effects which may be separated into 3 categories:

* **Potentiation of postganglionic parasympathetic activity:** The following structures are affected: pupil (concstricted), intestinal muscles (stimulated) salivatory and sweat glands (stimulated), bronchial muscles (constricted), urinary bladder (contracted), sinus node (inhibited), and atrioventricular node (blocked).

* **Persistent depolarization of skeletal muscles**, resulting in initial fasciculations followed by neuromuscular block and paralysis.

* **Initial stimulation followed by depression of cells of the CNS**, resulting in inhibition of the inspiratory center (depression of phrenic discharge) and convulsions of central origin.

Chlorinated organocompounds (halogenated insecticides and herbicides)

The mechanism of poisoning by these agents is not known. They are mostly stable lipid soluble compounds. Their stability poses an environmental threat because they can circulate many years in the nature and cause chronic intoxications far away from the site of their original application. Their toxic

action does not require metabolic alteration of their chemical structure. The most known agent from this group, **DDT** (2,2-Bis(4-chlorphenyl)-1,1,1-trichlorethan; Fig. 4.2b) acts chiefly on the cerebellum and motor cortex of the CNS, causing characteristic hyperexcitability, tremors, muscular weakness and convulsions. The myocardium becomes sensitized so that injection of small doses of adrenaline may induce ventricular fibrillation. DDT was widely used from the 1940s to the 1960s as a succesful agent in malaria eradication, agriculture and households. After the dangers of its cumulation were discovered, it was replaced by other compounds belonging to this group (e.g. chlordane, aldrin, lindan) but even these can pose ecological and health danger.

Dioxin (precisely 2,3,7, 8-tetrachlorodibenzo-p-dioxin, TCDD; Fig. 4.2c) is a highly toxic contaminant of a herbicide, (2,4,5-trichlorophenoxyacetic acid or "Agent Orange") used by the U.S. Army in Vietnam war. Dioxin is a very stable compound and circulates in the biosphere for a long time causing cancer, miscarriage, birth defects and other health damage years after the primary exposure.

Halogenated hydrocarbons

Carbon tetrachloride (CCl_4) is used as a solvent and intermediate in many industrial processes. CCl_4 injuries almost all cells of the body, including those of the central nervous system, liver, kidney, and blood vessels. The mechanism of toxicity appears to result from the intracellular breakdown of CCl_4 to more toxic intermediates. The oxidation of CCl_4 produce radicals such as CCl_3 with following lipid peroxidation and subsequent destruction of cellular components.

Trichlorethylene ($CHCl=CCl_2$) is used as an industrial solvent and cleaner. Trichlorethylene decomposes to dichlorethylene, phosgene, and carbon monoxide on contact with alkalies such as soda lime. The most striking effect of trichlorethylene is the depression of central nervous system function. Other areas affected include the myocardium, liver, and kidney.

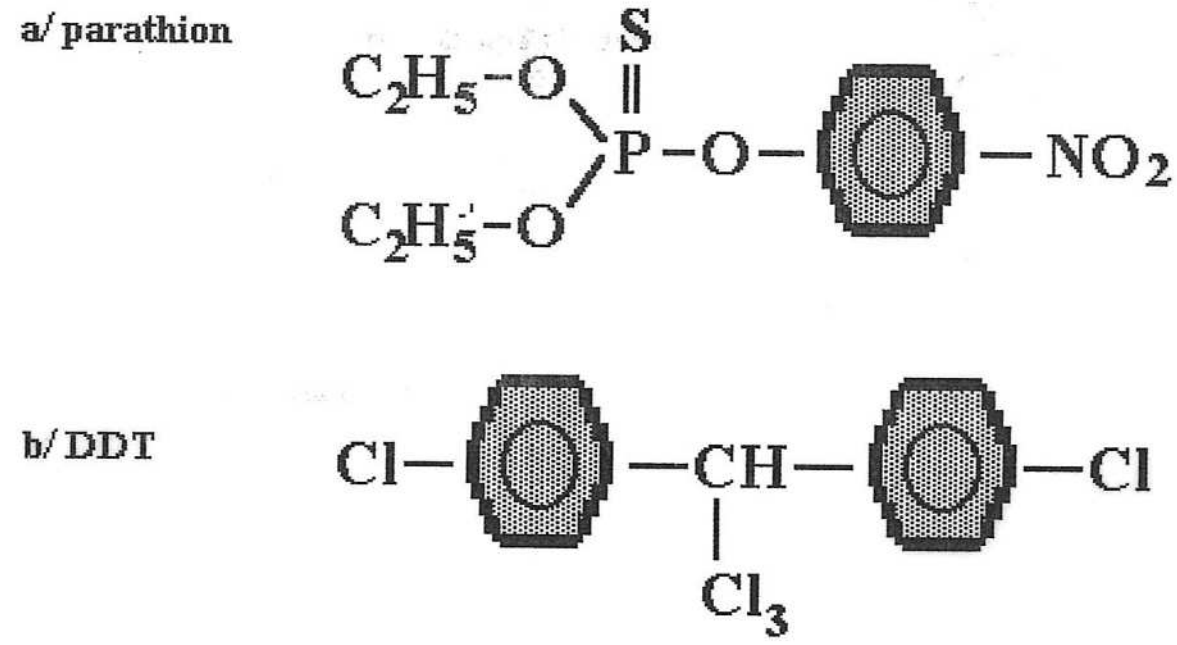


Fig. 4.2. Some important organic toxins

a/ Parathion - an organophosphate
b/ DDT - halogenated hydrocarbon
(2,2-Bis(4-chlorphenyl)-1,1,1-trichlorethan)
c/ Dioxin and the main component of Agent Orenge herbicide
(2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD
2,4,5-trichlorophenoxyacetic acid; 2,4,5-T)

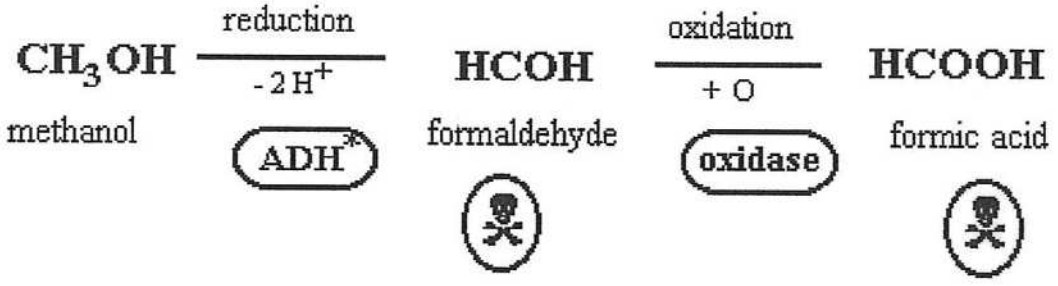
Aromatic organic solvents

In this group compounds we include aromatic hydrocarbons: **benzol** (the most toxic among them), **xylol**, **toluol**, etc. These compounds are commonly used as solvents. Inhaled in large amounts or ingested, these compounds depress the function of the central nervous system: repeated exposure to small amounts of benzene or toluene depresses the bone marrow.

Methylalkohol

Methanol (CH_3OH, methyl or wood alcohol) is a widely used commercial solvent and is often mistaken for ethanol. In poisoning, about 30% of the dose is excreted as methanol by the respiratory tract; the remainder is converted, principally in the liver, by alcohol dehydrogenase to formaldehyde and then to formic acid by aldehyde dehydrogenase (Fig. 4.3).

Symptoms of methanol poisoning may be delayed for 6-18 hours due to the delayed metabolism of methanol to the toxic products, formaldehyde and formic acid. The initial symptoms are similar to effects of ethanol followed by a mild drowsiness. This is followed by an asymptomatic period (6-30 hours) and then the characteristic symptoms and signs of methanol poisoning (dizziness, abdominal pain, vomiting, breathing



*alcohol dehydrogenase

Fig. 4.3. The metabolism of methanol.

difficulties, acidosis, blurred vision, dilated pupils, urinary formaldehyde smell) manifest. The local production of formaldehyde in the retina is thought to be responsible for the production of the **retinal edema and blindness**, the most characteristic signs of methanol poisoning.

The specific therapy for methanol poisoning is the administration of ethanol. The ethanol acts by competition for alcohol-metabolizing enzymes, thus permitting the excretion of methanol before it is transformed to formaldehyde and formic acid.

Alkaloids

Alkaloids are nitrogen-containig heterocyclic compounds of plant origin and complex structure. In plants they role is probably the defense from insects and animals. In animals and humans they exert a lot of pharmacologic and toxic effects and therefore from ancient times they are widely used as remedies, narcotic drugs or poisons. The difference is often only a matter of dosage. **Nicotine, atropine, cocaine, morphine, codeine, papaverine, chinin, strychnine, coffeine, theobromine, digitalis, ergotamin** and **LSD** are some examples of this group.

TOXINS OF ANIMAL ORIGIN

Snakes

Poisonous snakes occur throughout most parts of the tropical and temperate zone of the world. The degree of toxicity resulting from snakebite depends on the potency of the venom, the amount of venom injected, and the size of the person bitten. Poisoning may occur from injection or absorption of venom through cuts or scratches. Snake venoms are complex and include proteins, some of which have enzymatic activity. The

effects produced by venoms include neurotoxic effects eith senzory, motor, cardial, and respiratory difficulties, cytotoxic effects on red cells, blood vessels, heart muscle, kidneys, and lungs, defects in coagulation, and effects from local release of substances by enzymatic action (local swelling, local pain) and one or more puncture wounds or tooth marks.

Insects

Black widow spider (Latrodectus mactans)

The toxicity of the venom is probably greater than that of the snake venoms, but the spider injects only a minute amount of poison. The venom of the black widow spider causes various neurologic effects which have not been completely elucidated. The pathologic findings are not characteristic. The principal manifestation of black widow spider bite is immediate muscle spasm. Symptoms and signs consist of slight pain, blanching, and swelling at the site of the bite, progressing rapidly to pain in the chest, abdomen and joints and to nausea, salivation and sweating.

Scorpions

The mortality rate from scorpion stings may be over 1 % in children under 6 years but is negligible over this age. Local evidence of a sting is sometimes minimal or absent. The usual symptoms are a mild tingling or burning at the site of the sting, which may progress up the extremity. In severe cases, spasm in the throat, a feeling of thick tongue, restlessness, muscular fibrillation, abdominal cramps, convulsions, oliguria, cardiac arrhytmias, pulmonary edema, and failure of respiration occur.

TOXINS OF PLANT ORIGIN

Hemlock

The poisonous plants of the parsley family include poison hemlock (Conium maculatum), water hemlock (Cicuta maculata) and dog parsley (Aethusa cynapium).

Conium maculatum and Aethusa cynapium contain a number of piperidine derivatives, including coniine, which cause peripheral muscular paralysis similar to that from curare. Nicotine-like ganglionic blockade also occurs. The pathologic findings in Cicuta poisoning are similar to those from picrotoxin.

MYCOTOXINS

Mushrooms

The most dangerous species are Amanita phalloides, and other species of Amanita family. In this country about 100 accidents occur each year from eating poisonous mushrooms, some of them with fatal outcome.

Amanita muscaria is a nice red mushroom (fly-agaric), which in variable amounts contains, an atropine-like alkaloid that cause narcosis, convulsions, and hallucinations. Some mushrooms contain the alkaloid muscarine, which produces the same effect as parasympathetic stimulation on smooth muscles and glands.

The most fatal accidents are caused by Amanita phalloides (death cup) mistaken for champion mushrooms. It contains polypeptides amanitin and phalloidin, which damage cells throughout the body. These peptides are thermostable and cannot destroyed by cooking. Liver, kidneys, brain, and heart are especially affected. The intoxication often manifests only 24 - 48 hours after eating the mushrooms. The symptoms be-

gin with intense colic pain and diarrhea, later jaundice with acute liver insufficiency develop together with signs of kidney and heart muscle damage. Due to early diagnosis and intensive treatment methods (e.g. hemoperfusion) the lethality of Amanita mushroom poisoning decreased in the past few years from 90 to 30 - 40 %.

Other mycotoxins

A great number of moulds produce biologically active compounds from which the different **antiobiotics** are the most important. The ergot alkaloids **Ergotoxin** and **ergotamin** produced by Claviceps purpurea, a parazite of grain also belong here. **Aflatoxin B_1** produced by Aspergillus flavus striving on peanuts and other not properly stored and mildewy foods has recently been identified as an important carcinogen.

BACTERIAL EXOTOXINS

Botulotoxin

Botulism is caused by the exotoxin (protein, $M_r \approx 150$ kDa) produced by the anaerobic growth of Clostridium botulinum. Seven antigenic types of toxin occur, marked A - G; types A,B, and E are the most important. Botulotoxin is probable the most effective toxin at all - its lethal dose for humans is about 10^{-9} mg/kg. Among the foodstuffs most often responsible for it are meat, fish, and vegetables; olives and fruits are responsible only occasionally. The anaerobic environment of improperly canned foods favours the growth of bacteria and the production of toxin. The affected cans are filled with gas ("bombed"). Intoxication can occur also in infants fed honey, fresh fruit or vegetables or other foods containing the spores. Exotoxin production then occurs in the gut.

Botulotoxin causes paralysis of muscles by blocking the transfer of nerve impulses at the motor end plate. In acute poisoning, the symptoms begin 8 hours to 8 days after ingestion, with nausea, vomiting, and sometimes diarrhea and abdominal distress, progressing to muscle involvement with marked fatigability, ptosis, dysarthria, blurred or double vision, dilated pupils, paralysis of the respiratory muscles, and quadriplegia.

Some other important bacterial exotoxins are listed in Tab. 4.2.

AIR AND WATER POLLUTION

Both the nature and source of air pollutants vary with the location. Open country remote from industry or heavy traffic will clearly differ from the center of a large city or an area downwind from a coal-fired power plant or other industry. In general, the principal air pollutants are CO, oxides of nitrogen, oxides of sulfur, hydrocarbons, ozone, freons and particulates.

Of the organic constituens, hydrocarbons such as benzo(a)pyrene are produced by incomplete combustion and are probably associated primarily with the automobile engines. The hydrocarbons are important in formation of photochemical air pollution. This pollution is formed as a result of interactions between oxides of nitrogen and hydrocarbons in the presence of ultraviolet light, the resultant reactions giving rise to such lung irritants as **peroxyacetyl nitrate, acrolein, and formaldehyde.**

Ozone (O_3) is an important substance absorbing the short-wave UV lights in the high regions of the athmosphere. At the surface, however, it is a dangerous compound (one of

the bioreactive forms of oxygen, see Chapter 6), causing serious respiratory problems in areas with heavy automobile traffic.

Nitrogen oxides

The nitrogen oxides are important in air contamination and in reactions forming atmospheric oxidants. They include **nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen trioxide (N_2O_3); they can be transformed to nitric acid (HNO_3).** The nitrogen oxides are emitted into the atmosphere as a result of combustion of any nitrogen-containing substances. The principal manifestation of nitrogen oxide poisoning is dyspnea.

Water pollution by toxic chemicals comes from run-off urban streets or of agricultural chemicals from cultivated fields, from sewage, or from specific industrial sources such as refineries, smelters, or chemical plants.

Agricultural chemicals found in water may include insecticides such as chlorinated hydrocarbons, organophosphates, and carbamates.

4.2. THE EFFECTS OF SMOKING

Cigarette smoking is the largest **preventable public health problem** in the western world. Approximately one sixth of the total mortality in these countries are secondary consequences of the cigarette smoking. The cigarette consumption in the USA culminated in the sixties at 4300 pieces per capita and year and was declining slowly since.

According to recent research results cigarette smoking fulfills the criteria for an addiction, including a defined withdrawal syndrome. The effect of nicotine on the central

nervous system is probably the key factor in the addictive process.

Tobacco smoke is a complex mixture containing nicotine and a great number of pyrolysis products. The main particulate matter of the condensed smoke is tar which is repsonsible to its carcinogenic effect. The gas phase of the smoke contains agents with deleterious effect on cilia of the respiratory epithel and high concentration (1 - 5 %) of carbon monoxide.

The major health risks of smoking are outlined in Tab. 4.3. Of course the individual effects depend on the daily and cumulative dose, depth of inhalation, type of cigarettes or other tobacco products and many other factors.

Cardiovascular disease. Smoking is an independent risk factor of ischemic heart disease. The risk of developing myocardial infarction in smokers is almost twofold as compared to nonsmokers and the difference is even greater in young people. Smoking increases the adhesiveness of the platelets and leads to endothelial damage, increases the heart rate and the blood pressure which represent higher oxygen demand for the heart and decreases the oxygen delivering capacity of the blood through increased concentration of carboxyhemoglobin.

The damaging effect of smoking on **peripheral vessels** is even more pronounced. Over 90 % of patients with atherosclerotic peripheral vascular disease are smokers. Cessation of smoking in time is critical in these patients and can prevent amputation of limbs.

Respiratory problems and lung cancer. Every heavy smoker coughs and has mucus hypersecretion. Many of them develop chronic bronchitis with airflow obstruction and emphysema.

Lungs of smokers contain increased number of macrophages and polymorphonuclear leukocytes as a part of the inflammatory response to the irritative effect of cigarette smoke. These cells produce elastase which degrades the elastic structural elements of the lung, resulting in a loss of elastic recoil.

Tab. 4.3. Increased health risks due to smoking

CARDIOVASCULAR DISEASE Ischemic heart disease, myocardial infarction Peripheral vascular disease Stroke
LUNG DISEASE Cancer Chronic obstructive bronchitis Emphysema
GASTROINTESTINAL DISEASE Cancer of oral cavity, larynx, esophagus Peptic ulcer Esophageal reflux Cancer of pancreas
UROGENITAL DISEASE Cancer of bladder
COMPLICATIONS OF PREGNANCY Infants small for gestational age High perinatal mortality Abnormalities of placenta

The damaged airways represent a favourable basis for the action of the carcinogens, tumor initiators and promoters of the cigarette tar. The rates of the lung cancer begin to increase in smokers after age of 35. The average risk factor of smoking for the development of lung cancer is about ten but heavy smokers (more than one pack per day) have about 20 - 25 times higher likelihood developing lung cancer (and other malignancies) as nonsmokers.

Involuntary or passive smoking. Inhalation of smoke cons-

tituents from the environment has the same deleterious effect as active smoking. Although the concentration of the smoke (and its constituents) in rooms and workplaces does not reach the level of the concentration in the airways of a smoker, the exposed persons are often infants, pregnant women or people with various health problems with exaggerated vulnerability towards the effect of tobacco smoke.

4.3. ALCOHOL ABUSE

The medical problems associated with alcohol consuption are fourfold:

1. **Acute alcohol intoxication**
2. **Alcohol abuse or alcoholism**
3. **Alcohol withdrawal syndromes**
4. **Alcohol related illnesses**

ALCOHOL METABOLISM

Alcohol is usually ingested in the form of different alcoholic beverages which contain 5 - 40 % of ethanol. Ethanol is rapidly absorbed from the stomach and small intestine, enters the bloodstream and diffuses to all compartments of the body (it is miscible both with water and lipids); therefore its action is manifest already in some minutes.

About 10 % of the ingested ethanol is eliminated directly through the kidneys and lungs, the remaining is metabolized in the liver. (Fig. 4.4). In the rate-limiting step catalyzed by alcohol dehydrogenase (an average, non-trained adult with undamaged liver can oxidize about 9 g ethanol per hour) toxic acetaldehyde is formed which is quickly transformed to active acetate. If the two reactions are not coordinated, acetaldehyde can cumulate (e.g. in individuals belonging to the mon-

golid race) and instead of alcoholic euforia first flush, later headache and nausea occurs. Acetaldehyde and the congeners (aldehydes, higher alcohols) are responsible for the hangover effects.

During alcohol metabolism the balance between the oxidized and reduced forms of NAD is shifted towards NADH. The rate of lactate to pyruvate is increased and **hyperlactacidemia** leads to **metabolic acidosis**. The excretion of uric acid in

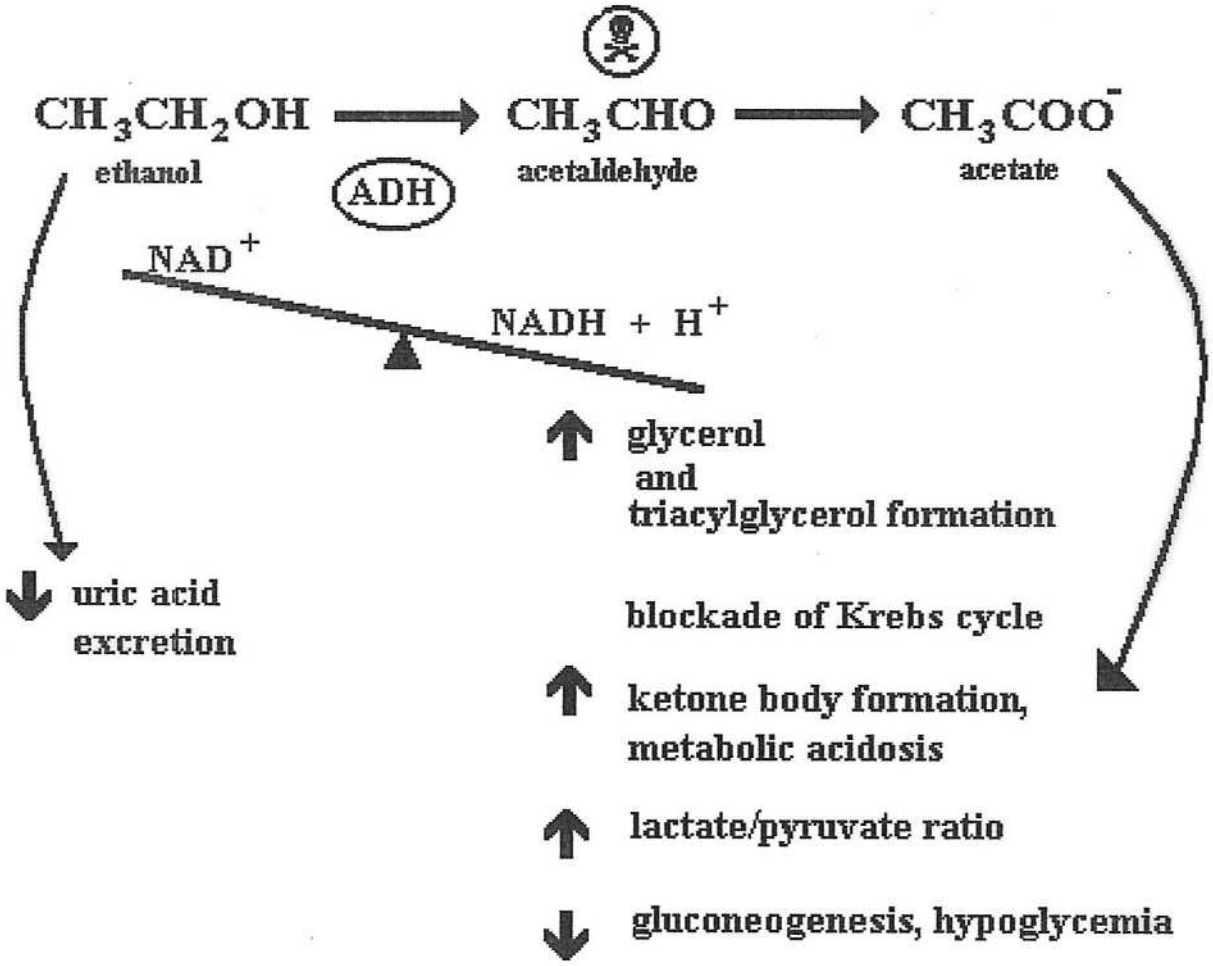


Fig. 4.4. The metabolism of ethanol.

kidneys is diminished -**hyperuricemia** can lead to gout especially in obese and genetically predisposed people. As a consequence of the increased availability of NADH the **lipogenesis**

is augmented, the Krebs cycle is blocked and from acetate **ketone bodies** are formed. The excess fat deposites in the liver and causes **steatosis** present in the liver of almost every alcoholic.

Acute alcohol abuse can cause **hypoglycemia** - by inhibiting the gluconeogenesis in the liver. Chronic alcoholics, on the other side may develop secundary diabetes due to damage of the pancreas.

EFFECT OF ALCOHOL ON THE BRAIN

Ethanol in small doses has euphoric and anxiolytic effect. It causes first **excitation** by blocking the inhibitory functions. In the excitatory stage some persons instead of euphoria and relaxation may become hostile and aggressive. At higher doses a **depressive** phase follows which can end in coma and death.

The different parts of the brain are affected by ethanol from above downward - first the cortex, then the limbic system and the cerebellum, the reticular system and finally the brain stem. Its effect on neurons is probably exercised through activation of the calcium ion in the cell, upon the action of the Na/K ATPase and through increasing the fluidity of the cell membrane.

The dependence of the symptoms on alcohol level in the blood are summarized in the Tab. 4.4. Heavy drinkers with yet undamaged liver can tolerate higher doses. After occasional heavy drinking postintoxication symptoms **(hangover)** occur with headache, giddiness, tremor, nausea and digestive complaints (alcohol directly damages the mucosa of stomach).

CHRONIC ALCOHOLISM AND WITHDRAVAL SYNDROMES

Dependence on alcohol develops in "high risk" individuals

in favourable social conditions. The predisposing factors include a genetic component but its nature is not yet elucidated. Chronic alcoholism is characterized by an **addictive cycle** that perpetuate heavy drinking. The ingestion of alcohol provides some relief from psychologic and physical tension. Drinking, on the other side, induces psychologic and somatic processes which increase the desire for more alcohol.

Tab. 4.4. Acute alcohol intoxication

BLOOD LEVEL OF ALCOHOL mg/l	**PHASE**	**MAIN SYMPTOMS***
0.50 0.75 1.0 1.5	**excitatory**	euphoria garrulity sometimes aggresivity loss of motor coordination unrestrained behaviour
2.0 3.0 5.0	**depressive**	alertness loss stupor coma and death

*In heavy drinkers whose physical and mental state is not yet compeletely deteriorated the symptoms appear at higher alcohol concentrations.

In chronic alcoholics first a **primary psychologic dependence** develops followed by **increased tolerance** to alcohol. This allows the increases of the dose which in turn leads to **physical dependence**. In this stage abstinence causes alcohol withdrawal syndromes and these force the alcoholic to drink steadily. At the end of this course **complete inability to abstain** ensues.

Cessation of alcohol intake from whatever reason in chronic alcoholics leads to withdrawal syndromes, from which **delirium tremens** is the most severe. Delirium tremens repre-

sents an acute medical emergency. The patients are disoriented, agitated, hallucinating, tremulous. The heart and respiration rate is rapid, the body temperature elevated and the blood pressure low. Muscle cramps and general seizures can occur. The symptoms in untreated patients may last weeks and complications (penumonia, hepatitis) can develop.

ALCOHOL-RELATED DISEASES

The pathogenesis of alcohol-related diseases can be explained by

* **direct toxic effects of ethanol and**
* **dietary insufficiency**

Alcohol and alcoholic beverages are rich in energy and therefore the caloric intake of heavy drinkers can be covered by alcohol alone. This "diet" is, however, deficient in every essential component of healthy diet (proteins, trace elements and vitamins). The dietary insufficiency is superimposed to the toxic effects of ethanol and therefore in actual organ or system damage usually both type of damage is involved.

Alcohol related diseases involve every organ and system of the human body and even small doses of alcohol pose a tremendous threat to the fetus during intrauterine development (Tab. 4.5).

Tab. 4.5. Alcohol related diseases and pathological processes

ORGAN OR SYSTEM	DAMAGE OR DISEASE
Brain	Alcoholic dementia
	Wernicke-Korsakoff sy.
Nerves	Polyneuropathy
Heart	Cardiomyopathy
Blood	Anemia
Gastrointestinal tract	Acute and chronic gastritis
	Acute and chronic pancreatitis
	Carcinoma of the oesohpagus
Liver	Steatosis
	Acute hepatitis
	Cirrhosis
Endocrine system and reproduction	Male sexual impairment
	Fetal alcohol syndrome
Metabolism	Hyperlipidemia (triacylglycerols)
	Hyperuricemia, gout
	Hypoglycemia
	Secondary diabetes
	Hypovitaminoses
	Acidosis, ketosis
Immune system	Increased susceptibility to infections

5. DISORDERS OF NUTRITION

5.1. NUTRIENT REQUIREMENTS IN HEALTH AND DISEASE

A healthy diet ensuring the normal function of the organism (and its adequate development and growth in childhood) should supply the body with energy, balanced amount of macronutients (protein, carbohydrate and fat), enough pure water, minerals, vitamins and trace elements.

The individual requirements of nutrients depend on age (especially vulnerable are very young and elderly people) and sex, body constitution, special circumstances (pregnancy, lactation) type of work and physical activity, climatic conditions and many other factors.

Detailed informations about energy and nutrient requirements can be found in tables of Food and Nutritional Board of the National Academy of Sciences (Recommended Dietary Allowances, RDA) and in similar materials of WHO, FAO and other organizations. These doses are average doses recommended for healthy people. For people with a particular disease or at risk developing some disease special **therapeutic or preventive diets are** recommended. In some cases (e.g.vitamins) the optimal amount (ODA, Opitmal Dietary Allowance) is higher than the RDA and for micronutrients which in high amount exert toxic effects (e.g. Mn, Se) it is better to speak about SADI (Safe and Adequate Daily Intake).

Developed countries are able to produce and purchase enough food to ensure a well-balanced diet for all their people. On the other side under-developed countries where unfavourable climatic and soil conditions exist together with

the persistence of primitive methods of agriculture, some form of protein-calorie malnutrition endangers the health and life of more than 1500 million people.

The eating customs of many people in affluent countries are unhealthy as well and this can promote the development of obesity, atherosclerosis, hypertension, cancer and other diseases. Our understanding of active constituents in foods that foster or hamper disease development is incomplete but epidemiological proofs are solid enough to advise changes in eating customs of the population. With **judicious diet** (Tab. 5.1) the danger of these diseases could be diminished. On the other side drastic or extreme diets, fashionable due to lack of scientific education or cultism can do more harm than good especially in young people or in people with endangered health.

5.2. UNDERNUTRITION

Undernutrition (mostly as protein-calorie deficiency) occurs when inadequate amount of protein is consumed and/or the food is poor in its energy content. For many parts of the world undernutrition is the most important health problem and occurs as **marasmus** (protein + energy deficiency) or **kwashiorkor** (deficient protein intake with nearly adequate energy supply).

In developed countries these distinct syndromes are rare, yet sublclinical malnutrition is common and often nondiagnosed (Tab. 5.2.) and can promote the development of various diseases or worsen the course of already existing diseases.

ABSOLUTE STARVATION

Absolute starvation without water intake leads to death

Tab. 5.1. Composition of a healthy diet for adult people

1	Caloric intake should be adjusted to achieve and maintain ideal body weight.
2	Fat intake should be reduced to 30 %[1] of total energy intake (max. 8 % as saturated fat) and cholesterol intake should not be more than 300 mg per day (the lower the better[2]). Mono- and polyunsaturated fats (protected from peroxidation) and marine fish oil are highly recommended.
3	Complex carbohydrates should be used to make up the caloric deficit resulting from changes in fat intake.
4	Food containing fiber (fruit, vegetables) should be preferred at every serving.
5	Alcohol use should be restricted. In persons with hypertriacylglycerolemia should be avoided completely.
6	Use of salt should be less than 4 g per day[3], especially in persons prone to hypertension.
7	Reasonable limitation of charcoal-broiled and smooked foods rich in nitrites is recommended.
8	Food containing toxicants (from air, soil and water pollution) should be avoided if possible.
9	Natural sources of micronutrients should be preferred but if deficiency threatens, artificial supplementation is reasonable.
10	Having a meal in humans is also a social event with an important psychological background influencing physiological functions. Eating in a hurry should be avoided and the servings should be palatable and joyful for the eye.

Notes:
1 Now 40 % with 15 % saturated fat, 500 mg cholesterol/day
2 Strict vegetarian diet contains no cholesterol
3 Now between 10 - 20 g/day in most western countries

within a week due to dehydratation. A well-nourished adult with adequate water supply can survive without food as long as two months.

The most striking sign of starvation is weight loss, which is rapid in the first days of starvation and later slows down. A weight loss of 5 - 10 % is well tolerated but loss of 40 - 50 % of the body mass threatens the life.

Tab. 5.2. Possible causes of protein-calorie malnutrition in hospitalized patients

DECREASED ORAL INTAKE	
Anorexia	Poverty
Nausea	Old age
Dysphagia	Social isolation
Pain	Substance abuse
Gastrointestinal obstruction	Depression
Poor dentition	
INCREASED NUTRIENT LOSSES	
Malabsorption	Nephrotic sy.(proteinuria)
Diarrhea	Fistula drainage
Bleeding	Protein-losing enteropathy
Glycosuria	
INCREASED NUTRIENT REQURIEMENTS	
Fever	Trauma
Infection	Burns
Neoplasma	Medication
Surgery	Hyperthyreosis

If external sources of energy are not available, the body mobilizes its own reserves. (Fig. 5.1.) First the stores of glycogen are converted into glucose but these last only some hours. After this period glucose (essential to brain metabolism) is formed in gluconeogenetic pathway from glucoplastic aminoacids and glycerol. The concentration of blood glucose usually does not decrease to hypoglycemic values. The remaining energy demand is covered by catabolism of fat and protein. This leads to hyperlipemia, ketosis, ketonuria and acidosis. The nitrogen balance is negative. There is a negative balance of the most minerals as well.

The physiological and biochemical processes of the body (heart rate, blood pressure, body temperature, basal metabolic rate and the secretion of the exocrine and endocrine

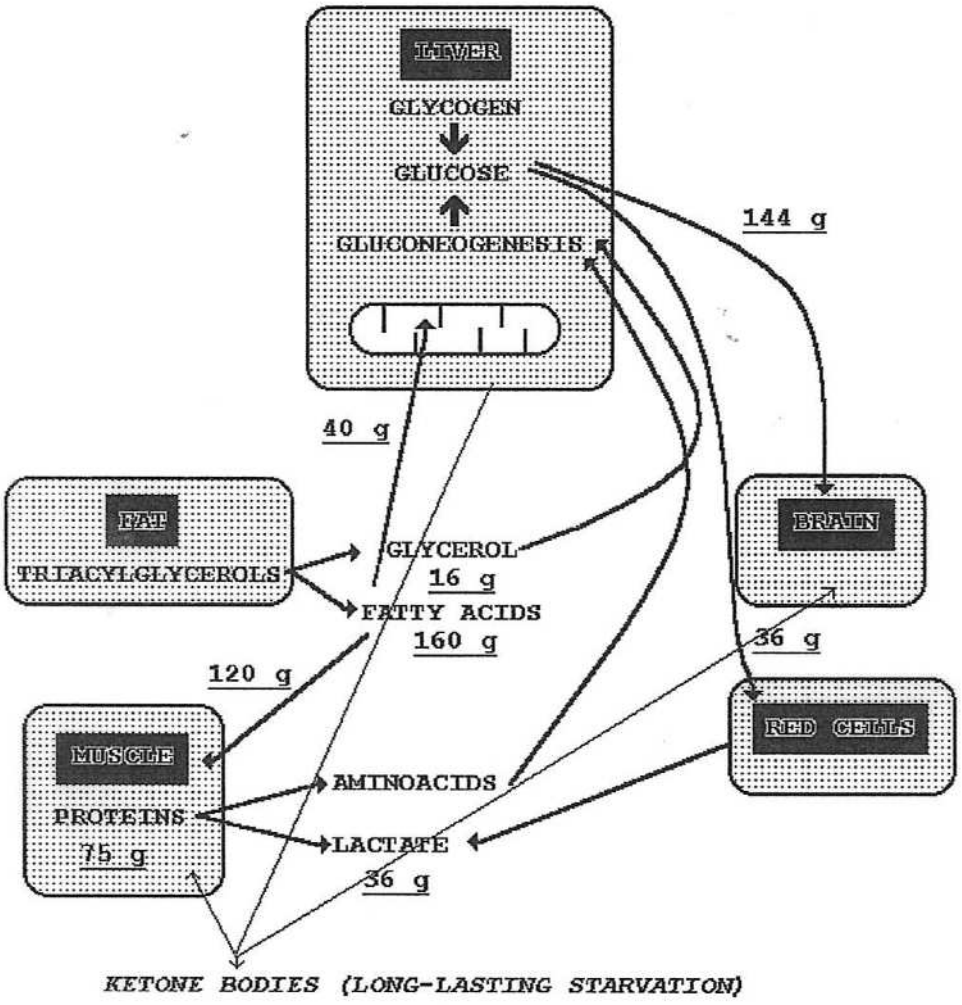


Fig. 5.1. Metabolism during starvation.

glands) are curtailed. The lymphocyte count falls dramatically (down to $1.2*10^9/l$) and both the cellular and humoral immunological response is impaired carrying an increased risk of infection.

After about two months of absolute starvation the fat reserves are completely exhausted and the breakdown of structural proteins leads to irreversible morphological damage of organs and their functions.

CHRONIC UNDERNOURISHMENT - MARASMUS

The weight loss and the development of the symptoms is similar but less dramatic than in absolute starvation. The nitrogen balance is negative and the concentration of albumin and other plasmatic proteins is low. The same is true for the essential lipid constituents and the blood glucose level is usually on the edge of the hypoglycemia. Loss of minerals from the body (Ca, P, Mg and K) occurs.

In addition to weight loss weakness, fatigue, decreased immune functions, anemia, delayed wound healing are the main symtomps of marasmus.

KWASHIORKOR

Kwashiorkor is the example of qualitative undernourishment (protein malnutrition with adequate or nearly adequate energy supply). It is a common disease in the poorest countries of the world, affecting mostly children of age 1 - 3 years. During lactation, which in these countries usually lasts longer than in western world, the protein supply of the child is appropriate.

After lactation growth retardation with weakness, wasting of muscle mass, apatia and depigmentations of the skin develop. The heart rate is slow, the blood pressure and body temperature low. The abdomen is distensed owing to hepatomegaly (with steatosis) and ascites. The concentration of serum albumin and other serum proteins are very low as well as the lymphocyte count. The children usually die on intercurrent infection.

EATING DISORDERS

The centres for the appetite and satiety are located in hypothalamus. In healthy and physically active person the ap-

petite corresponds to the energy requirement of the body. In sick people, in people with sedentary occupation and people under stress the regulation of appetite is disturbed and they eat more or less than they need. Cultural (great feasts) and culinar (unhealthy modern western diet) customs promote the loss of proper regulation of the appetite. A striking example is feeding of infants from bottle on milk powder formulas instead of breast feeding.

Anorexia nervosa is a self-imposed energy depletion afflicting predominantly young women. The patients have intense fear of being obese, have a disturbance of body image (they feel fat despite their normal weight) and refuse to eat appropriate amount of food. The disease has certain genetic and a strong psychical background. Sociocultural factors which advances the slim female image may act as a trigger. In some patients the weight loss is accomplished through strict dietary regime and exercise and in others through self-induced vomiting or use of laxatives. The clinical picture corresponds to that of chronic starvation with gonadal dysfunction (amenorrhoea).

Bulimia (bous [greek] = ox, limos = hunger) is the opposite behavioral eating disorder characterized by periods of overeating (binging) usually followed by acts (physical activity, strict diet, vomiting) to undo the dietary sins.

5.3. DISORDERS OF VITAMIN METABOLISM

It is generally known that vitamins (Tabs. 5.3 - 5.6, Figs. 5.2 - 5.14) must be acquired from dietary sources because they cannot be synthesized in the body. However, there are some exceptions to this rule. Niacin is formed in vivo

Tab. 5.3. The water soluble vitamins

VITAMIN	ACTIVE FORM	FUNCTION	ABSORPTION
THIAMIN Vitamin B_1	Thiaminpyrophosphate (TPP)	Coenzyme - oxidative decarboxylation transketolase	Active transport + passive diffusion Alcohol inhibition!
RIBOFLAVIN Vitamin B_2	Flavinmononucleotide, Flavin adenine dinucleotide (FMN, FAD)	Coenzyme - redox reactions glutathione reductase	Specific saturable transport process
NICOTINIC ACID AND NICOTINAMIDE (NIACIN)	Nicotinamide dinucleotide, Nicotinamide dinucleotide phosphate (NAD, NADP)	Coenzyme - redox reactions, H^+ transfer	Simple diffusion
PYRIDOXINE Vitamin B_6	Pyridoxalphosphate	Coenzyme - amino acid metabolism, heme and sphingosine synth.	Simple diffusion
BIOTIN Vitamin H	8 stereoisomers, only (+)-biotin is active	Coenzyme of carboxylases	
PANTHOTENIC ACID	Only the right-turning stereoismer is active	Component of coenzyme A	
COBALAMIN Vitamin B_{12}	Hydroxycobalamin	Coenzyme, transport of C_1, folate metabolism isomerisation of methylmalonyl-CoA to succinyl-CoA	As complex with intrinsic factor Specific receptor in terminal ileum
FOLIC ACID	Tetrahydrofolic acid	C_1 carrier, biosynthesis of purines -> DNA	
ASCORBIC ACID Vitamin C	Redox system ascorbic/dehydroascorbic acid	Reducing agent, antioxidant Collagen biosynthesis Iron absorption Carnitine biosynthesis Immune function	Limited-capacity transport

from tryptophan but a diet poor in tryptophan cannot provide sufficient amount of precursor to its synthesis. Vitamin D can be synthesized in the skin after exposure to light. The intestinal microflora provides the body vitamin K and biotin and therefore deficiency of these vitamins may result from long-term antiobiotic therapy.

Tab. 5.4. The lipid soluble vitamins

VITAMIN	ACTIVE FORM	FUNCTION	ABSORPTION
RETINOL Vitamin A β-CAROTENE as provitamine	Retinal (Vitamin A aldehyde)	Vision - Prosthetic group, rhodopsine in rods, iodopsines in cones Growth and differentiation of epithels	Cleavage of carotene, esterification, transport via lymph in chylomicrones
VITAMIN D Erkalciol (D_2) plants Kalciol (D_3) animals photoreaction from provitamine 7-dehydrocholesterol	hydroxylation in liver (position 25) and in kidney (position 1) -> calcitriol	Resembles more the action of hormones. Induces the synthesis of transport protein necessary for Ca binding (intestinal absorption)	Together with lipids, transport in LDL
VITAMIN E Tochopherols	D-α-tocopherol is the most potent from a series of isomers	Antioxidant - Protection of polyunsaturated lipids in membranes from lipid peroxidation	Together with lipids, transport in chylomicrones and lipoproteins
VITAMIN K	K_1 Phylloquinone, plant K_2 Menaquinone, intestinal bacteria; K_3 Menadione, atreficial	Blood clotting; coenzyme - carboxylation of τ-glutamic acid moieties in precursors of factors II, VII, IX, X	Similar as vitamin E

Classical vitamin deficieny syndromes as scurvy, rickets or beri-beri are now encountered only rarely. The typical recent picture is multiple marginal deficiency (combined usually with general malnutrition and various diseases) because a diet poor in one vitamin is usually poor in several others. In western countries drug and alcohol abuse are significant causes of vitamin deficiency and old people are particulary vulnerable to this deleterious effect of ethanol.

Most vitamins act as coenzymes. Disturbances of pathways converting them into their active forms (caused by genetic factors, different diseases and medications) can mimic external vitamin deficiencies despite adequate supply. In some cases the absorption of vitamins is impaired. As an example the deficiency syndrome of vitamin B_{12} occurs mostly as consequ-

Tab. 5.5. Recommended daily doses, sources, stability and toxicity of water soluble vitamins

VITAMIN	DAILY DOSE	MAIN SOURCES	STABILITY	TOXICITY
Thiamin	m: 1.2 - 1.5 mg f: 1.0 - 1.1 mg p,l : + 0.5 mg	meat, whole grains, peas, beans, nuts	heat and alkali sensitive	p.o. nontoxic (limited absorption
Riboflavin	m: 1.4 - 1.7 mg f: 1.2 - 1.3 mg p,l: + 0.4 mg	milk, meat, fish poultry, eggs, legumes, fruits	light, acid, and alkali sensitive	nontoxic
Pyridoxine	0.3 - 2.2 mg	meat, liver, vegetables, grains		
Nicotinamide	m: 16 - 19 mg f: 13 - 14 mg p: + 2 mg l: + 5 mg	60 mg tryptophan = 1 mg nicotinamide (animal proteins) decreased availability of nicotinamide in corn, grain		> 2g/d can cause neuropathy ?
Biotin	100 - 200 µg	intestinal bacteria liver, yeast		
Panthotenic acid	4 - 7 mg	Royal jelly of bees, beans, vegetables meat, milk, eggs whole meat, fish		
Cobalamin	3 µg p,l: + 1 µg	synthesized only in bacteria, found in liver, kidney, meat, not found in plants	termostabil	
Folic acid	400 µg p: + 400 µg l: + 100 µg	green parts of plants liver, yeast		
Ascorbic acid	m,f: 60 mg p: + 20 mg l: + 40 mg	citrus fruits, green vegetables - broccoli green paprika, cabbage, potatoes	alkali, heat and oxidation sensitive	> 1g/d digestive problems, kidney stones, increased absorption of toxic heavy metals. Possible prooxidant effect in the presence of high concentration of iron

m = males; f = females; p = pregnancy; l = lactation

Tab. 5.6. Recommended daily doses, sources, stability and toxicity of lipid soluble vitamins

VITAMIN	DAILY DOSE	MAIN SOURCES	STABILITY	TOXICITY
Carotene and Vitamin A	m: 1 mg retinol f: 0.8 mg 1 mg retinol = 6 mg β-carotene 1 mg retinol = 3.33 IU	Carotene: carrots, potatoes, leafy green vegetables, fruits, palm oil Vitamin A:fish liver, animal liver		carotenes can cause benign yellow-orange color of skin A vit. > 15 mg/d skin lesions, vomiting, CNS symptoms and liver damage
Vitamin D	growth: 10 mg adults: 5 mg p,l: 10 mg 1 mg cholecalciferol = 40 000 IU	provitamin in the skin egg yolk cod-liver oil		gastrointestinal complaints (vomitus, nausea) decalcification of bones and calcium deposition in soft tissues
Vitamin E D-α-tocopherol	m: 10 mg f: 8 mg p:+ 2 mg, l:+3 mg 1 mg α-tocopherol = 1.5 IU	soybean, corn, wheat germ, cottonsead and safflower oils (also high in polyunsaturated fatty acids)	storage, oxidation and heat sensitive	
Vitamin K	70 - 140 µg	K_1: green leafy vegetables: spinach, lettuce, broccoli, turnip green K_2: intestinal bacterial flora		water soluble formulas given parenterally can cause hemolysis and jaundice

m = males; f = females; p = pregnancy; l = lactation

ence of the lack of intrinsic factor - a protein enabling the transport of the cobalamin through the intestinal microvilli.

The stores of individual vitamins in the body are different - B_{12} stores can last years, folic acid, niacin, thiamin reserves for weeks or months. Excess amounts of water-soluble vitamins are rapidly excreted into urine but considerably amount of fat-soluble vitamins can accumulate in the body sometimes with adverse effects.

Some vitamins are employed not only to cover the require-

ments of the body but also in high doses as remedies for different diseases (Tab. 5.7).

Tab. 5.7. Therapeutic applications of vitamins[1]

VITAMIN	APPLICATION
Thiamin	Several rare inborn errors of metabolism
Riboflavin	Several rare inborn errors of metabolism
Nicotinic acid	Elevated serum cholesterol
Nicotinamide	Prevention of autoimmune destruction of B cells in insulin-dependent diabetes mellitus
Pyridoxine	Pyridoxine-dependency syndromes (anemia, certain forms of cystinuria, aciduria)
Panthotenic acid	Diseases of skin and hair
Cobalamin	Peripheral neuropathies
Folic acid	Prevention of neural tube defects in fetus
Ascorbic acid	Some inborn errors of bone and collagen metabolism (Ehlers-Danlos sy., osteogenesis imperfecta Prevention and treatment of common cold (?) Prevention and treatment of cancer (?) Iron deficiency (increase of absorption)
Vitamin A	Cystic acne, psoriasis and other diseases of the skin
Carotene	Prevention of epithelial cancer
Vitamin D	Osteoporosis, osteomalacia
Vitamin E	Hemolytic anemia and retrolental fibroplasia in newborns Prevention of atherosclerosis (?) Infertility (?) Prolongation of life (???) Enhanced sexual performace (???)

[1]In addition to the treatment of clear-cut deficiency syndromes

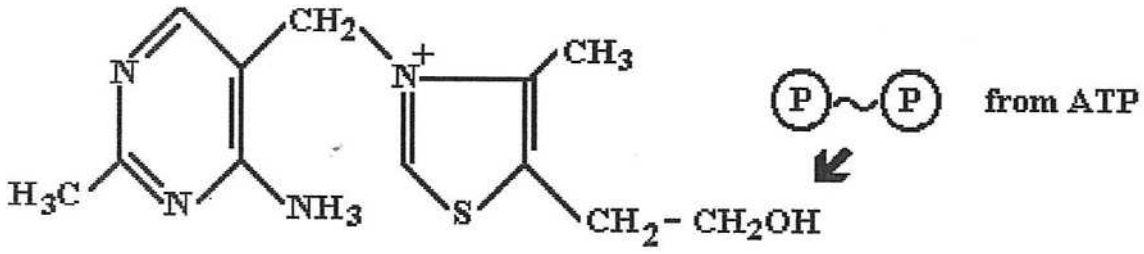


Fig. 5.2. Thiamin and TPP.

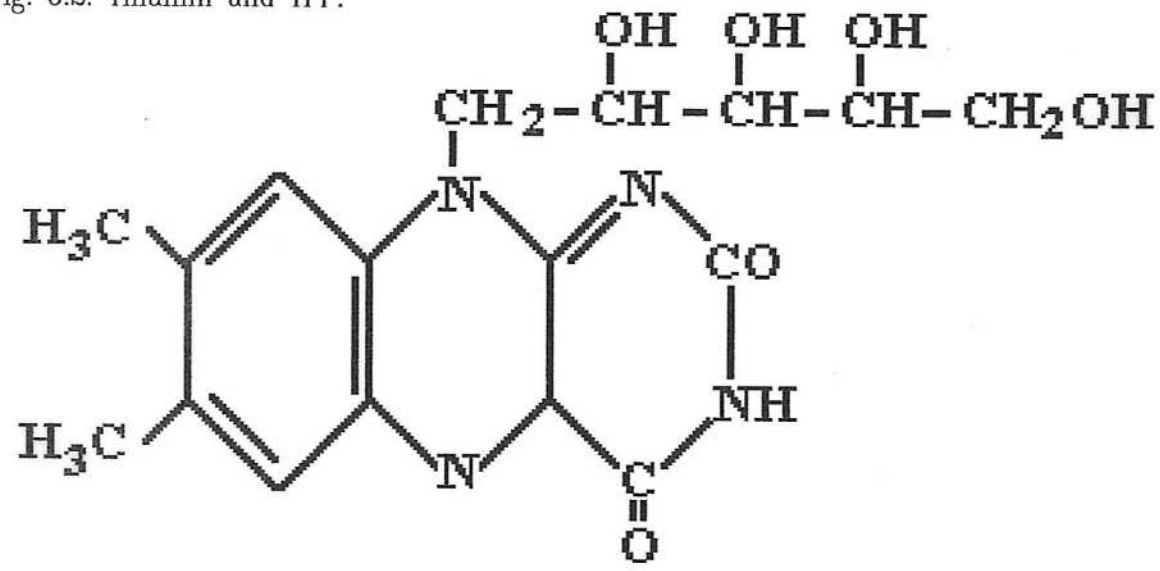


Fig. 5.3. Riboflavin.

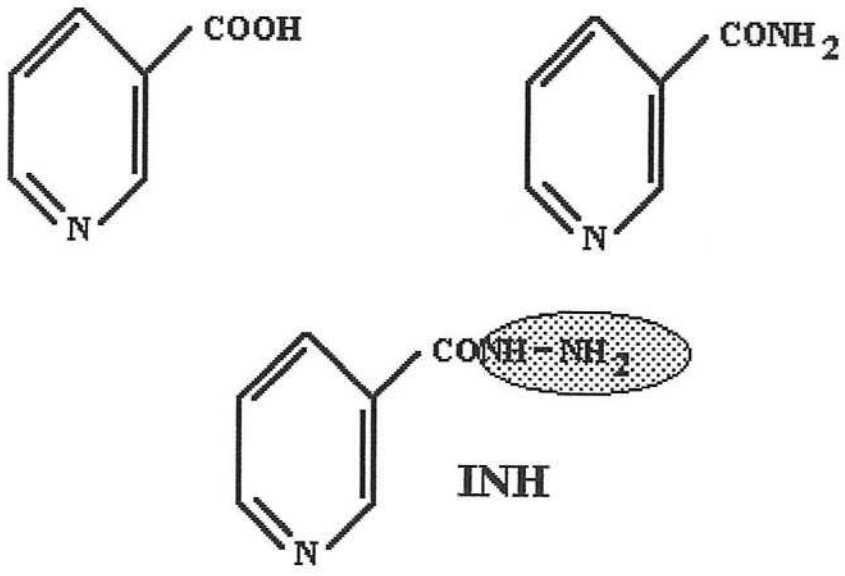


Fig. 5.4. Niacin (nicotinic acid and nicotinamide) and the structure of INH, an antagonist of niacin.

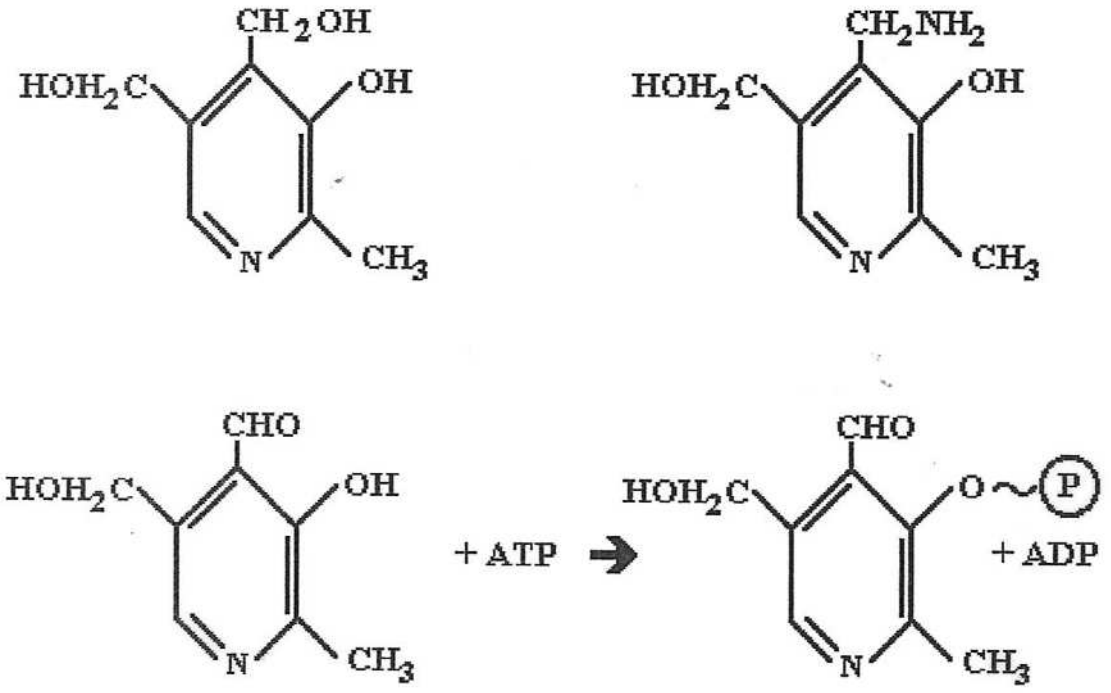


Fig. 5.5. Pyridoxin, pyridoxamin and pyridoxal-5-phosphate.

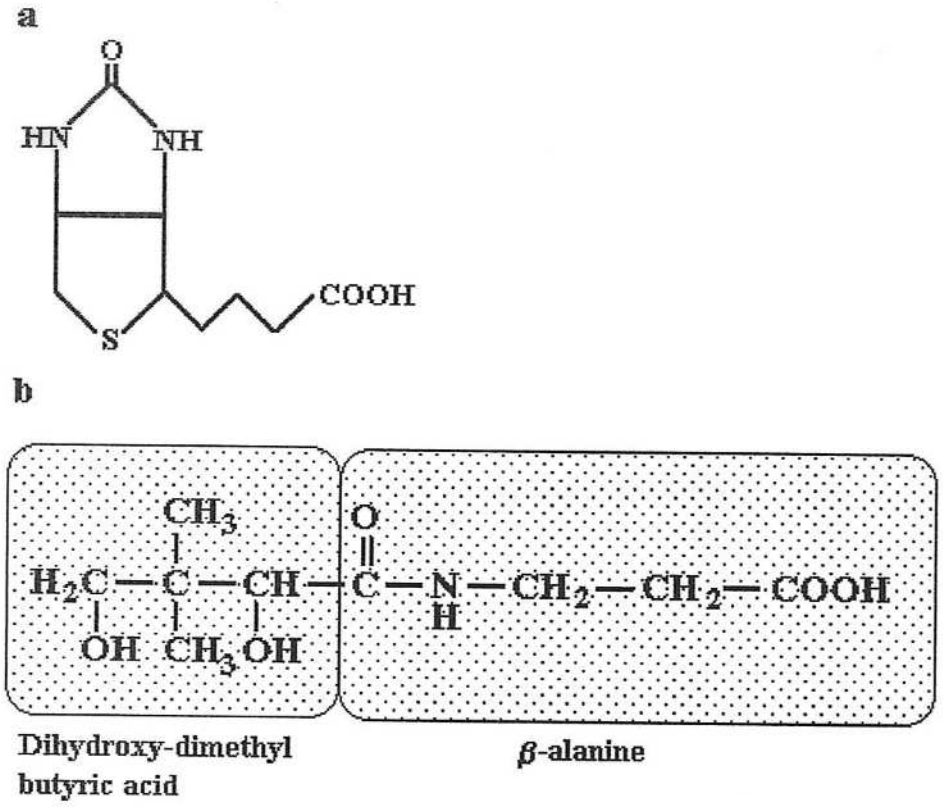
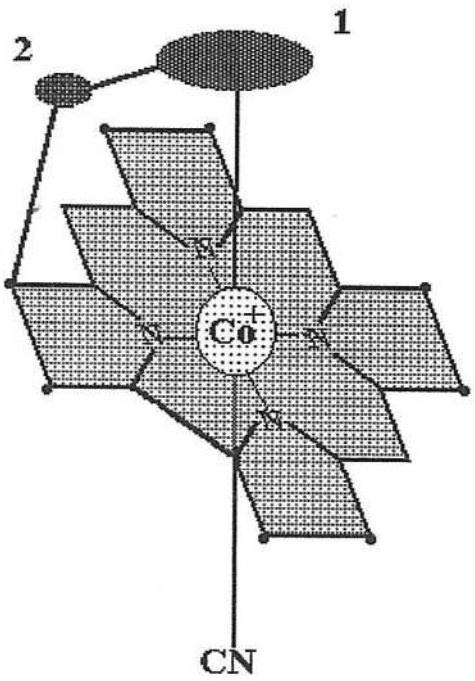


Fig. 5.6. Biotin (a) and panthotenic acid (b).



the double bonds of the corrine ring and the acetate and propionate side groups are omitted

1 - 5,6-dimethylbenzimidazol, attached to the cobalt atom

2 - pentosephosphate attached to the dimethylbenzimidazol and through an aminopropanol moiety to the ring

Fig. 5.7. The structure of cobalamine (simplefied).

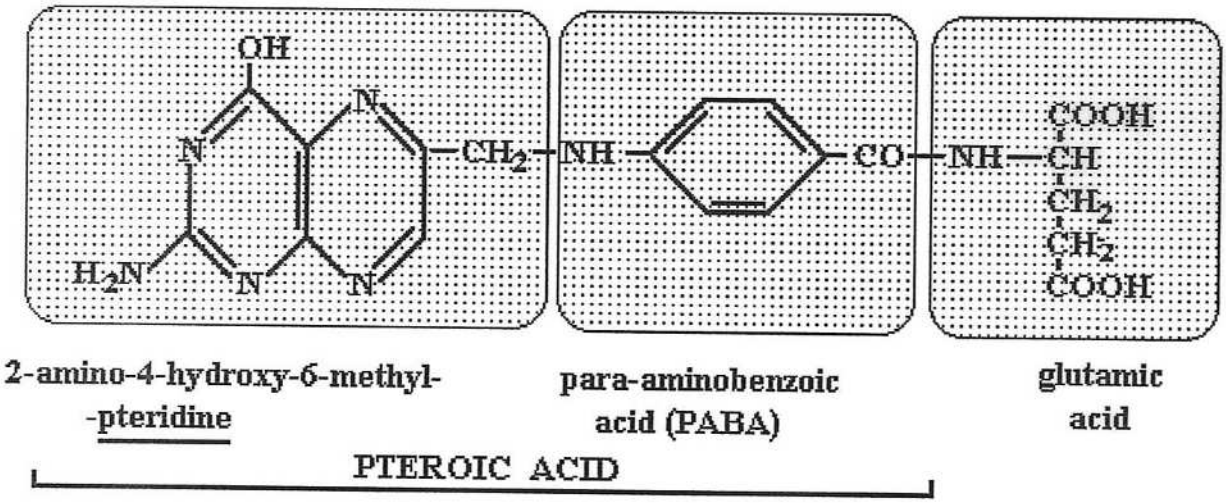


Fig. 5.8. The structure of folic acid.

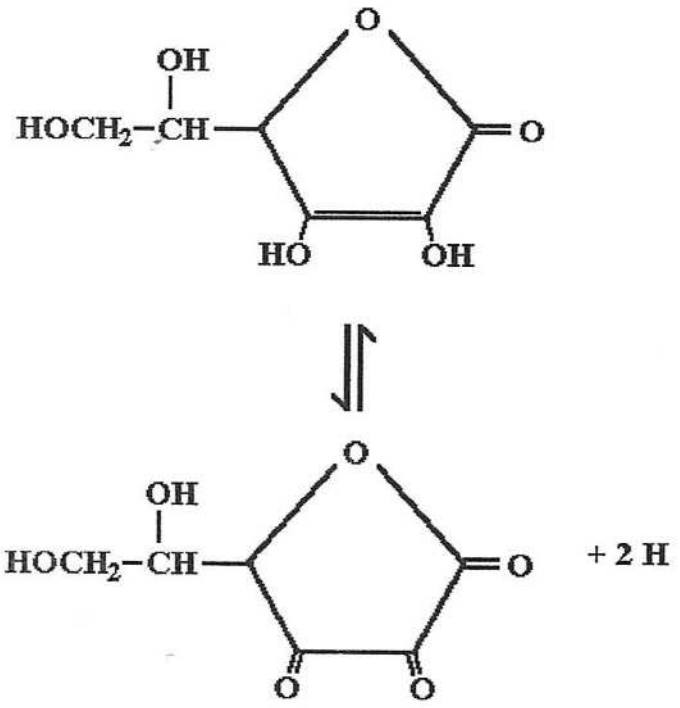


Fig. 5.9. Ascorbic and dehydroascorbic acid.

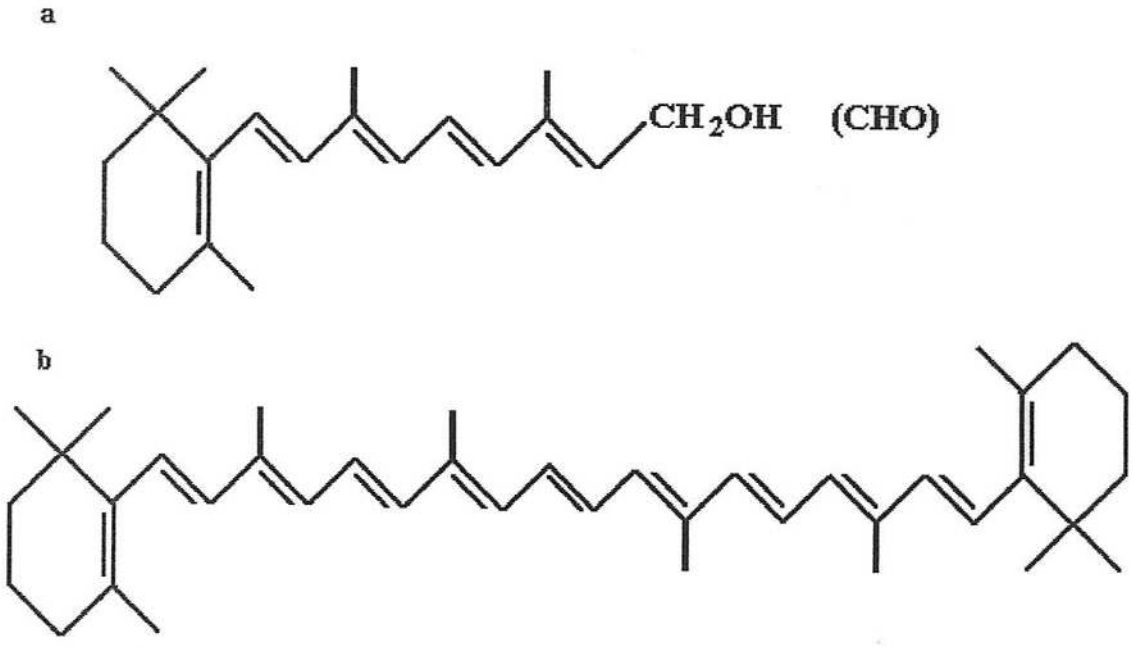


Fig. 5.10a. Vitamin A (retinol and retinal; a) and β–carotene (b).

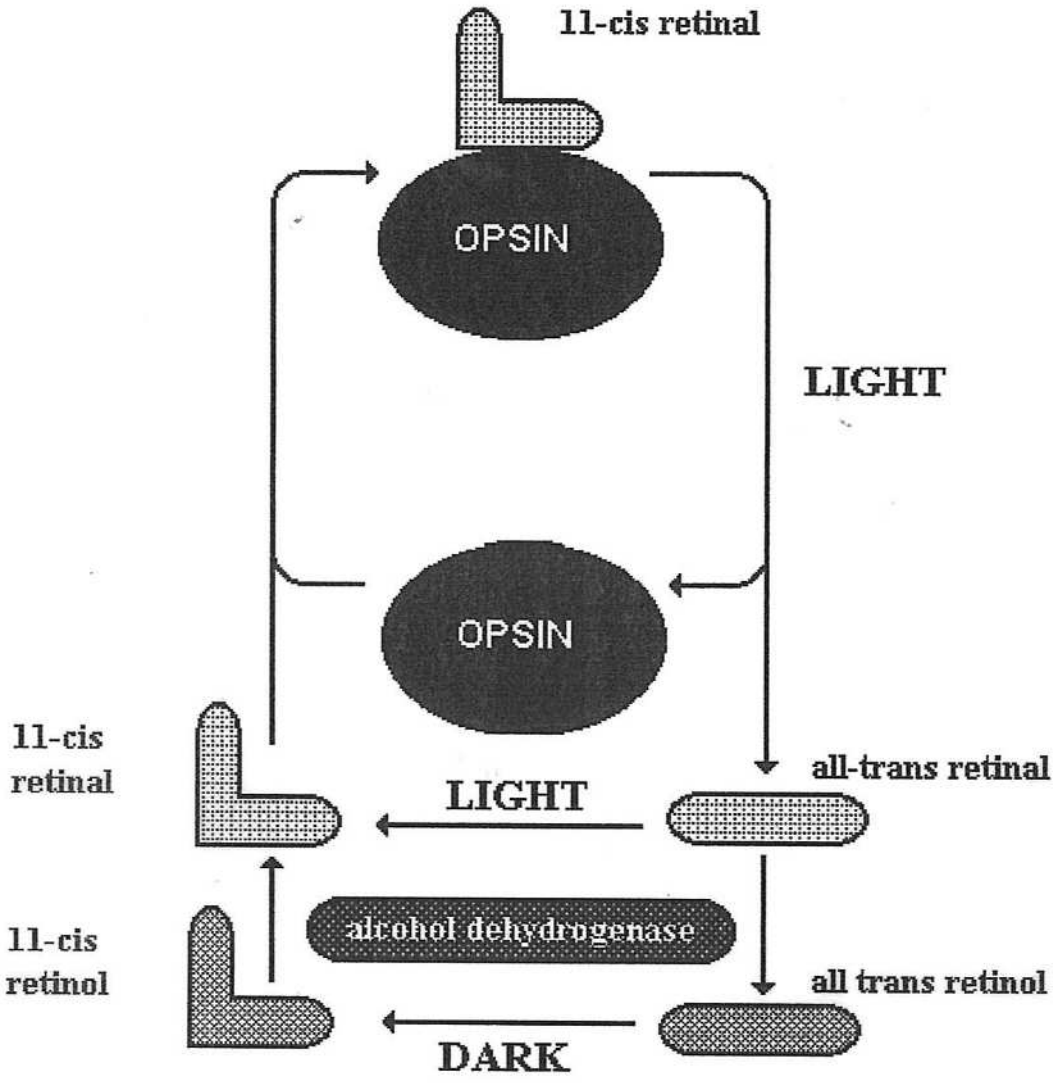


Fig. 5.10b. The transformation of retinal and retinol in light and dark.

WATER SOLUBLE VITAMINS

Thiamin (vitamin B_1)

Thiamin is the precursor of thiamin pyrophosphate (TPP, Fig. 5.2), an important coenzyme of **oxidative decarboxylation** of alfa-ketoacids to aldehydes. Without this coenzyme pyruvic acid cannot transform to active acetate and enter the Krebs cycle with an obvious adverse effect on energy production of the cells. The synthesis of acetylcholine is also deprived. TPP is also a coenzyme of transketolase, (an enzyme of the

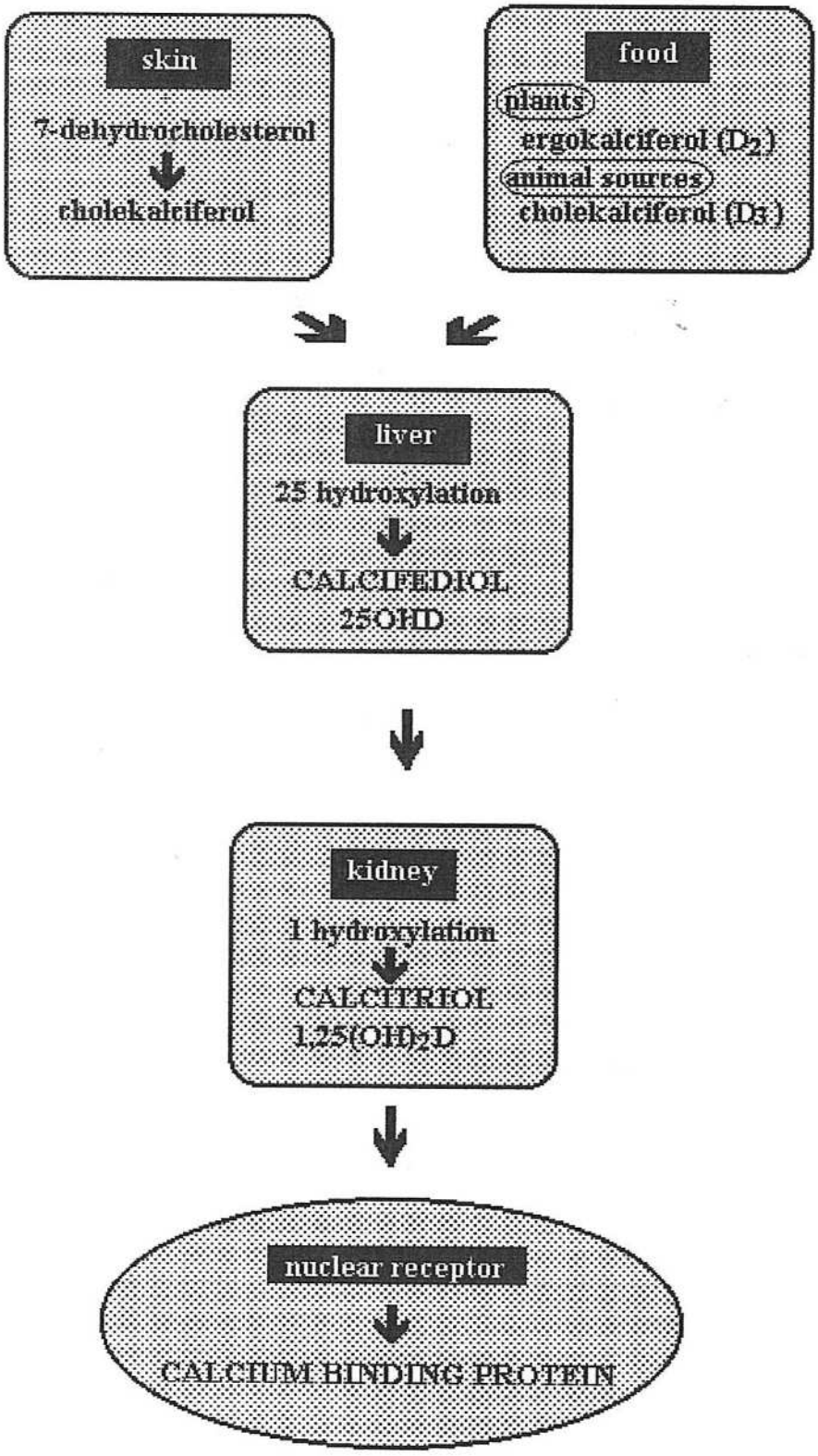


Fig. 5.11. The metabolism of vitamin D.

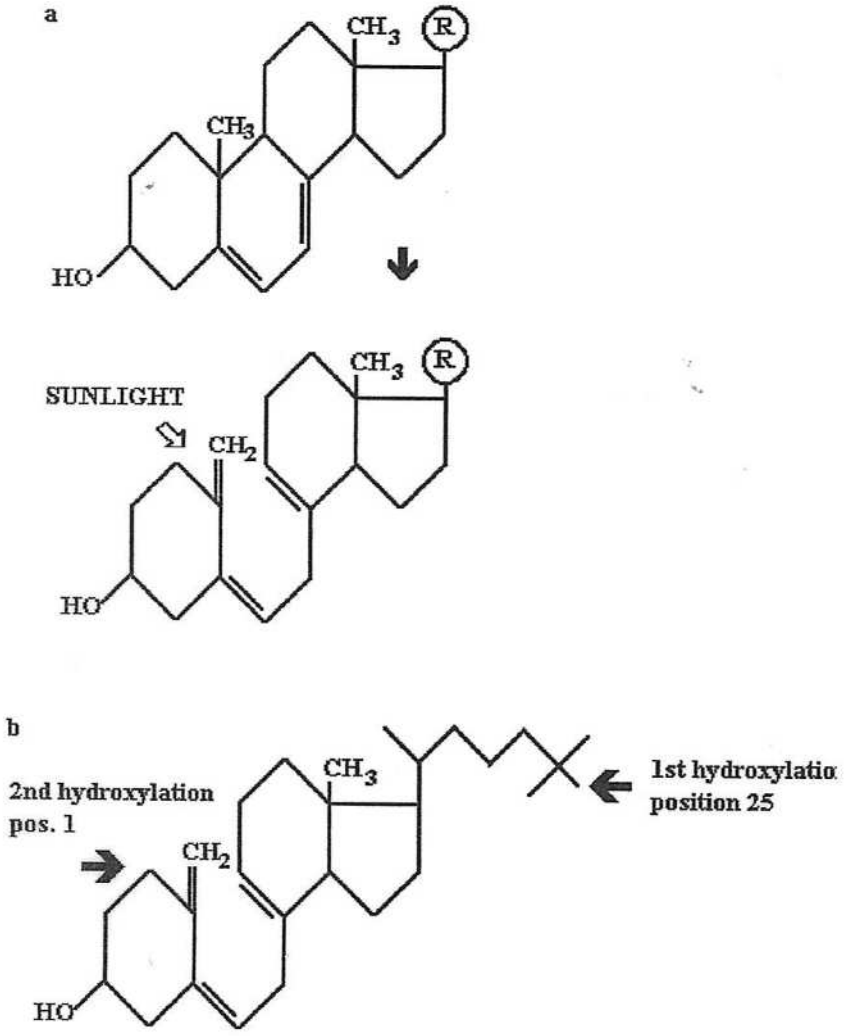


Fig. 5.12. The photoconversion of 7–dehydrocholesterol to calciferol (a) and the hydroxylation sites of calciferol (b).

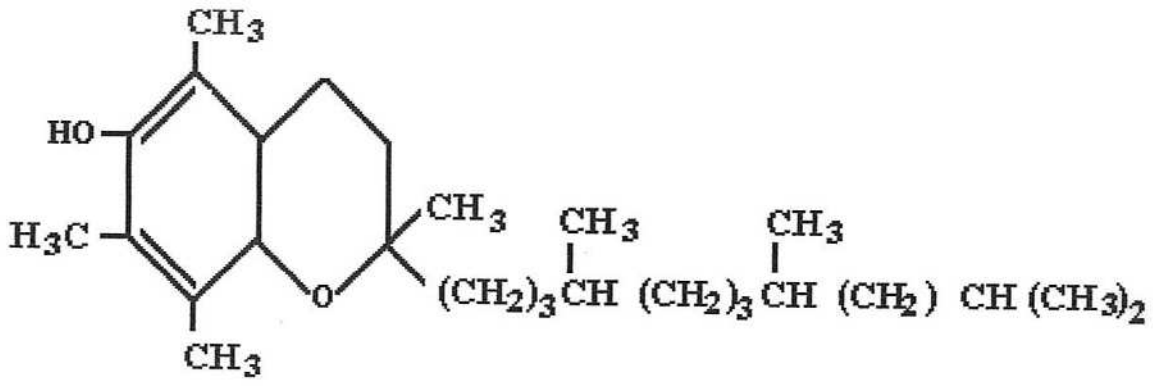


Fig. 5.13. Vitamin E (D–α–tocopherol).

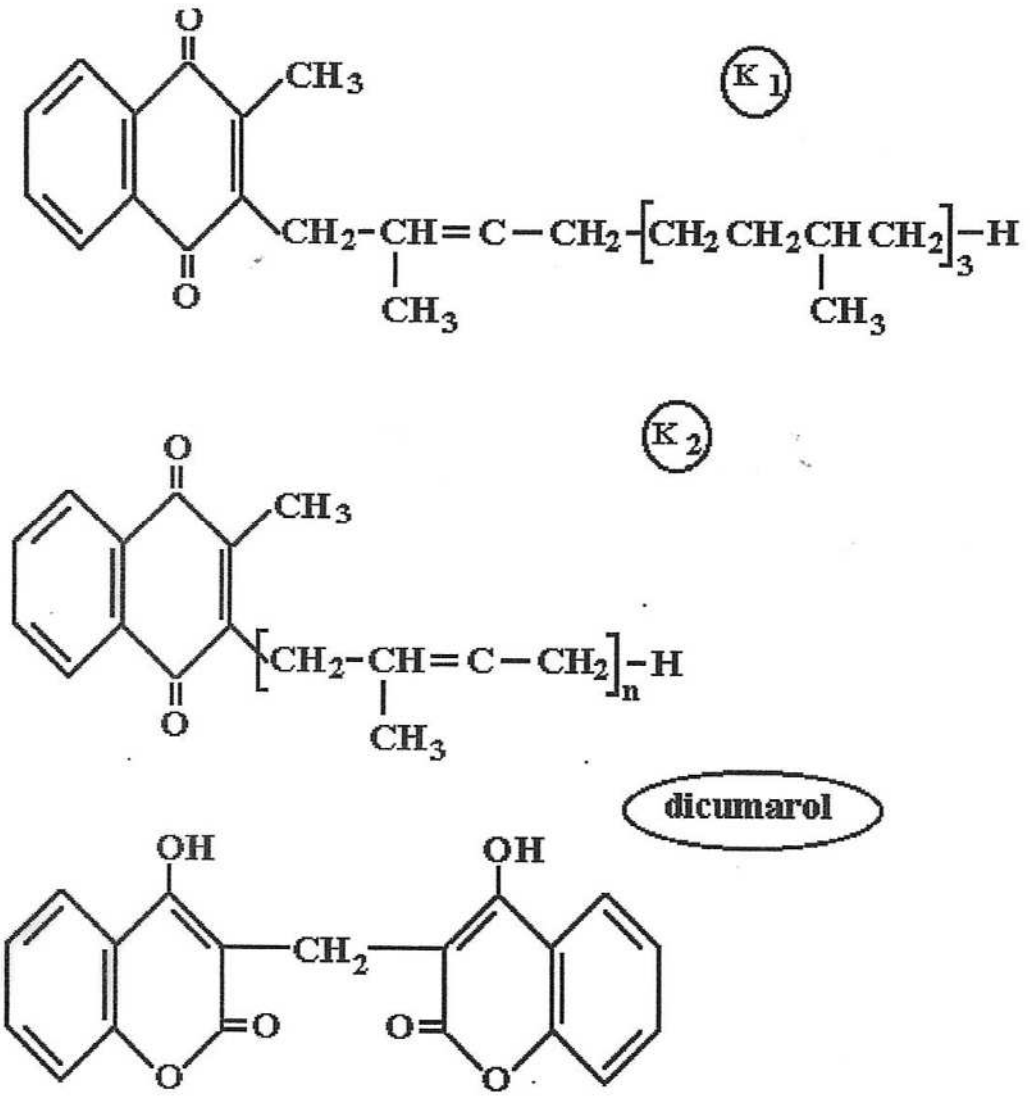


Fig. 5.14. Vitamin K (phylloquinone, menaquionone) and the vitamin K antagonist dicumarol.

pentose-phosphate cycle) which is an important source of pentoses and reduced nucleotides essential for synhesis of nucleic acids and fatty acids, respectively.

The most common cause of thiamin deficiency is alcoholism. Alcohol interferes strongly with thiamin absorption which is partly a passive diffusion process, partly active transport. The common malabsorption of the chronic alcoholism further deteriorate the situation togehter with the diminished conversion of the vitamin to TPP in the damaged liver.

The classic thiamin deficiency syndrome is called **beri-beri** and involves two major organ systems: the cardiovascular and nervous systems. Beri-beri heart disease presents itself with enlarged heart, resting tachycardia and high cardiac output (due to peripheral vasodilatation).

The central nervous system manifestations correspond to the Wernicke-Korsakoff syndrome of chronic alcoholism - vomiting, nystagmus, ophtalmoplegia, ataxia and progressive mental impairment. The peripheral nervous system abnormalities consist of symmetric motor and sensory lesions affecting earlier and more completely the legs than the arms.

The symptoms respond rapidly to thiamin supplementation. The high cardiac output may diminish and the vascular resistance increases within 30 minutes of intravenous administration of 100 mg thiamin. Thiamin may be given in large doses by mouth without fear of adverse effects because its intestinal transport capacity is limited.

Riboflavin (vitamin B_2)

Riboflavin (Fig. 5.3) is absorbed from the intestine by a specific transport mechanism. In the body the vitamin is converted to flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) which act as coenzymes of enzymes catalyzing oxidation- -reduction reactions (α-glycerophosphat dehydrogenase, xanthine oxidase, NADPH-cytochrome C reductase, glutathione reductase).

Deificiency of this vitamin can arise not only as a consequence of poor diet, but also when different circumstances decrease its absorption or transformation to active forms. Some metals and drugs (Cu, Zn, Fe, saccharin, tryptophan, ascorbic acid) form chelates with riboflavin and decrease its

bioavailability. Chlorpromazine, adriamycine and other drugs inhibit flavokinase, an enzyme which converts riboflavin to FMN. Deficiency of riboflavin may result after severe trauma, burns, chronic diseases and prolonged diarrhea. In poorly compensated diabetes the excretion of riboflavin is increased.

Riboflavin deficiency alters the plasma and tissue concentrations of phospholipids. Early symptoms include soreness of the mouth and burning of the eyes. Later cheilosis, seborrhoic dermatitis and anemia develop together with intellectual retardation. The deficiency can be treated with food high in riboflavin (milk, liver, meat, eggs and legumes) or the vitamin itself. Riboflavin and its coenzyme derivatives are not toxic.

Nicotinic acid, nicotinamide (niacin)

The pyrimidine derivates nicotinic acid and nicotinamide (common term: niacin, Fig. 5.4) are the precursors of NAD and NADP, which are very important and widespread coenzymes of redox enzymes. They are involved in almost every metabolic pathway were hydrogen is employed in the reaction.

Poultry, beef and salmon meat are abundant in niacin as well as green peas and hazelnuts. Both forms of niacin are easily absorbed from the gut, but the body stores are small. The amino acid tryptohan can be converted into niacin but the efficiency of the process is low - 60 mg tryptophan is necessary to the synthesis of 1 mg niacin.

Niacin deficiency was once very common in parts of the world where corn was the major source of food. (Corn contains niacin in biologically nonavailable bound form.) The classic sydrome, **pellagra** was characterized by three D: **dermatitis,**

diarrhea and dementia. The skin lesions are dark and rough (*pelle agra* = rough skin) and occur in areas exposed to light. Mild deficiency with vague symptoms occur as a part of the general undernourishment in people on deficient diet. The symptoms respond dramatically to oral nicotinamide within days.

Pyridoxine (vitamin B_6)

The phosphate derivative of the vitamin, pyridoxal-5--phosphate (Fig. 5.5) acts as coenzyme involved in the metabolism of aminoacids (aminotransferases, decarboxylases, racemases, synthetases), synthesis of heme and sphingosine. Pyridoxine and its related compounds, pyridoxal and pyridoxamine are absorbed from the gastrointestinal tract by diffusion and stored mainly in the muscles. Pyridoxine is widely distributed in food and its deficiency is mainly connected with certain medications. Isoniazid (an important antituberculotic drug) forms a complex compound with pyridoxal phosphate and therefore in the course of prolonged treatment vitamin B_6 deficiency (symptoms: neuritis, diarrhea, anemia and seizures) can occur. The symptoms rapidly disappear after supplementation with pyridoxine. Prolonged treatment with L-dopa (treatment of Parkinson's disease) and alcoholism may also lead to pyridoxine deficiency.

In addition to deficiency states there is a group of disorders in which treatment with vitamin B_6 has beneficial effects (pyridoxine dependency syndromes; e.g. some forms of homocystinuria, aciduria, hyperoxaluria and anemia). As an example the pyridoxine-responsive anemia displays the morphological features of iron-deficiency anemia (microcytic hypochromic red cells) but responds well to vitamin and not to

iron treatment which in this case is contraindicated.

Biotin

Biotin (older name vitamin H, Fig. 5.6a) acts as prosthetic group of carboxylases. Biotin deficiency is rare, because it can be produced by the bacterial flora in the intestine. Raw egg white contains a protein called **ovidin**, which combines with biotin in the intestinal tract and depletes the body of this vitamin. Rancid fats, saccharine and some drugs inhibit the absorption of biotin. The symptoms of biotin deficiency (dermatitis, loss of hair) in humans are not defined precisely

Panthotenic acid (Fig. 5.6b)

As a component of coenzyme A has a central role in the energy metabolism of all cells. Its deficiency is rare because it is abundant in most foods - in the highest concetration in royal jelly of bees. The deficiency symptomes include psychic depression, muscle weakness, dermatitis and disturbances of renal function.

Cobalamin and folic acid (Figs. 5.7 and 5.8)

The typical consequence of vitamin B_{12} deficiency is **anemia perniciosa** with characteristic immature macrocytic erythrocytes (megaloblasts), low count of leukocytes and thrombocytes. Later degeneration of the nerve tracts in the spinal cord develops.

Cobalamin is, however, not only a simple factor of blood cell maturation. It has central role as a **coenzyme in transport of one-carbon (C_1) groups**. In the process of methylation of homocysteine to methione (an important step in the synthesis of DNA) methylcobalamin acts as coenzyme and N^5-methyltetrahydrofolate as donor of the methyl group. In

another reaction adenosylcoabalamine is utilized in the process of **isomerisation of L-methylmalonyl-CoA to succinyl-CoA** which in turn enters the Krebs cycle. This step forms a link between lipid and carbohydrate metabolism and is probably important in the biosynthesis of myelin. This provides a possible explanation of the nerve tract degeneration observed in cobalamin deficiency.

In absence of cobalamin the transformation of methyltetrahydrofolate to tetrahydrofolate is interrupted. As tetrahydrofolate is the main carrier of C_1 groups essential for purine nucleotide biosynthesis the final consequence is a disturbance of DNA synthesis. This affects all dividing cells of the body and the red cell maturation defect is only the visible tip of the iceberg.

The deficiency syndrome is usually not caused by the deficit of the vitamin itself (with exception of strict vegetarians) but it is a consequence of the lack of the **intrinsic factor**, a 115 kDa glycoprotein produced in the parietal cells of the stomach. The intrinsic factor forms a complex with cobalamin and only this complex can be absorbed from the ileum into the cells coating the microvilli. Typical causes of intrinsic factor deficiency are gastrectomy and autoimmune atrophic gastritis. Disturbances of ileum can also cause cobalamin deficiency through impaired absorption of the intrinsic factor - cobalamin complex.

In blood the vitamin is transported attached to another transport proteins. In the case of cessation of the supply, the stores of vitamin B_{12} in the liver can last as long as 2 years.

The main consequence of cobalamin deficiency, the mega-

loblastic anemia, responds very quickly to parenteral application of cobalamin. (In the case of intrinsic factor deficiency the oral application of vitamin has no sense.) Large doses (0.3 - 1 mg) of parenterally given B_{12} vitamin are employed in the treatment of different neuropathies.

Folic acid and folate are generic names for a group of compounds of which **pteroylglutamic acid** is the parent form. The molecule consist of a pteridine moiety linked to paraaminobenzoic acid (PABA) by a methylene group. Animal cells are unable to sythesize PABA and attach it to the pteroic acid. Folate-poor diet is common in alcoholics, in the elderly and in faddists. Oral contraceptives and fenylbutazone increase the folate requirements of the body. The same is true for diseases with elevated rate of cell division (e.g. hemolytic anemia and exfoliative dermatitis). Folate deficiency leads to megaloblastic anemia from the same reason as does cobalamin deficiency.

Ascorbic acid (vitamin C)

The classic vitamin C deficiency syndrome, **scurvy (scorbut)** was already more than 200 years ago succesfully prevented and cured with fresh vegetables and lemons and in 1932 Albert Szent-Györgyi identified the anti-scorbutic factor as ascorbic acid (Fig. 5.9).

Ascorbic acid and its reduced form, dehydroascorbic acid constitute an important redox system. Most animals are able to synthesize ascorbic acid from glucose. Humans, monkeys, guinea pig, flying mammals and some birds (e.g. sparrow) are exceptions before they lack **L-gulono-τ-lactone oxidase**, the last enzyme of the ascorbate biosynthesis.

Ascorbic acid affects the activities of a number of me-

talloenzymes providing electrons to their function (Tab. 5.8). Vitamin C is not bound firmly to these enzymes (it is not a coenzyme) but keeps their metal ion in reduced state. The most important reaction of this type is the hydroxylation of proline and lysine residues in tropocollagen molecule, an essential step in the postsynthetic pathway leading from tropocollagen biosynthesis to the formation of collagen fibers. In addition to the involvement in this enzymatic reaction ascorbic acid enhances the intracellular synthesis of tropocollagen and its excretion in the extracellular space.

Tab. 5.8. Enzymatic reactions influenced by ascorbic acid

PROCESS	REACTION	ENZYME
Collagen synthesis	proline hydroxylation	Prolyl-4-hydroxylase Prolyl-3-hydroxylase
	lysine hydroxylation	Lysyl hydroxylase
Carnitine synthesis	2 hydroxylation steps	Trimethyllysine hydroxylase Butyrobetaine hydroxylase
Noradrenaline synthesis	hydroxylation	Dopamine monoxygenase
Peptide hormone activation	amidation with glycine	Peptidylglycine amidating monoxygenase
Tyrosine catabolism	4-hydroxyphenyl pyruvate --> homogentisate	4-hydroxyphelyl pyruvate hydroxylase

Ascorbic acid is an important **antioxidant** and can scavenge many types of free radicals and oxidants. Furthermore it is able to regenerate the oxidized form of tocopherol in membranes. In certain circumstances, however, the ascorbate - dehydroascorbate cycle can turn in the opposite direction and in this case (e.g. in iron overload) the cycle acts as a dangerous prooxidant.

Despite considerably progress at biochemical level not all physiological effects of ascorbic acid are well understood and some of them are controversial (Tab. 5.9) There is also an ongoing discusssion about recommended or optimal dose of vitamin C. Proponents of megadoses (> 1 g ascorbic acid per day) do not surrender despite the lack of hard scientific evidence of any beneficial effect of such high doses. Ascorbic acid is absorbed by a limited-capacity mechanism in the small intestine. From a dose of 100 mg about 95 % is absorbed but from 5 g only 20 %, that is about 1 g.

Tab. 5.9 Physiologic and disease-preventing functions of ascorbic acid

FUNCTION	RELATED BIOCHEMICAL ACTIVITY
Extracellular matrix metabolism (vessel wall integrity, bone formation, wound healing)	Collagen biosynthesis
Immune reactions (phagocytosis, common cold prevention and treatment)	Not known
Drug metabolism in liver	Induction of enzymes
Cancer prevention	Antioxidant
Prevention of diabetic complications	Antioxidant
Prevention of cataract	Antioxidant
Alleviation of symptoms of rheumatoid arthritis	Antioxidant

According the latest recommendations of National Research Council in USA the RDA should be 60 mg for healthy people and slightly more for pregnant women and children. The dose should be elevated during infections and in some chronic diseases (e.g. diabetes).The advice for smokers to take eleva-

ted doses of C vitamin is questionable because it can give them a false feeling of being protected against lung cancer.

Good sources of C vitamin are fresh fruits (sorts of citrus genus, kiwi) and vegetables (cabbage, potato, green paprika). Cooking, prolonged storage and oxidation easily destroys ascorbic acid in these foodstuffs.

In severe vitamin C deficiency two groups of symptoms occur, but both are related to collagen metabolism:

* **the fragility of the vessel wall** with following hemorrhages into the skin (petechiae), bleeding from the swollen gums and around the hair follicles;

* **the impaired development of bones** - separation of periosteum from cortex with hemorrhages, lesions in the epiphyseal - diaphyseal junction. These pathological processes manifest as pain of bones and joints. Teeth may fall out because of alveolar bone resorption.

Marginal vitamin C deficiency with nonspecific symptoms as weakness, general malaise, possible immune dysfunction, low antioxidant capacity and danger of cancer development is common in poor urban population, people on strict marobiotic diet, old people on "tea and toast" diet, children reared on cow's milk and in alcoholics.

THE FAT SOLUBLE VITAMINS

Retinol (vitamin A)

The aldehyde derived from vitamin A (retinal, Fig.5.10a) has a very important function in the biochemistry of vision as a coenzyme-like part of rhodopsine and iodopsines. Durig this process the retinal bound to the protein **opsin** (M_r 27 kDa) undergoes cis-trans isomerisation (Fig. 5.10b). In addition to this basic function vitamin A has a not yet fully

elucidated effect in cell growth, differentiation and development. It is possible that this is connected with the transport of mannose and galactose moieties to glycoproteins.

Vitamin A deficiency leads to deteriorated adaptation to dark (**night blindness, hemeralopy**), to dessication and ulceration of the cornea and conjuctiva of the eye (**xerophtalmia**) and to dry, vulnerable skin with increased keratinization.

The main sources of vitamin A are liver, fish oil, dairy products and egg yolk. Plants (leafy vegetables, cabbage and especially carrots) contain different orange-colored pigments called carotenoids, from which **β-carotene** is the most effective provitamin of retinol. β-carotene is composed of two tail-to-tail coupled molecules of retinol and acts as an **antioxidant** and a natural **anticarcinogenic agent**.

In developing countries vitamin A deficiency is a very common problem and constitute the leading cause of blindness in young children. In other countries alcoholics, poor old people on insufficient diet are vulnerable to vitamin A deficiency. It can be a consequence of **impaired intestinal fat absorption** (e.g. pancreatic disease, biliary obstruction, sprue and uclerative colitis) as well. Zinc deficiency interferes with the conversion of retinol to the aldehyde form, retinal and may intensify the symptoms of the vitamin deficiency.

High doses of vitamin A are toxic (with adverse effects on the skin. liver and nervous system) but carotene overdosage leads only to a benign hyperpigmentation of the skin.

Vitamin D

Some years ago vitamin D was considered a simple **antirachitic factor** enhancing the intestinal absorption of calci-

um. According to recent knowledge the active form of vitamin D (1,25-dihydroxy vitamin D_3 or **calcitriol** - for nomenclature and abbreviation see Tab. 5.10) is a **steroid hormone** without any direct effect on calcium absorption.

Tab. 5.10. Vitamin D and its metabolites

Name and synonyms	Abbreviation	Serum concentration
Calciferol Vitamin D	D	1.2 - 2.0 mg/l
Cholecalciferol Vitamin D_3 Calciol	D_3	
Ergocalciferol Vitamin D_2 Ercalciol	D_2	
Calcifediol 25-hydroxy vitamin D Dicalciol	25(OH)D	20 - 30 mg/l
Calcitriol 1,25-dihydroxy vitamin D Tricalciol	$1,25(OH)_2D$	25 - 45 ng/l (!)

There are two possibilities to obtain sufficient amount of the precursors of this compound:

* **photoconversion** of 7-dehydrocholesterol, a normal constituent of the skin to **cholecalciferol** through action of sunlight. The effective wavelength (250 - 300 nm) is in the UV region (Fig. 5.11);

* **oral intake of cholecalciferol or ergocalciferol**. Cholecalciferol is found in butter, egg yolk, fish oil and liver; whereas ergocalciferol is of plant origin.

In the next step both compounds are hydroxylated in the position 25 in the liver, transported to the kidneys and con-

verted here in a tightly regulated second hydroxylation step (position 1) into active form (Fig. 5.12). The concentration of the active hormone in the blood is about thousand times lower than the concetration of its precursors.

Calcitriol* binds to a **specific receptor in the nuclei** of target cells. There are receptors not only in the cell nuclei of known effector organs of the calcium metabolism (intestinal epithel, kidney tubuli and bone) but also in the cells of immune system, striated and smooth muscle, endocrine and liver cells which suggest to date unrevealed effects of this peculiar hormone. The binding of calcitriol to its nuclear receptor triggers the biosynthesis of **proteins responsible for calcium binding and transport - CaBP**.

In vitamin D deficiency (due to lack of sunlight or disturbances of intestinal fat absorption or dietary insufficiency) in children **rickets (rachitis)** and in adults **osteomalacia** develops. Both conditions are characterized with decreased absorption of calcium from the intestinal tract and disturbance of mineral deposition in the bones. The bones become therefore soft and deformed. In children growth is retarded and the skeleton is deformed.

The impaired absorption of calcium is not caused by the deficiency of vitamin D itself but by the decreased biosynthesis of calcium binding proteins. In the light of recent knowledge it is possible to understand the pathogenesis of **vitamin D resistant rickets** - due to the inherited deficiency of the calcitriol nuclear receptor.

---

* The precursor of the active form already has one OH group therefore after 2 further hydroxylation steps it has altogether 3 - it is expressed in the term trikalciol or kalcitriol

In contrast to most other vitamins the interval between the optimal and toxic dose of vitamin D is narrow - a tenfold overdose (50 - 100 mg for several weeks) already can lead to hypervitaminosis. Its main features are gastrointestinal complaints, mobilisation of calcium from bones and calcium deposition into the soft tissues.

The calcium homeostasis is regulated by calcitriol and two other hormones, namely **parathormone** from parathyroid glands and **calcitonin** from the thyroid - the detailed description of their mutual interactions is beyond the scope of this chapter.

Vitamin E

Vitamin E belongs to **tocopherols** consisting of a hydroxychroman moiety and three isoprene residues (Fig. 5.13). In plants a lot of tocopherol isomers occur differing in the number of methyl residues on the hydroxychroman part of the molecule. The physiologically effective isomer is 5,7,8-trimethyltocol or **D-α-tocopherol**. The biochemical and physiological role of E vitamin was elucidated only recently as one of the most important **antioxidants** and **free radical scavengers**. The special importance of this lipid soluble compound is due to its site of action - embedded into biomembranes and lipoprotein particles it protects the unsaturated fatty acids from peroxidation. If tocopherol is oxidized in this process, ascorbic acid can regenerate it.

Tocopherol was discovered as an essential factor maintaining reproductive function in rats. Although no clear-cut deficiency state was described in humans, the role of vitamin E in pathological processes due to **oxidative damage** (Chapter 6.1) was postulated. Its effectiveness against accelerated

atherosclerosis is probable but expectations to prolong human life or enhance male sexual performance with vitamin E pills belong to the world of medical quackery.

The main sources of tocopherols are green leafy plants, wheatgerm oil and rice. In contrast to other fat soluble vitamins fish oil does not contain tocopherols.Vitamin E is also added to vegetable oils and margarine partly to protect them from oxidation, partly as a food additive.

Vitamin K

As vitamin K a group of similar compounds is called, all derivatives of naphtochinone exerting **antihemorrhagic** function (Fig. 5.14). Vitamin K acts as a coenzyme in the **postsynthetic carboxylation of τ-glutamic acid moieties** in precursors of plasmatic clotting factors II (prothrombin), VII, IX and X, synthesized in the liver. These carboxyl groups make the binding of calcium to the clotting factors possible and the bound calcium is essential to the proper function of the clotting system. Intestinal bacteria synthesize enough vitamin K to cover the requirements of healthy humans. Bleeding disorders due to deficiency of K vitamin can occur in malabsorption, in hepatic disease or as a consequence of antagonists as **dicumarol**.

5.4. DISTURBANCES OF TRACE ELEMENT METABOLISM

THE ELEMENTS OF LIFE

The bulk of human and animal body consists of 6 main biogenic elements: carbon, hydrogen, oxygen, nitrogen, phosphorus and sulphur (Tab. 5.11). The first four comprise 99% of

Tab. 5.11. The elements playing important role in human physiology and pathology

GROUP	ELEMENT				
	BIOGENIC	ELECTROLYTE	TRACE a	TRACE b	TOXIC*
I	$_{1}H$	$_{11}Na$ $_{19}K$	$_{29}Cu$		$_{47}Ag$ $_{79}Au$
II		$_{12}Mg$ $_{20}Ca$	$_{30}Zn$		$_{4}Be$ $_{48}Cd$ $_{56}Ba$ $_{80}Hg$
III				$_{5}B$	$_{5}B$ $_{13}Al$
IV	$_{6}C$		$_{50}Sn$	$_{14}Si$	$_{82}Pb$
V	$_{7}N$ $_{15}P$		$_{23}V$		$_{33}As$ $_{73}Ta$ $_{83}Bi$
VI	$_{8}O$ $_{16}S$		$_{24}Cr$ $_{42}Mo$	$_{34}Se$	$_{24}Cr$ $_{34}Se$ $_{42}Mo$
VII		$_{17}Cl$	$_{25}Mn$	$_{9}F$ $_{53}I$	$_{9}F$ $_{35}Br$
VIII			$_{26}Fe$ $_{27}Co$ $_{28}Ni$		$_{26}Fe$ $_{27}Co$ $_{28}Ni$

* The same element may be an important trace element and a dangerous toxin at the same time. The difference is due to the dose and the compound form of the element. (Compounds containing other elements may be also toxic). On the other side toxic elements in proper compound form and appropriate dosage often act as therapeutical agents

a Metallic trace elements - with the exception of tin all belong to the group of the transient metals

b Nonmetals

all atoms of the body as building stones of water, protein, lipid and carbohydrate molecules. In body fluids and in the cytoplasm of cells 5 other elements fulfill important functions as electrolytes. Sodium, potassium, magnesium and calcium are cations whereas chloride is the only elementary anion (the other anions are compounds).

A great number of other elements plays an important role in different physiological functions, although they are present in the body in minute amounts, from 5 g (iron) down to 0.1 mg (vanadium). They are called **trace elements** and their list is given in the third part of Tab. 5.11. Most of them (8) are transition metals characterized by strong propensity to form complexes.

All trace (and biogenic) elements belong to the lighter ones - only four of them have atomic numbers higher than 30 (selenium, tin, molybdenium and iodine).

The occurence of an element in the body does not mean inevitably that it is an **essential trace element**. Non-essential elements from soil, food and water can be present in tissues without any function or as toxins. Trace elements themselves are toxic (see Chapter 4 and Tab. 5.11 - last column) at concentrations higher than optimal and sometimes when they are administered in an inappropriate compound form (e.g. cobalt or chromium).

Some trace elements are abundant in the soil and in the plants (e.g. boron, silicium and manganese) and therefore their deficit is hardly expectable because they circulate in the food chain. The occurence of other elements varies considerable among different geographic areas and accordingly both their harmful accumulation and deficit can occur (e.g. selenium and molybdenum).

RECENT KNOWLEDGE AND UNANSWERED QUESTIONS ON THE TRACE ELEMENT METABOLISM

Although our knowledge on the distribution of trace elements in the body and their function at the biochemical level is quite advanced, there is a lot of uncharted territory in this exciting field between chemistry and medicine and in the near future considerable progress in understanding of the following issues can be expected:

* **The physiologic role of some trace elements** as boron, silicium, fluoride, vanadium is far from being elucidated and even the thoroughly studied elements have some unknown functions, e.g. the role of zinc in taste and smell reception.

* **Complexes of trace elements with organic and biological macromolecules.** It is evident that transient metals cannot exist in free (ionic) form in the body. The structure of complexes which form prosthetic groups of enzymes and other metalloproteins is mostly elucidated (Tab. 5.12). Little is known, however, about the structure and the properties of complexes of trace elements which are not firmly bound to specific proteins.

Tab. 5.12. Firmly bound trace elements in metalloenzymes and selenoproteins

ELEMENT	ENZYME
Heme iron	Hemoglobin[1]
	Myoglobin[1]
	Cytochromes
	Catalase
Nonheme iron	Some dehydrogenases
	Ferredoxin
Copper and zinc	Superoxide dismutase (cytosolic)
Copper	Ceruloplasmin[2]
	Lysin oxidase
	Tyrosinase
	Hemocyanin[3]
Zinc	Carboanhydrase
	Carboxypeptidase
	Some dehydrogenases
	DNA/RNA polymerases
Manganese	Superoxide dismutase (mitochondrial)
	Arginase
	Pyruvate Carboxylase
	Galactosyltransferase
Cobalt in corrine	Homocysteine:methionine methyltransferase
	Ribonucleotide reductase (bacterial)
Molybden	Xanthine oxidase
	Nitrate reductase (plant)
Nickel	Urease
Chromium	Phosphoglucomutase ?
Selenium	Glutathione peroxidase

Notes
1 Not enzymes, but posses similar properties as the enzymes
2 Both transport and catalytic function
3 Oxygen carrying protein of snails

* **The circulation of the trace elements in the body.** With the exception of iron, zinc, copper and iodine litlle is known about the factors which influence and regulate the absorption, transport, distribution and excretion of the trace elements. These factors determine the overall balance of the given element and every disturbance of the balance can lead to deficiency syndrome or chronic intoxication.

* **The circulation of the trace elements in the biosphere.** Although it is not a medical issue, knowledge in this topic can be useful in understanding deficiency states and harmful accumulation of trace elements in the human body. Mining and metal industry have disturbed the natural cycles of some elements and pose ecological threat with possible health effects.

* **Biochemical markers of trace element metabolism.** Although modern methods enable precise measurements of very low concentrations of elements in biological materials, the sole concentration of a trace element in blood plasma or other body fluids reveal very little about the metabolism of the given element.

* **The mutual interactions among trace elements.** Some interactions (e.g. between iron and copper in erythropoesis, zinc and copper in inflammation, molybdenium and copper, etc.) are known but these are only the first examples of a yet hidden complex network of mutual interactions with tremendous physiological importance.

IRON METABOLISM

The most abundant trace element (Tab. 5.13) has a particularly interesting cycle in the body. Human red cells live 120 days and therefore daily 0.8 % of the old red cells are

Tab. 5.13. The distribution and balance of the iron in human body

DISTRIBUTION	TOTAL, mg	%
Total amount	4000	100
Hemoglobin	2500	63
Myoglobin	160	4
Enzymes	8	0.2
Stores (ferritin, hemosiderin)	1350	33
Transport (transferin)	5	0.12
BALANCE	mg/d	%
turnover (Hb)	20 - 25	100
usual losses	1 - 2	4 - 10
intake (RDA)	10 - 15	100
resorbtion	1 - 2	7 - 20
LOSSES IN WOMEN	mg	
menstruation	30	in 3-6 days
gravidity	300	in 9 months
lactation	180	in 6 months

replaced with young cells. This represent about 6.5 g of hemoglobin and about 20 mg iron. The daily loss of iron in healthy men is, however, only 1 to 2 mg what means that 90 - 95 % of the iron is recirculated and from the gut only the lost amount is absorbed. If the losses are greater due to any physiological or pathological (hemolysis, bleeding) cause, the absorption increases. This mechanism avoids both iron loss and iron overload at the same time but its buffering capacity is limited. In the case of long-term increased iron supplementation iron overload can develop.

Iron enters the lumen of the intestine in the form of complexes in the foodstuffs. Its bioavailability is good from meat and other animal sources (heme iron) but poor from vegetables (e.g. spinach, lentils). The prerequisite of resorpti-

on are the reduction of Fe^{3+} to Fe^{2+} and the presence of hydrochloric acid in the gastric juice. In blood iron circulates bound to **transferrin** a 90 kDa glycoprotein with 2 specific binding sites for Fe^{3+}. The concentration of transferrin in blood is 2 - 3 mg/l and its saturation with iron in healthy people is between 20 - 55 % (Tab. 5.14). The main iron storage protein, **ferritin** is a 480 kDa macromolecule formed in liver and consisting of 20 subunits. Ferritin holds in its central cavity as much as 4500 thousands molecules of ferrous hydroxide and phosphate. The concentration of ferritin in the blood is very low, but it is the best marker of the iron stores of the body.

Tab. 5.14. Biochemical diagnostic markers of iron metabolism

1. Hb CONCENTRATION, HEMATOCRIT AND RED CELL COUNT (160 g/l; 0.45; $5*10^{12}$/l - normal values in adult men)
2a. Fe in serum: m: 14 - 28, f: 12 - 23 µmol/l up to 30 % diurnal variation 2b. Total iron binding capacity - TIBC (Saturation of the serum [= transferrin] with iron) m: 53 - 80, f: 44 - 70 µmol/l 2c. SATURATION INDEX (Fe/TIBC) < 0.2 - iron deficiency > 0.55 - iron overload
3. TRANSFERRIN 2 - 3 mg/l 90 kDa glycoprotein, 2 Fe^{3+}
4. FERRITIN 40 - 50 ng/l 20 subunits per 24 kDa = 480 kDa, 4500 ions of Fe in cavity

Iron deficiency or **sideropenia** is common in women living in poor regions of the world as a consequence of malnutriti-

on, frequent pregnancies and different diseases. Marginal deficiency of iron, however, is not rare in other parts of the world. Diseases of the gastrointestinal tract (achlorhydria, decreased absorption) and chronic, often undiagnosed losses of blood (urogenital diseases, gastric and duodenal ulcus and other gastrointestinal diseases) are precipitating factors whoch lead to the manifestation of iron deficiency in such conditions. The main consequence of iron deficiency is **microcytic hypochromic anemia**. The other signs (changes of skin and mucous membranes, fatigability, paresthesia of nerves) are mostly hidden behind the symptoms of anemia.

Hemochromatosis occurs in two forms. **Primary hemochromatosis** is a recessive genetic disorder due to excessive intestinal absorption of iron leading to its high deposition in all parechymal cells of body. The clinical signs are bronze-colored skin, cardiomyopathy, liver cirrhosis, damage of joints and disorders of endocrine glands (e.g. diabetes). In **secondary hemochromatosis or hemosiderosis** the iron accumulates predominantly in macrophages and not in parenchymal cells. This condition may be a consequence of deteriorated iron cycle in liver cirrhosis or of increased turnover of the red cells in hemolytic anemias and thalassemia. In dialysed patients who usual have very low red cell count and hemoglobin concentration repeated transfusions may cause hemochromatosis as well because the transformed red cells have shortened survival and the iron cycle is disturbed. In these patients both severe anemia and signs of iron overload can occur at the same time.

Recent results of research in cardiovascular diseases revealed that **iron overload** characterized only through elevated

concentration of ferritin is an important **risk factor** of **coronary heart disease** with all its possible consequences. Iron can cause oxidative damage and this is the most plausible explanation of the connection between iron overload and atherosclerosis (see Chapter 6).

COPPER

Copper is present in the active centre of several very important enzymes with redox function (Tab. 5.12). Its RDA is between 2 - 5 mg and the main sources of copper in food are nuts, oysters and sea fish. In the body the liver has the highest concentration of the copper followed by the brain, heart and kidney. Its main excretory route is through bile and only very little copper is excreted in the urine. The main transport protein of copper in blood is **ceruloplasmin**, an α_2-globulin with M_r of 160 kDa carrying 8 copper atoms. Ceruloplasmin exhibits also enzymatic (oxidase) activity. Among other substrates it is able to oxidize ferrous ion to ferric state and this is probable a very important point of interaction between copper and iron metabolism.

Experimental **copper deficiency** in rats causes anemia. In humans copper deficiency can occur as a part of malnutrition and can manifest when the copper supply is inadequate during the recovery from this state . In the patients microcytic hypochromic anemia and leukopenia develop together with brittle bones despite feeding with a diet sufficient in macronutrients and vitamins.

Wilson's disease (hepatolenticular degeneration) is an autosomal recessive disorder characterized by deficiency of cerulopasmin (Tab. 5.15). The improperly complexed copper (in the form of readily diffusible complexes with aminoacids and

Tab. 5.15. Biochemical indices of Wilson's disease

INDEX	NORMAL VALUE	VILSON'S DISEASE
Ceruloplasmin in plasma	1.8 - 2.5 µmol/l (290 - 400 mg/l)	< 1.8 µmol/l
Copper in plasma	16 - 31 µmol/l	< 16 µmol/l
Copper in liver		> 100/150 µg/g
Copper in urine		> 100 µg/day

nonspecific proteins) accumulates in tissues and damages the brain (degeneration of nc. lentiformis leading to motor disturbances) and the liver. In the outer edge of cornea a greenish pigment, the **Kayser - Fleischer ring** is deposited. The excretion of copper in urine is increased but the biliar and fecal excretion is below normal.

ZINC

Zinc is an important constituent of active centers of more than 100 enzymes and for others acts as an activator. Zinc is also essential for the synthesis of nucleic acids and function of genes. **Zinc fingers** are parts of nuclear receptor proteins and are essential to the binding of the receptors to the hormone response elements on DNA. The fingers are specific short sequences of aminoacids fixed in a finger- or loop-like spatial configuration by a zinc ion chelated with two pairs of cysteins.

Zinc furthermore has a role in maintaining insulin in active hexamere form in the secretory granula of B cells of the islets of Langerhans and also plays a not fully elucidated role in the function of smell and taste receptors.

The main sources of zinc in food are: liver, kidney, mushrooms and red beet. The RDA is between 12 - 15 mg but

zinc absorption may be imparied from different reasons. As an example phytates from cereals form complexes with zinc which are not absorbed from the gut.

Zinc deficiency in experimental animals is characterized by fetal malformations, growth retardation, hypogonadism, impaired immune function and wound healing.

Human zinc deficiency occurs in some parts of the Middle East due to the high amount of cereals consumed. The affected infants are small for their age, have a delay in sexual development, small testes and sparse pubic hair. In cirrhotics and patients with nephrotic syndrome marginal zinc deficiency can occur due to increased losses of this trace element.

CHROMIUM

Chromium is transported by a specific protein - **siderophilin**. In the cells chromium activates the enzyme phosphoglucomutase and interacts in a not clarified way with the SH groups of biomembranes.

The total content of chromium in the body (≈ 1 mg) decreases with age and in experimental chromium deficiency insulin resistance develops with impaired glucose tolerance. It is possible that there is a causal connection between the age-dependent decrease of chromium content and the deterioration of glucose tolerance in the elderly. Administration of chromium (as complexes of Cr^{3+}) can improve the glucose tolerance in humans.

VANADIUM

Sea animals, some bacteria and posionous mushrooms contain high concentration of vanadium. Recently an insulin-like effect of vanadium compounds was discovered but its is not yet known if it is a physiological or pharmacological effect.

In humans vanadium deficiency syndrome is not known.

MANGANESE

Manganese is integral part of some metalloenzymes and is involved in the metabolism of cartilage mucopolysaccharides. Plants are abundant in this element and therefore its deficiency can hardly develop. One or two cups of tea already cover the daily requirements of manganese. In acid rain the concentration of manganese is high and pose an ecologic problem

COBALT

Insufficient amount of cobalt in the food of ruminants in some parts of Australia and New Zealand can cause disease. For humans cobalt is essential only as **cobalamin** (-> vitamins). Cobalt salts used in the past in the treatment of refractery anemia or as a foam-stabilizing additive to bear caused serious intoxications characterized by damage of the heart muscle.

MOLYBDENIUM

An antagonist of copper. In some parts of word the soil contains high concentration of molybdenium and cause diseases in cattle. Although it is a constituent of certain enzymes, its deficiency in humans is not known.

NICKEL

No deficiency syndrome is known. Nickel salts are not very toxic but can cause allergic dermatitis. Cigarette smoke contains significant amounts of nickel carbonyl which contributes to the risk of lung cancer in heavy smokers.

TIN (Sn, stannum)

The only non-transient trace metal with probable function in bone metabolism.

SELENIUM

Selenium is structural component of the active centre of the **glutathione peroxidase**, a key enzyme of the antioxidant defense in the cells, some related enzymes found in plasma and of type I **iodothyronine deiodinase**, an enzyme of thyroid gland dealing with metabolism of another trace element - iodine.

In striking contrast to all other trace elements Se is not coupled with these enzymes after their synthesis but is incorporated into the polypetide chain during translation as a selenocysteine.

The main sources of selenium are garlic, yeast and sea fish. The RDA is about 70 µg for men and 50 µg but the difference between optimal and toxic dose is small.

Severe selenium deficiency due to low concentration of Se in the soil is common in some regions of China. It leads to degenerative myocardiopathy (**Keshan disease**).

The physiological role of selenium is plausibly related to the role of glutathione peroxidase and to the function of the antioxidant defense system as a whole. Oxidative damage (Chapter 6) might be an important causal factor in atherosclerosis, carcinogenesis and other pathological processes. Selenium might be beneficial in prevention of these pathological processes if **selenium deprivation** is present but its use as an overall remedy is not scientificallly founded.

Selenium overload (occuring naturally in some parts of Ireland, USA, Canada and South America) leads to **selenosis** in animals with gastrointestinal symptoms and cachexia.

IODINE

An average human body contains about 50 mg of iodine

which is accumulated mainly in the thyroid (10-20 mg) as anorganic iodine and as thyroid hormones bound to storage protein. The main sources of iodine are sea fish and alga, egg yolk. The recommneded daily dose is between 100 - 200 µg. The food contains mainly jodide salts which are enzymatically oxidized in the thyroid to I_2. The thyroid hormones (triiodthyronine, reverse triiodthyronine and thyroxine are derivatives of the aminoacid tyrosine. The iodination takes place in the molecule of thyreoglobulin and the hormone is released through proteolysis. The plasmatic concentration of iodide in normal conditions is between 8 - 10 µg/100 ml. A good marker of iodine balance is iodine excretion in urine - it should be above 100 µg per day. In iodine deficiency the percentage of monoiodthyrosine and triiodthyrosine is increased as compared with the amount of diiothyrosine and thyroxine.

On the earth iodine deficiency and its consequences (endemic goiter, thyroid hypofunction with mental retardation) threaten more than 500 million people. In some regions of this country fourty years ago the occurence of endemic goiter was about 70 %. Large-scale preventive measures (jodidation of salt; 25 mg KI/kg NaCl) changed this picture dramatically. In addition to iodine deficiency **strumigens** found in certain foods can interfere with iodine metabolism causing thyroid hypofunction. The occurence of inborn enzyme defects of iodine metabolism is a rare but very severe pathologic condition.

FLUORINE

This halogen is a metabolic toxin but in small concetration (1 - 2 mg/day) has an important role in caries preventi-

on. Its effect is probable threefold:

* Already **0.1 mmol/l fluoride blocks the glycolytic enzyme enolase of the bacteria dwelling in the oral cavity**, whereas this concentration has no effect on the glycolysis in the human cells.

* **Fluoroapatite**, which normally forms 10 % of tooth enamel is **more resistant to acids** and other damaging agents than hydroxylapatite.

* **Fluorine enhances the conversion** of amorphous calciumphosphate into crystallic **apatite** form.

The supply can be realized through fluoridation of tap water (optimal concentration 0.08 mmol/l), mouthwash, tooth pasta or giving KF pills to children. Too high fluoride supplementation blocks the mineralisation of bones and teeth and enhances caries formation **(fluorosis)**.

BORON AND SILICIUM

Both are important elements for plants, but boron is toxic for animals and humans. They have certain role in the metabolism of calcium and affect bone formation. Their deficiency is not known.

5.5. OBESITY

It is one of the tragic ironies of modern civilization that while roughly one-third of the people in underdeveloped countries are subject to various forms of food shortage, the most serious nutritional problem in the more affluent countries is overnutrition leading to obesity. The prevalence of obesity is rather difficult to assess, since there is no objective criterion to define the limits of body fat content.

DEFINITION AND MEASURE

Obesity is a condition in which the relative proportion of fat in the body is abnormally increased. Another term - **overweight**, which is used interchangeably with obesity, signifies an increase of body weight above an arbitrary standard ussually defined in relation to height. To determine whether a person is obese or simply overweight (due to increased muscle bulk for example in athletes or in manual workers) one needs techniques and standards for quantitating body fat.

From anthropometric measurements comparing height with weight, the **body-mass or Quetelet index (BMI)**, which is the most highly correlated with degree of body fat, is preferred. BMI is derived from body weight in kilograms divided by the square of height in metres (kg/m^2). A desirable BMI for general population lies between 19 and 25. According to BMI, people can be divided into four grades of obesity (Tab. 5.16). Persons with a BMI of 25 to 30 kg/m^2 have a low risk of health problems, those with a BMI of 30 to 40 kg/m^2 have a moderate risk, and those with a BMI above 40 kg/m^2 have a high risk.

Tab. 5.16. Body mass index and grades of obesity

BMI = body mass in kg/(body height in m)^2	
BMI	GRADE OF OBESITY
< 25.0	0
25.0 - 29.9	I
30.0 - 40.0	II
> 40.0	III

As over half of the fat in the body is deposited under skin, the most widely used criterion for the diagnosis of obesity is the **thickness of skinfold**. The skinfold thickness is measured over four separate sites (biceps, triceps, subscapular and suprailiac) and then by applying the equations derived from underwater densitometric measurements the proportion of body fat is estimated.

A number of factors, including age, sex, enviromental temperature, and the degree of physical activity, determine the relative proportion of fat in the body. By age 18, the male body is about 15 to 18% fat, and the fermale body is about 20 to 25% fat. The body content of fat in both sexes after puberty increases. Acceptable body fat content in the general population is 10 - 20% in men and 20 - 30% in women.

It has been suggested that fat distribution may be a more important factor for morbidity and mortality associated with obesity than obesity per se. The higher the proportion of upper body fat, the greater the risk of health problems. Fat distribution can be assessed simply from **waist to hip ratio (WHR)**, i.e. the ratio of circumferencial measurement at the waist (midway between the iliac crest and lowest rib) to that around the hips (at the level of trochanters). In most populations, WHR is continuously distributed within the range 0.7 - 1.0. A WHR greater than 1.0 in men and 0.8 in women indicates upper body obesity.

ETIOLOGY

Excess body fat is generated when the energy intake exceeds that expended through basal metabolic rate (usually about 75 % of total energy expenditure), physical activity (10 - 15%) and thermogenic response to food (10 - 15%) and other

stimuli (stress, cold, etc.). An imbalance of only 1% in energy balance represents weight gain of 1 kg every year. As adipose tissue containes about 75% of fat, which is the main form of energy store, it means, that overweight subjects have stored approximately 30 000 kJ (7 000 kcal) per kilogram excess weight. Factors contributing to the energy imbalance are numerous and probably exist in differing combinations among obese individuals.

The basal metabolic rate (BMR) varies as usual as 25 - 30% from individual to individual. If a difference in metabolic rate can be as high, it is clear that at a given energy intake one individual may gain weight and another may lose it.

Energy is also required for muscular contraction at various forms of **physical activity**. The efficiency of muscular work (the proportion of exercise-produced energy that is used for work) is about 30%, and is the same for lean and obese subjects, but most obese subjects are usually less physically active.

As for expenditure of energy after food (former called specific dynamic action of food), **thermogenic responses** are small per se, and differences between lean and obese individuals are small to nonexistent. There are, however, differences in energy expenditure after **overfeeding**.

In studies in lean humans significant overfeeding (of the order of 500 kJ extra calories daily) for about 10 days or more may lead to energy wastage, but no similar energy wastage has been found in studies of overfeeding done in obese volunteers. The calories required to maintain a previosly lean individual at an overweight level is much higher than that

required to maintain an already obese individual at the same overweight level. While the reason of this is unclear, it does suggest an increased "efficiency" of at least some obese subjects.

There is not much experimental evidence to date explaining why some obese people lack a protective mechanism (i.e. heat dissipation) that lean persons posses if they overeat. There are, however some speculations concerning for example an increased activity of so-called **substrate cycles** in lean and decreased activity of those in obese individuals. The mechanism of a substrate cycle can be illustrated in the phosphorylation and dephosphorylation of glucose: the energy of ATP consumed in the phosphorylation of glucose by the hydrolytic cleavage of glucose-6-phosphate is released in the form of heat; the repeating of the cycle leads to the wastage of excess energy instead of storing it as a fat. (Fig. 5.15).

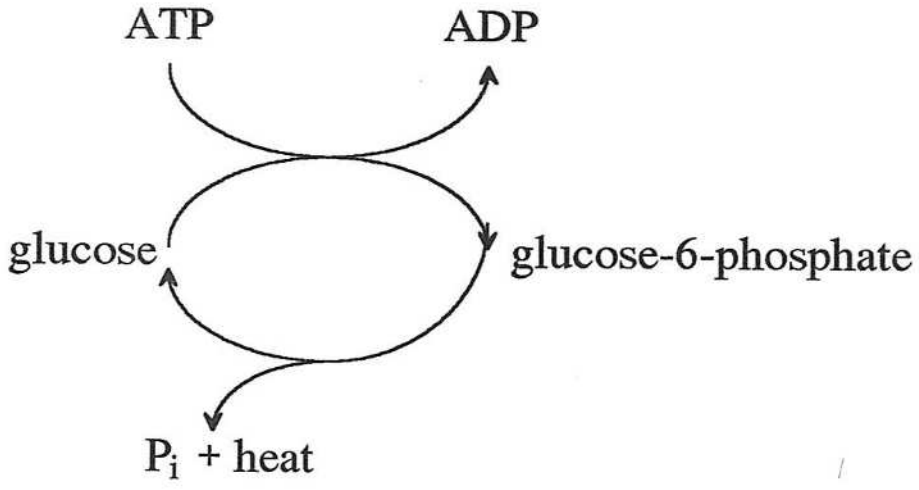


Fig. 5.15. Substrate cycle illustrated as the phosphorylation and dephosphoration of glucose.

Another example is the possible difference in **energy-requiring transport systems**. The energy requirements of the most widely distributed active transport system (Na^+-K^+ ATPase) is 20 - 45% of basal energy requirement of the body; if less energy is expended through pumping sodium in exchange for potassium, then more energy would be available to be stored as fat.

Variations among individuals in body energy gains after overfeeding are undoubtedly influenced by the genotype. This effect seems to be even more important for the determination of the sites of fat accumulation. Obese people tend to have more visceral fat and obese men have more visceral fat on the average than obese women.

The role of **genetic factors** in the development of obesity has been supported by experiments with animals, as well as by studies on body weight in families of obese persons, studies of twins, of adopted children and their adoptees. This role can be either in direct transmission or in providing the biochemical and physiological mechanisms through which enviromental factors can operate.

Enviromental influences which must be taken into account in connection with excess fat include:

* **family dietary patterns,**
* **decreased level of physical activity,**
* **easy access to food,**
* **social and economic conditions,**
* **cultural and ethnic background,** as well as
* **psychologic influences** (for example using food as a reward or as a means of avoiding threatening situations).

Endocrine disorders are rarely a cause of obesity. The increase of body fat is observed in patients with **Cushing's syndrome, insulinoma, hypoganadism and hypopituitarism.**

Hypothalamic obesity is a rare syndrome in human beings, too, but it can be readily produced in animals. The most common causes of hypothalamic damage in humans which may be associated also with obesity are trauma, malignancy and inflammatory disease.

GROWTH OF ADIPOSE TISSUE

The growth of adipose tissue occurs by an increase in the **number of adipocytes (hyperplasia)** as well as by an increase in the **size of fat cells (hypertrophy)** up to about 1 µg of mass. (Fig. 5.16).

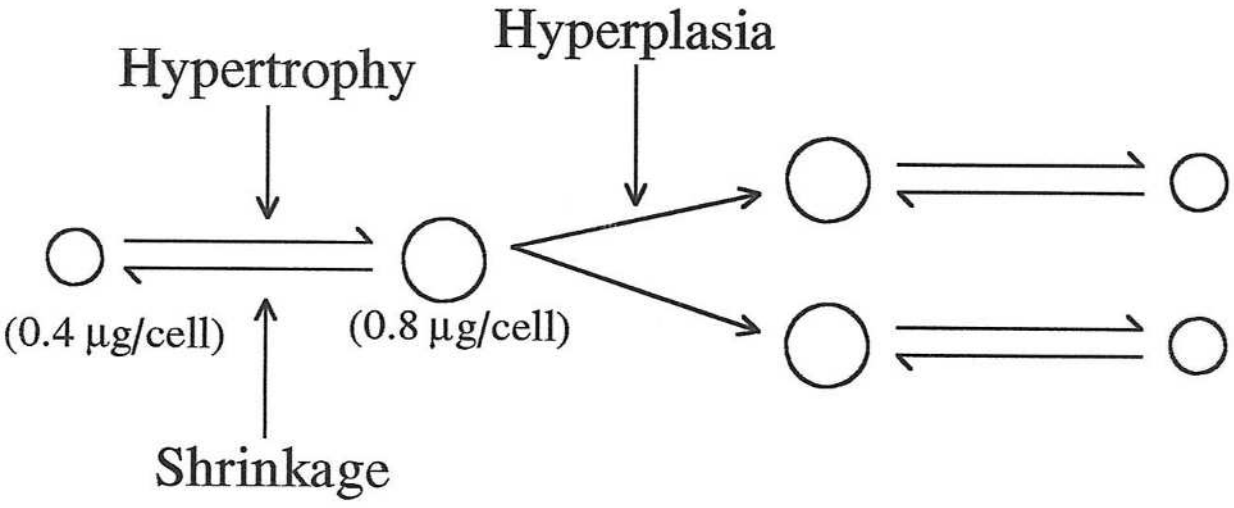


Fig. 5.16. Hypertrophy and hyperplasia of fat cells.

Although fat cell number is partly determined in the early stages of life, the total number of adipocytes, formed from precursor cells (preadipocytes), may increase during later life due to continuing positive energy balance. The size of adipocytes responds to the balance between storage and release of triacylglycerols (TAG). Increased food intake and increased insulin secretion will favour lipogenesis; increased exercise and increased secretion of the lipolytic hormones (the catecholamines as the most potent regulators of lipolysis, as well as glucagon, growth hormone and ACTH) will promote fat utilization.

As the life span of the fat cells is very long, their size varies with the amount of stored TAG, but there is little or no change in their total number. It means that subjects with "hyperplastic" obesity have a lifelong increase in the total mass of fat cells and any weight loss that occurs is by shrinkage of adipocytes (to normal or even below normal) without a decrease in their number.

TYPES OF OBESITY

Two types of obesity based on distribution of fat has been generally accepted (Fig. 5.17):

* **upper body obesity**, also referred to as **abdominal, android or male** obesity, and

* **lower body obesity**, also known as **gluteal-femoral, gynoid or female obesity.**

J.Vague was the first who in 1947 envisioned the importance of regional adipose tissue distribution as the most significant correlate of the metabolic complications of obesity. He suggested that android obesity was, both in men and women, associated with **atherosclerosis, diabetes mellitus and**

gout. Vague's pioneering contribution has been reemphasized by many observations published in 1980s.

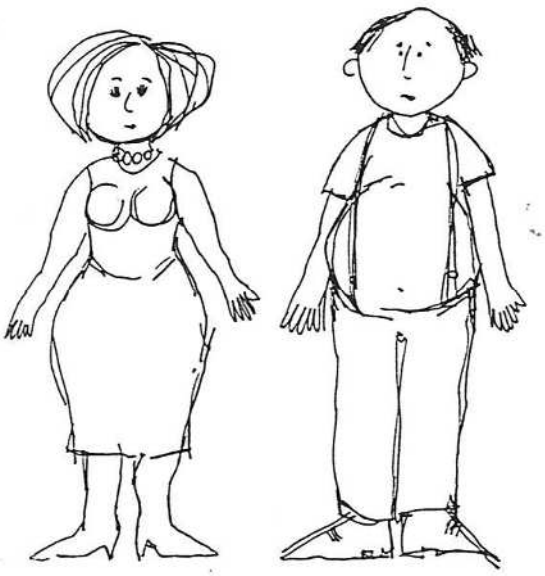


Fig. 5.17. Gynoid (pear-shapped) and android (apple-shaped) ditribution of body fat.

Simple and convenient anthropometric measurements of body fat distribution such as skinfolds and WHR cannot fully account for individual differences in adipose tissue distribution. Computed tomography allows for the precise measurement of cross-sectional areas of deep and subcutaneous (sc) adipose tissue at any site of the body , particularly in the abdominal area. Based on the precise estimation of the topography of the adipose tissue, C. Bouchard in 1991 proposed four different types of human obesity:

The first type is characterized by excess total body mass or body fat without any particular concentration.

The second type is defined as excess subcutaneous fat on the trunk, particularly in the abdominal area, and is equivalent to the **android or male** type of fat deposition.

The third type is characterized by an excessive amount of fat in the abdominal visceral area and can be labelled **abdominal visceral obesity.**

The fourth type is defined as **gluteo-femoral** obesity and is observed primarily in women **(gynoid obesity).**

Men and women with abdominal subcutaneous or visceral obesity (types 2 and 3) tend to be characterized by large fat cells, increased lipoprotein lipase (a key regulator of fat accumulation) activity, enhanced lipolysis, and low antilipolytic effect of insulin. In contrast, lower body fat deposition (type 4) is by differentiation of new fat cells (hyperplasia); this may explain the weight loss difficulties of many women with lower body obesity.

The data concerning the determinants of truncal-abdominal and visceral fat levels in each gender are inconclusive at this time.

HEALTH RISKS ASSOCIATED WITH OBESITY

Impaired social relationships, loss of self-esteem, anxiety, anger, self-doubt, etc. are not the only complications of obese individuals. Since Hippocrates it has been known that obesity is associated with premature death, and since Vague it has been suggested that upper body fat has a significantly worse prognosis than does lower body fat.

The metabolic and clinical alterations observed in abdominal obesity are analogous to the **"metabolic syndrome"** described in 1988 by Reaven, which in addition to obesity includes:

* **insulin resistance,**
* **hyperinsulinemia,**
* **impaired glucose tolerance or non-insulin dependent di-**

abetes mellitus,

* elevated levels of TAG (particularly in VLDL),

* decreased levels of HDL-cholesterol,

* hypertension,

* increased risk of macrovascular disease (atherosclerosis, coronary heart disease).

Although significant associations have been found between indices of abdominal obesity, insulin resistance and dyslipoproteinemia, the mechanisms underlying these interrelationships are not fully understood. What is (are) the causal factor(s) in these interrelationships is not clear.

On the pathway from visceral obesity to disease outcomes free faty acids (FFA) may play an important role. It has been suggested that the high lipolytic activity of omental adipocytes contributes to a greater flux of FFA to the liver through the portal circulation. High FFA levels have been shown to reduce the hepatic extraction of insulin, contributing to the hyperinsulinemia. High FFA levels also stimulate hepatic glucose production and TAG synthesis. The increased availability of glycerol as a substrate for hepatic gluconeogenesis may contribute to the elevated hepatic glucose production. However, there are alterations in carbohydrate metabolism and plasma lipid transport that are likely independent from changes in FFA metabolism. Steroid hormone levels (both sexual and adrenal) and the activity of enzymes involved in lipoprotein metabolism may contribute to the reduction in the catabolic rate of TAG-rich lipoprotein and to the increase of degradation of HDL-cholesterol.

But not every viscerally obese individual will be at high risk of developing diabetes, dyslipoproteinemia and atherosc-

lerosis - all health disorders which have a significant genetic component. In this context, subcutaneous truncal-abdominal obesity and visceral obesity (type 2 and 3) are conditions that appear to unmask and exacerbate existing and probably genetically determined propensity for diabetes, dyslipoproteinemia, and atherosclerosis.

Obese individuals are more likely to develop gallbladder disease, pancreatitis, cancer (endometrial cancer and breast cancer in women and cancer of the colon, rectum and prostate in men are more common in obese than in lean subjects), intertrigo (in rebundant folds of skin), fungal and yeast infections of skin. The increased weight associated with obesity stresses the bones and joints (particularly of the lower extremities and the lower back), increasing the likelihood of arthritis. Sleep apnea and Pickwickian syndrome (hypoventilation, somnolence and polythemia) are prevalent in morbidly obese individuals. Severely obese persons often have varicose veins and venous stasis. Obese hypertensive individuals are at greater risk for congestive heart failure. There is also a strong relation between body weight and serum uric acid level (Fig 5.18).

Almost all health disorders associated with obesity, improve with weight loss.

The causes of **incresed mortality** of obese individuals include coronary heart disease, cerebral hemorrhage, diabetes, digestive diseases, and cancer.

TREATMENT OF OBESITY

The treatment of obese persons is one of the most troublesome and frustrating enterprises, particularly from the long-range standpoint, because the maintenance of a reduced

body weight is a very difficult problem. The "success" of treatment may depend on the severity of obesity and the amount of hypercellularity of the adipocytes in a given person. An individual who is modestly overweight with enlarged fat cells but little proliferation of extra adipocytes can more easily maintain weight loss. The adipocyte hyperplasia of greater obesity may create a much greater problem in maintenance of weight loss.

There is no single effective treatment for obesity. Treatment methods include nutritionally adequate weight loss diet, behaviour modification, exercise, social support and in situations of marked obesity surgical methods.

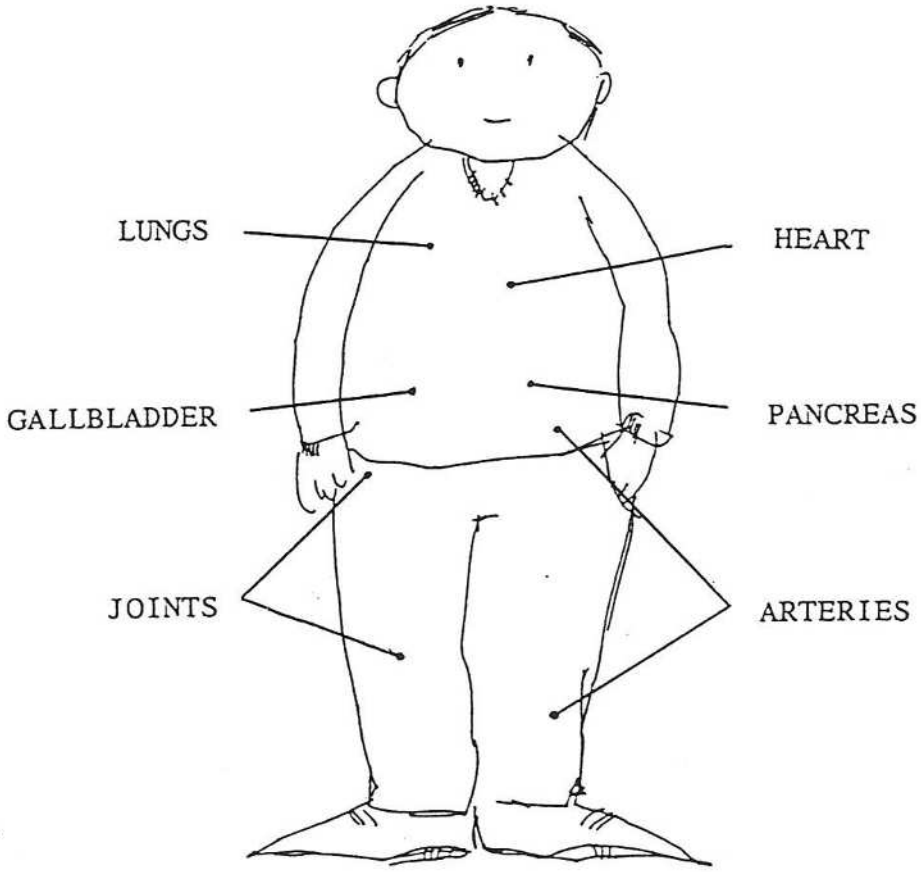


Fig. 5.18. Organs and systems frequently demaged in obese subjects.

6.1. RANDOM POSTSYNTHETIC CHANGES OF BIOLOGICAL MACROMOLECULES

SPECIFIC AND RANDOM PROCESSES

The biosynthetic reactions in which nucleic acids, proteins, lipids and complex carbohydrates are synthesized, are described in every textbook of biochemistry. All steps in these pathways are specific and enzyme catalyzed reactions as well as the metabolism and degradation of these substances.

But what occurs with these molecules in the time elapsing between their synthesis and degradation? Some of them have a short life-span of some hours or a few days (e.g. most intracellular enzymes) but others survive months (haemoglobin and all enzymes of the red cell) or even years (collagen).

Interestingly the most dangerous substances which can damage the biological macromolecules are those essential for higher forms of life - oxygen and glucose, resp. their progeny. They can react with proteins, lipids, carbohydrates and nucleic acids without involvement of catalysts. These reactions obey the basic laws of chemistry but lack the specificity of enzyme catalyzed reactions and are not regulated nor in space neither in time - they occur in a **random (stochastic)** way.

Single random reactions usually do not exert any measurable effect on biochemical and physiological processes. They must cumulate for a long time to come to surface. From the opposite point of view random reactions are probably involved in physiological (aging) or pathological processes (atherosclerosis, complications of diabetes, cataract of the eye lens

and others), where time is a determining factor of their development.

Random reactions damaging biological macromolecules occur postsynthetically (in the case of proteins posttranslationally) and they should be distinguished from specific, enzyme catalyzed postsynthetic reactions (e.g. the hydroxylation of proline and lysine in tropocollagen, the activation of digestive enzymes, clotting factors, the splitting of peptide prehormones, etc.)

THE DUAL ROLE OF OXYGEN IN LIFE

Molecular oxygen, which forms of 21 % of the athmosphere, is one of the prerequisites of higher forms of life on Earth. In ultimate metabolic pathways it undergoes reduction and at the same time substances rich in carbon and hydrogen become oxidized to carbon dioxide and water. During these reactions large amount of energy is released. The final physiological consequence of the aerobic metabolism is that man can survive without oxygen only about five minutes.

However, at the beginnings of the life on the Earth there was no free oxygen at all in the athmosphere. Blue-green algae began form it through photolysis of water about 2.6 billion years ago but the oxygen concentration in the air 1.3 billion years ago was only 0.2 % and 500 million years ago 2 %. As the first primates appeared on the Earth, (about 65 million years ago) the concentration of oxygen was already the same as now.

The employment of oxygen, this energetically highly efficient compound on one side rendered the evolution of higher forms of life possible but on the other side it posed a serious danger to the same creatures. This danger is due to ran-

dom postsynthetic reactions of biological macromolecules with partly reduced and other very reactive forms of oxygen.

THE BIOREACTIVE FORMS OF OXYGEN

The structure of oxygen

The oxygen atom has 8 electrons, 2 on the first and 6 on the second orbital in configuration s^2p^4. In the dioxygen molecule the four "s" electrons occupy 2 and the six of the eight "p" electrons 3 molecular orbitals. The spin of the two remaining electrons has the same sign and therefore they cannot form an electron pair. As every compound with unpaired electron(s) is a **free radical***, the dioxygen molecule is very peculiar, being a **biradical**.

The reduction of oxygen to water

The complete reduction of oxygen (addition of 4 electrons and 4 protons yields water (1).

1/ $O_2 + 4\ e^- + 4\ p^+ \ \text{---> } 2\ H_2O \qquad (4e^- + 4p^+ \text{ ---> } 4\ H)$

Mitochondria of aerobic creatures are able to carry out this reaction (**terminal oxidation**) at relatively low temperature and conserve the released energy in macroergic phosphate bonds of ATP.

The four-electron reduction of molecular oxygen can be divided into four consecutive steps.

Addition of one electron (2a) to oxygen yields **superoxide radical anion** which is a free radical although it has paradoxically less by one unpaired electron as the original oxygen molecule. The superoxide radical is not extremely reactive but it is the precursor of other, more reactive forms of oxygen. Its protonized form is the **perhydroxyl** radical (2b)

---

*Free radical is every atom, molecule or ion with one or more unpaired electrons. Free radicals are paramagnetic and usually highly reactive.

2a/ $O_2 + e^- \longrightarrow \cdot O_2^-$

2b/ $\cdot O_2^- + H^+ \longrightarrow \cdot HO_2$

Addition of the second electron (and two protons) leads to **hydrogen peroxide** (3) which is not a free radical but it is a highly reactive and relatively stable compound diffusible through biomembranes.

3/ $O_2 + 2\ e^- + 2\ H^+ \longrightarrow H_2O_2$

The formal addition of the third electron (4a) creates two compounds, the hydroxyl anion (which is not a free radical) and the **hydroxyl radical** (which is not an ion).

4a/ $H_2O_2 + e^- \longrightarrow \cdot OH + OH^-$

In actual fact this reaction is more complex and is catalyzed by small amounts of transient metals as iron, copper or manganese and is termed the **Haber-Weiss reaction** (4b-4e).

4b/ $Me^{n+} + \cdot O_2^- \longrightarrow Me^{/n-1/+} + O_2$

4c/ $2 \cdot O_2^- + 2\ H^+ \longrightarrow H_2O_2 + O_2$

4d/ $Me^{/n-1/+} + H_2O_2 \longrightarrow Me^{n+} + OH^- + \cdot OH$

The overall reaction:

4e/ $\cdot O_2^- + H_2O_2 \xrightarrow{Fe^{3+}/\ Fe^{2+}} \cdot OH + OH^- + O_2$

The hydroxyl radical is extremely reactive and reacts immediately with every surrounding biological macromolecule. On the other side this high reactivity shortens its lifespan and action radius.

The reduction of oxygen ends with the addition of last electron and one proton (5).

5/ $\cdot OH + e^- + p^+ \longrightarrow H_2O$

Singlet oxygen, free radicals and the bioreactive forms of oxygen

The two inpaired electrons of dioxygen are at the lowest possible energetic level. Through absorption of energy one of

these electrons can change its spin and the molecule becomes excited. According to their spectral properties in magnetic field the nonexcited form is termed as **triplet** oxygen and the two possible excited forms as **singlet** oxygens. Although singlet oxygen does not differ chemically from normal oxygen molecule, it is very reactive. Singlet oxygen in the human body can arise in the process of superoxide radical dismutation (6a), in the Haber-Weiss reaction and in the reaction of hypochlorite with hydrogen peroxide (6b).

6a/ $\cdot O_2^- + \cdot O_2^- + 2\ H^+ \longrightarrow H_2O_2 + {}^1O_2$

6b/ $\cdot OCl^- + H_2O_2 \longrightarrow Cl^- + {}^1O_2 + H_2O$

From this description it is clear that not every partially reduced or excited form of oxygen is a free radical and therefore the proper term for all potentially harmful forms of oxygen, that is for

* **singlet oxygen**
* **superoxide radical**
* **hydrogen peroxide** and
* **hydroxyl radical** is

** <u>bioreactive forms of oxygen</u> or

** <u>reactive oxygen species (ROS)</u>

CAUSES OF ROS FORMATION

Bioreactive forms of oxygen in living organisms can arise as a consequence of numerous exogeneous and endogeneous factors (Tab. 6.1). In this context one should realize two important but often neglected things about free radicals and bioreactive forms of oxygen:

* **Biochemical reactions involving free radicals are common** but this does not appear in the overall reaction scheme (e.g. terminal oxidation or arachidonic acid metabolism).

* **Bioreactive forms of oxygen** act not only as noxious, health damaging agents, but have **several important physiologic functions** (e.g. the respiratory burst of leucocytes).

Tab. 6.1. Causes of reactive oxygen species formation

ENDOGENEOUS CAUSES
Respiratory burst - ROS formation by activated phagocytes
Univalent leakage - escape of partially reduced oxygen species from mitochondria
The xanthinoxidase - xanthine system in **reperfusion damage**
The P450 system in microsomes
Arachidonic acid metabolism
Glycated proteins and **advanced glycation endproducts**
Autooxidation and **redox cycling** of different endogeneous compounds
EXOGENEOUS CAUSES
Ionizing and UV radiation, ultrasound
Ozone, nitrogen oxides and other air pollutants
Some drugs and oxidants (e.g. adriamycine, primaquine, phenylhydrazine)
Ions of transient metals (Fe, Cu, Cd)

DAMAGE OF BIOLOGICAL MACROMOLECULES CAUSED BY ROS

Lipid peroxidation

Double bonds in unsaturated fatty acids are especially prone to oxidation. In the biomembranes the fatty acid residues are in close spatial relationship with each other and this arranegemt allows the **propagation** and the **amplification** of the damage (Fig. 6.1). The consequences of lipid peroxidation at cellular level involves increased rigidity and the deterioration of transmembrane transport systems. Increased entry of calcium into the cell can lead to cell death. In the process of lipid peroxidation highly reactive aldehydes (**malondialdehyd** and **4-hydroxynonenal**) arise and exert further random damage.

Damage of proteins

SH groups are the most susceptible to oxidation in pro-

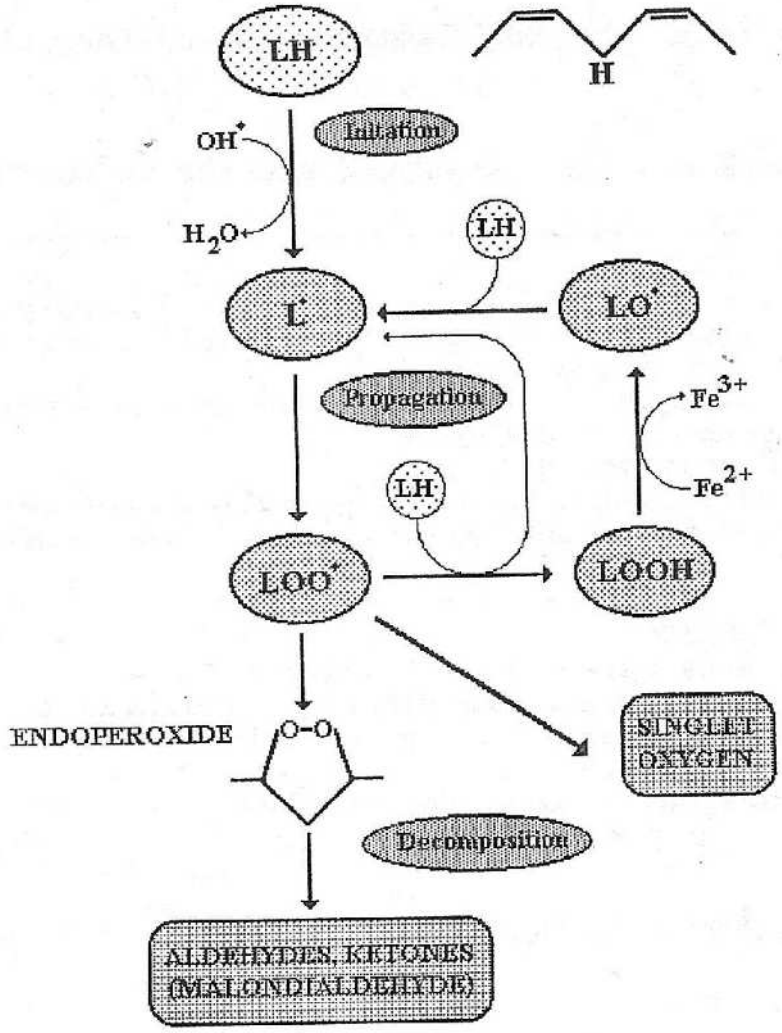


Fig. 6.1. The peroxidation of lipids.

teins but other side chains may be modified as well. As SH groups play often important role in the active centre of enzymes the consequence may be **inactivation of the enzyme**. Of particular importance in this respect is the posssible damage of **antioxidant enzymes**, e.g. glucose-6-phosphate dehydrogenase whith 18, oxidation-prone SH groups.

Bifunctional reagents as malondialdehyde can **crosslink adjacent polypeptide chains** with subsequent changes in protein conformation and function. An example can be oxidized LDL whith impaired binding to the specific LDL receptor.

Damage of nucleic acids

The main consequences of oxidative damage in DNA are changes in base structure, namely formation of 8-hydroxyguanin and 5-hydroxymetyluracil, chain fragmentation and mistaken activation of genes.

Damage of complex carbohydrates of extracellular matrix

ROS damage the proteins of extracellular matrix and cause depolimerization and structural alteration of the complex carbohydrates forming the bulk of it.

THE SYSTEM OF ANTIOXIDANT DEFENSE

Formation of free radicals and reactive forms of oxygen are inevitable side effects of biochemical reactions and living creatures during their evolution mastered methods to keep them under control. Oxidative damage occurs only when the radicals and ROS override the capacity of the defense system or when the defense system is damaged. The whole antioxidant defense system of higher organisms is built as a three-level system, where each level has its own specific mode of action.

The first line of defense

The basic line of antioxidant defense is the proper construction of structures where free radical reactions or oxygen reduction occur. In enzymes these reactions take place in safe depth of their active centres. Multienzyme complexes in mitochondria hand over the partly reduced forms of oxygen and do not allow their escape (univalent leakage) into the cytoplasm. The basic antioxidant principle in the plasma is the proper complexation of metals transferred.

The second line of defense

Despite the safety measures of the firts line the occu-

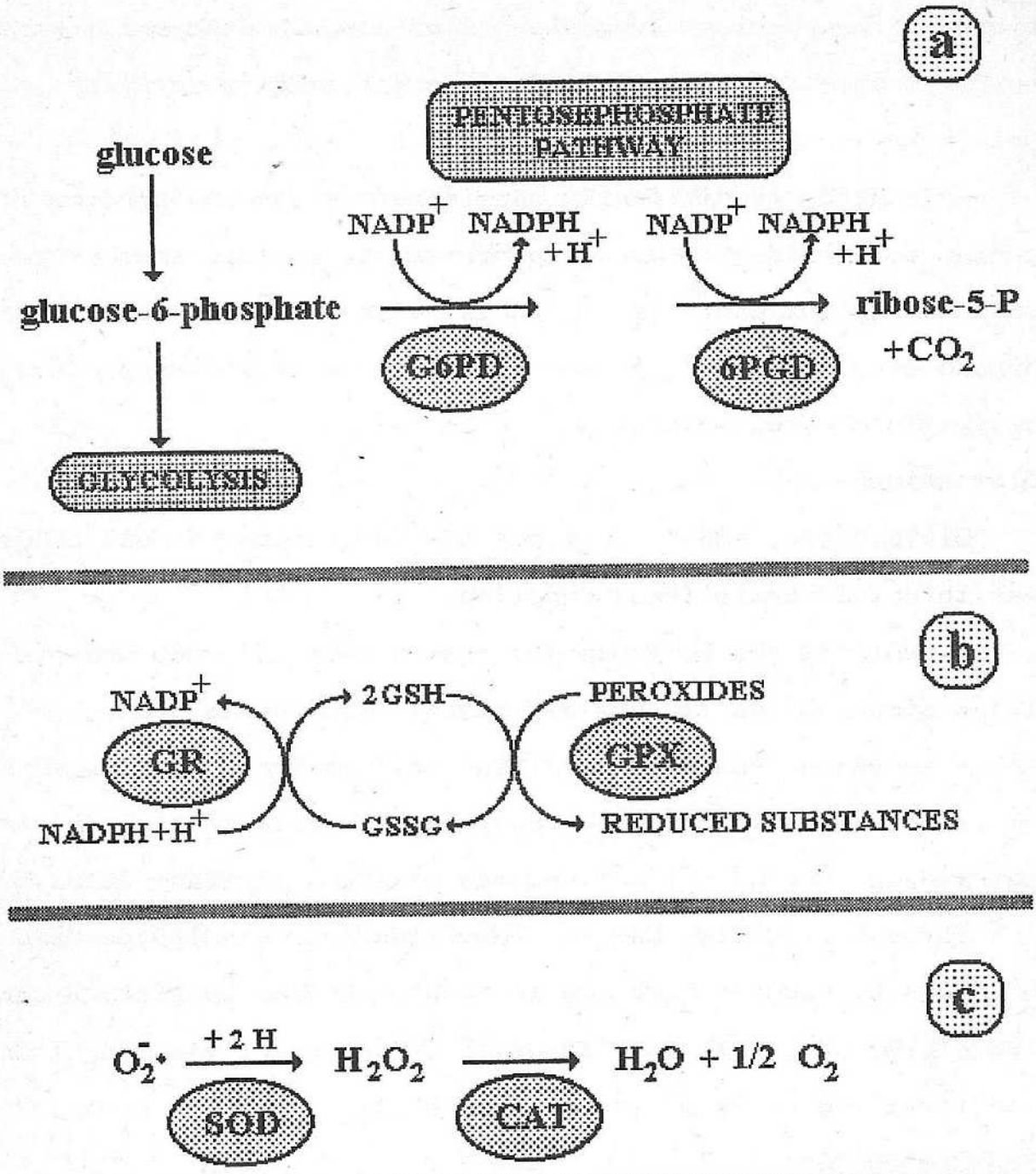
rence of ROS in the body is common and against them a series of active defense mechanisms are at disposal. Some of them are small molecules able to neutralize or scavenge ROS and free radicals, reduce the oxidized groups of proteins, etc. Others are complicated enzyme systems catalyzing decay of ROS (Tab. 6.2 and Fig. 6.2).

Tab. 6.2. The active antioxidant defense systems

LOW MOLECULAR WEIGHT ANTIOXIDANTS AND RADICAL SCAVENGERS
Glutathione (GSH) and other SH-compounds
Vitamin C, Vitamin E, β-carotene
Uric acid, taurine
ANTIOXIDANT ENZYME SYSTEMS
The first two steps of pentose cycle together with the enzymes of the glutathione metabolism
Superoxiddismutase and catalase
Red cell methemoglobin reductase

Exogeneous low molecular antioxidants

The exogeneous natural antioxidants were described in Chapter 5. Ascorbic acid is an important antioxidant of the extracellular and probably also the intracellular space. Tocopherols are embedded into membranes to guard them against lipid peroxidation. The long chain with conjugated double bonds is probably responsible for singlet oxygen quenching and radical scavenging effects of β-carotene and some other carotenoids. Selenium is not ranged among antioxidants in Tab. 6.2 because it acts indirectly, as a constituent of the enzyme glutathione peroxidase. On the other side ebselen,



a Production of reducing equivalents (NADPH) in the pentosephosphate pathway

G6PD = glucose-6-phosphate dehydrogenase

6PGD = 6-phosphogluconate dehydrogenase

b The metabolism of glutathione

GR = glutathione reductase GPX = glutathione peroxidase

c The superoxide dismutase (SOD) and catalase (CAT) tandem

Fig. 6.2. Enzymatic antioxidant systems.

a low molecular organic selenium compound exhibits strong antioxidant properties suggesting that also in the enzyme the selenium atom is responsible for the antioxidant activity.

Uric acid

Uric acid, traditionally considered as the end-product of purine metabolism in man has proven to be an important extracellular antioxidant. Urate reacts with hydroxyl radical and hypochlorous acid and is itself converted innocuous products (glyoxylate, urea, oxalate).

Glutathione

Glutathione, (GSH) a tripeptide ubiquitous in all cells has threefold antioxidant function:

* protects the SH groups of the enzymes and membrane proteins simply being the primary target of oxidants and

* keeps the redox state of the cell on the reduction site.

* Serves as the hydrogen donating subtrate of glutathione peroxidase, one of the key enzymes of the antioxdant defense.

Through oxidation GSH is converted into disulphide GSSG. GSSG can be reduced back to two GSH molecules by **glutathione reductase**, an enzyme working with hydrogens originating from the first two steps of the pentose cycle.

Pentose cycle

In the first two steps of the cycle glucose-6-phosphate is converted to 6-phosphogluconolactone and then to ribose-5-phospate and carbon dioxide by the enzymes **glucose-6-phospate dehydrogenase** and **6-phosphogluconate dehydrogenase** (Fig 6.2). The four hydrogens teared off from the substrate are attached to coenzyme $NADP^+$ and its reduced form ($NADPH + H^+$) in turn acts as hydrogen donor for glutathione reductase, methemoglobin reductase and other enzymes.

Superoxiddismutase and catalase

Superoxiddismutase was discovered only in 1962 by McCord and Fridovich. The enzyme speeds up the dismutation of superoxide radical many times (reaction 8). In higher animals it occurs in two forms. The cytoplasmatic form is a Cu-Zn metaloenzyme, whereas in mitochondria the same function is exerted by an enzyme containing manganese in the active centre. In the course of superoxide dismutation hydrogen peroxide evolves and this is destructed by catalase, a very efficient enzyme containing heme iron. Catalase is able to destruct other, organic hydroperoxides, as well.

The third line of defense

Both lines of defense can be overriden and in such case the best solution is the replacement of damaged parts. Red cells lack proteosynthetic machinery but they conatin specific proteolytic enzymes designed to recognize and destruct the damaged proteins. It is probable that the rapid turnover of proteins in most cells is a preventive measure against action of dmage by ROS or other noxious agents.

The repair systems of DNA fulfill similar task at the level of genetic code.

PROTEIN GLYCATION AND ADVANCED GLYCATION ENDPRODUCTS

Glucose is one of the most important energetic substrates for the human body. On the other side it is an aldehyde and is able to react in random way with aminoresidues of proteins. The most known reation of this type is the **hemoglobin glycation**.

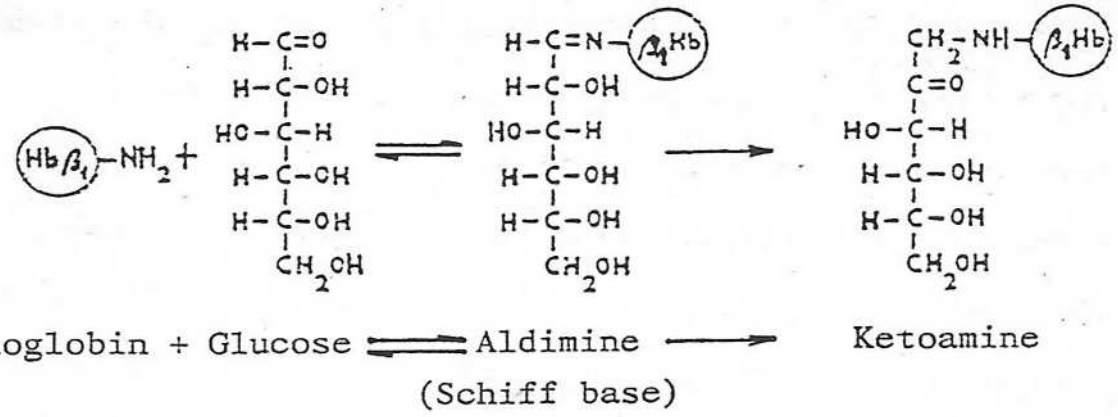
Human hemoglobin in adults is almost homogeneous. It consists of 95 % Hb A and some minor components (Tab. 6.3).

Tab. 6.3. Components of hemoglobin in blood of healthy adults

COMPONENT	PROPORTION %, approx.	STRUCTURE
Main component		
A	92	$\alpha_2\beta_2$
Minor components, genetic variants		
A_2	2.0	$\alpha_2\delta_2$
F	0.2	$\alpha_2\tau_2$
Minor components, postsynthetic modifications		
A_1	5.8	$\alpha_2\beta\text{-}x_2$
A_{1A}	0.2	x = ?
A_{1B}	0.6	x = ?
A_{1C}	5.0	x = glucose

Notes: Hb F is the main component of Hb in neonates
Hb A_{1C} can be elevated in diabetics up to 15 - 20 %

In 1968 a young genetic from Iran, Samuel Rahbar in two diabetics found an "unusual" hemoglobin component and one year later he discovered that it was identical with the component Hb A_{1c} and ten years later the origin of this component was fully elucidated. Hb A_{1c} is formed as a consequence of nonenzymatic reaction of glucose with the free terminal aminogroup of the β-chain of human hemoglobin A (Fig. 6.3). The process is so slow that during the 120 day long lifespan of human red cell only 5 % of Hb is transformed to Hb A_{1c}. In diabetics the concetration of Hb A_{1c} is elevated due to higher glucose level. Although the kinetics of hemoglobin glycation is rather complicated, the Hb A_{1c} concentration in diabetics reflects the blood glucose values of the past months in an integrated way and serves as an important marker of their glycemic compensation.



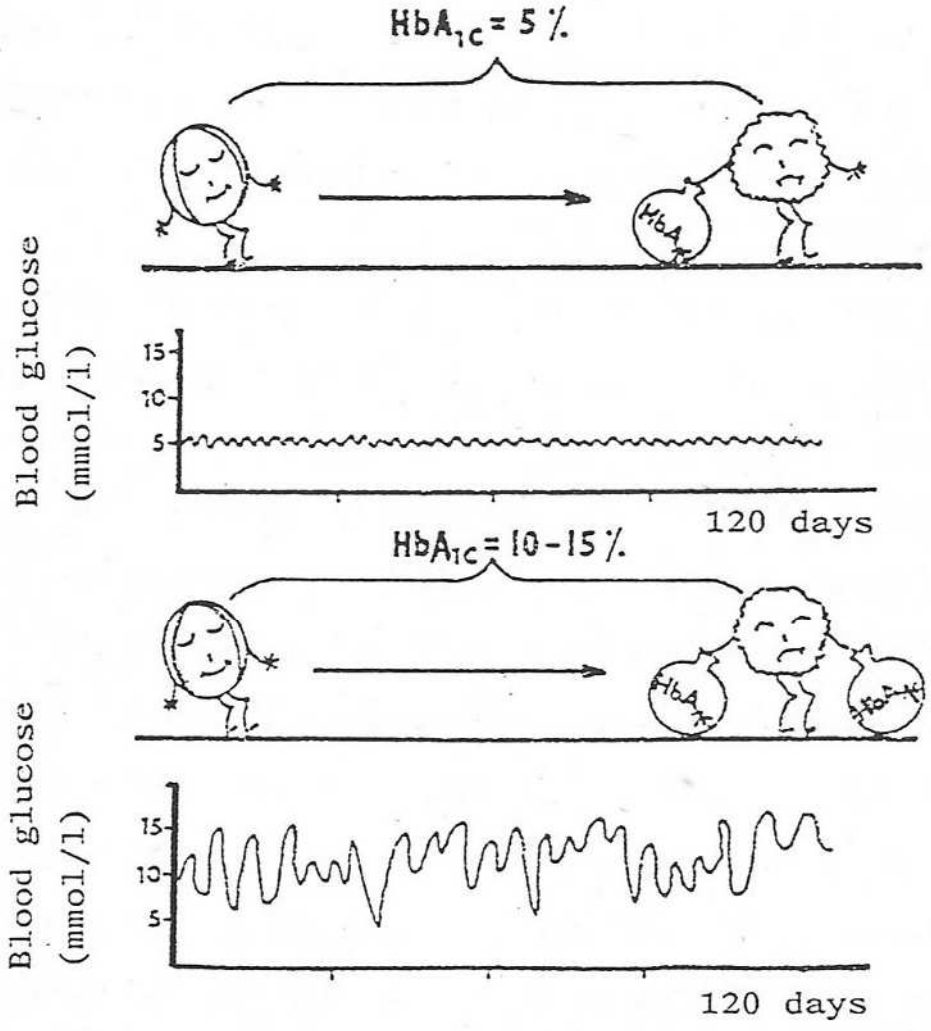


Fig. 6.3. Hb A_{1c} biosynthesis.

In the upper part of the picture chemical nature of the binding of glucose to hemoglobin is given, in the middle and lower part glycation of gemoglobin in red blood cells in the healthy man and in the patient with diabetes mellitus is figured.

The attachment of glucose to the β-terminal amino residue in hemoglobin is not the only random reaction of this type. On the contrary it is an ubiquitous reaction between aldehydes (or ketones) and aminocompounds.

Nonenzymatic glycation involves:

* Reaction of glucose with other aminogroups (namely the ∈-aminogroups of lysines) of human hemoglobin, with aminogroups of other human (e.g. Hb F, Hb S, Hb C) and animal hemoglobins.

* Reaction of glucose with other proteins possessing reactive aminogroups and dwelling long enough in an environment containing glucose (Tab. 6.4) or other sugar with free carboxyl group.

* Reaction of proteins with other sugars containing aldehyde or ketone group and other carboxy or carobonyl compounds. In experimental conditions almost each aldehyde, ketone or organic acid binds to proteins. At least two of these reactions occur also in vivo and their pathological significance cannot be excluded: Acetaldehyde present in blood of alcohol consumers binds to hemoglobin and other proteins and a similar reaction - carbamylation of hemoglobin takes place in blood of patients with uraemia due to kidney failure.

In actual fact monenzymatic glycation was a well-known phenomenon in food chemistry long before the discovery of Hb A_{1c}. It was described by Maillard already in 1922 and a nice example of the Maillard reaction is the **browning** of condensed milk (containing high concentration of protein and sugar) stored for a long time at ambient temperature.

Tab. 6.4. Examples of nonenzymatic glycation of proteins and its consequences

Hemoglobin	A, F, S, animal hemoglobins --> Hb A_{1c}, glycohemoglobin[1] *increased O_2 affinity*
Red cell enzymes	Superoxiddismutase, G6PD *inactivation*
Red cell membrane proteins	*Increased rigidity*
Blood plasma proteins[2]	Albumin, transferin, immunoglobulins, clotting factors *Impaired function and turnover*
Lipoproteins	*Impaired binding of LDL to its receptor --> atherosclerosis*
Extracellular matrix proteins	Collagen, fibronectin *changes in basal membrane structure and function --> diabetic nephropathy*
Eye lens proteins	*Cataract development*
Myelin	*Diabetic neuropathy*

Notes:

1 Glycohemoglobin (GHb) is the common term for all forms of glycated hemoglobin. Hb A_{1c} is Hb A glycated on the β-terminal aminogroup

2 Almost all plasma proteins are **glycoproteins** per se, but they are glycosylated by enzymes on specific sites. Nonenzymatic glycation is an additional process in this case. The same is true for collagen and other extracellular proteins

ADVANCED GLYCATION ENDPRODUCTS

The Maillard reaction in stored mixtures of protein and sugar does not stop after the first reaction but proceeds further and yields brownish nonsoluble polymers. The same is true for some proteins in vivo. The cause of the subsequent reactions is that after the first step (e.g. in hemoglobin glycation, Fig. 6.3) the carboxyl group of the glucose does not disappear but only pass to the second carbon as a ketone.

This has the same propensity towards aminogroups as that on the glucose and can crosslink adjacent parts of the polypeptide chain or neighbouring chains. The existence of such products termed **advanced glycation endproducts** or **AGE-s** was clearly established in the extracellular matrix of the vessel wall. It is possible, that the age-pigment **lipofuscin** also emerges as a consequence of similar reactions.

COOPERATION BETWEEN OXIDATIVE DAMAGE AND GLYCATION

Oxygen and glucose are the main substrates of aerobic life and at the same time both of them can damage the molecules of life in a random, nonspecific way. In addition their mutual cooperation can intensify the final damage:

* Glycated proteins and AGE may act as sources of ROS. Transient metals catalyze this process.

* Protein crosslinks may arise both as consequence of glycation and reaction with malondialdehyde (an endproduct of lipid peroxidation).

* Damaged LDL with impaired receptor binding may arise through both glycation and ROS.

* Glycation may impair the function of antioxidant enzymes (SOD, G6PD).

OTHER STOCHASTIC PROCESSES OCCURING IN LIVING SYSTEMS

In addition to oxidative damage and glycation other types of random postsynthetic reaction can occur in living systems. Racemisation and deamidation of aminoacid residues in proteins, nonenzymatic acylation, isopeptide bond formation, dityrosine formation and probably many others belong to this group.

The mechanism of action of many xenobiotics, toxicants (heavy metals, carcinogens, CO, etc.) can be also considered

as a stochastic process. It is already possible to monitor certain types of carcinogen exposition (e.g. benzo(a)pyrene) through assay of the concentration of the Hb-carcinogen adduct in the blood.

THE MEDICAL AND PATHOPHYSIOLOGICAL SIGNIFICANCE OF RANDOM POSTSYNTHETIC MODIFICATIONS OF MACROMOLECULES

The participation of random postsynthetic modifications due to ROS and other factors (e.g. glycation) is already proved in a number of diseases and in this exciting field almost every month new discoveries are announced. Despite this tremendeous advance one should not forget that in most cases random modifications are only one of many important aspects in the pathogenesis of a certain disease. It would be a serious mistake to neglect the role of elevated cholesterol or LDL-receptor disturbance in the atheroslcerotis, the role of oncogenes and the immune system in carcinogenesis, etc.

The pathologic processes and diseases in which random postsynthetic modifications are (or probably are) of significance should fulfill at least one of the following two criteria:

*** Manifestation after a long latency - random modifications cumulate slowly during the life.**

*** Disturbance of the equilibrium between damaging agents and the defense systems.**

An incomplete list of the diseases and processes due to random postsythetic modifications, divided according to these two main criteria, is given in Tab. 6.5. In most cases, however, both conditions contribute to the pathogenesis of the given disease. The actual role of random modifications (with the exception od reperfusion damage) in these diseases is

described under the appropriate headings.

Tab. 6.5. The siginificance of random postsynthetic modifications in medicine

A. Chronic diseases and processes in which time is important factor of pathogenesis (cumulation of stochastic modifications).
* aging * atherosclerosis * carcinogenesis * rheumatic diseases * diabetic angiopathy * cataract of the eye, etc. * degenerative processes of the nervous system (m. Alzheimer, sclerosis multiplex, m. Parkinson)
B. Disturbed equilibrium between damage and defense (or repair)
1. Conditions with impaired antioxidant defense * deficiency of antioxidant vitamins and selenium. (Probable as contribution to the development of chronic pathological processes such as atherosclerosis or cancer) * inborn errors of antioxidant defense systems - hemolytic anemia due to deficiency of G6PD, inherited forms of methemoglobinemia, amyotrophic lateral sclerosis (SOD deficiency), acatalasemia * inborn errors of DNA repair systems - Fanconi's anemia * reperfusion damage (univalent leakage from damaged mitochondria, changes in xanthine metabolism) **2. Conditions with elevated load of agents responsible for stochastic modifications (ROS, glucose, acetaldehyde, urea, etc.** **2A. - reactive oxygen species** * radiation disease * intoxication with certain toxicants promoting oxidation and ROS formation (e.g. cadmium, paraquat, CCl_4). Nitrite intoxications with methemoglobinemia, smoking, air pollution * disturbances of the trace element metabolism - iron overload (contribution to atherosclerosis), Wilson's disease * Increased respiratory burst activity of phagocytes - chronic inflammation, disturbances of the immune system and septic shock * alcoholic liver damage **2B. - other agents** * diabetes mellitus (hyperglycemia -> glycation, AGE formation) * alcohol intake (acetaldehyde -> acetylation of proteins) * kidney failure (urea -> carbamylation of proteins)

REPERFUSION INJURY

Decrease of oxy en concentration damage all cells of the body but ROS forma ion is possible even in hypoxic conditions. One source of OS during hypoxia is **univalent leakage** of partially reduced f rms of oxygen from damaged mitochondria. The escape of ROS s greatly enhanced after restoration of oxygen supply (**repe fusion**).

Another very in portant source of ROS during reperfusion is the enzyme **xanthine oxidase** which generates superoxide anion through oxidation of hypoxanthine to xanthine (Fig. 6.4). In normoxic conditions the flow of substrates through this pathway is not significant. With the onset of hypoxia high energy phosphate compounds (ATP) are broken down to hypoxanthine. At the same time the enzyme **xanthine dehydrogenase** present in abundance in almost all tissues undergoes proteolytic conversion and changes its reaction specifity to **xanthine oxidase**. The second substrate of the reaction, oxygen appears in sufficient amount at the moment of reperfusion.

Reperfusion injury can occur in almost all organs after transient arterial occlusion and during some types of surgical intervention - especially in organ transplantation. In contrast to slow cumulative action of ROS in most other cases, reperfusion injury is an acute condition.

Application of antioxidant agents (e.g. mixtures of SOD and catalase) or allopurinol, an inhibitor of xanthine oxidase can protect the tissues from reperfusion damage.

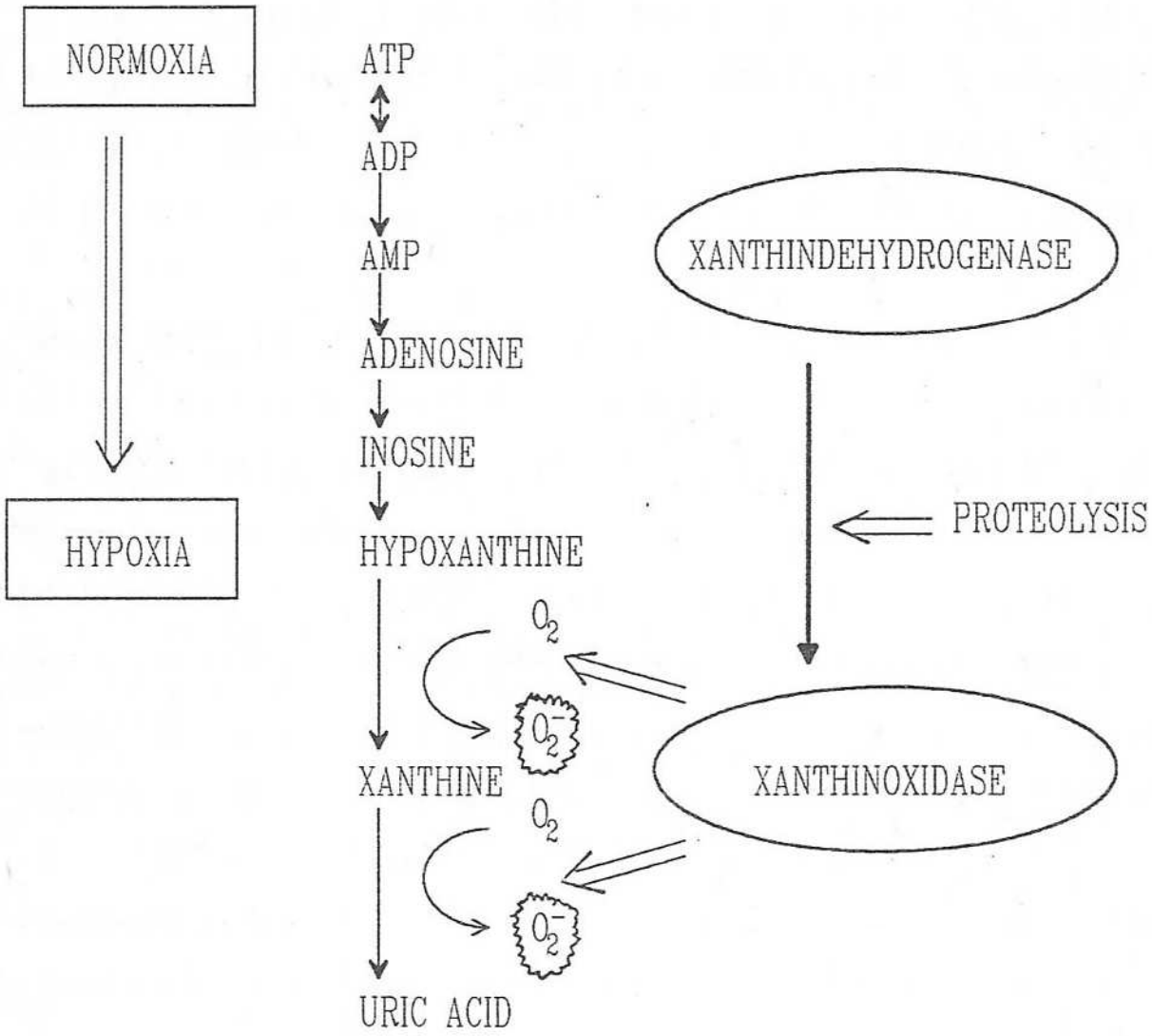


Fig. 6.4. Reperfusion damage. Increased production of the superoxide from hypoxanthine and xanthine during hypoxia in the posthypoxic period.

The activity of xanthinoxidase and the hypoxanthine concentration is low in normoxia. In hypoxic conditions massive catabolism of ATP and proteolysis of xanthindehydrogenase to xanthinoxidase occur. Substrate excess and high enzyme activity are the condition for the increase of superoxide production. In posthypoxic period the situation is worsened by the increase of partial oxygen tension.

6.2. THE BASIC FEATURES OF THE AGING PROCESS

THE LONGEVITY REVOLUTION

In the developed countries of the world the portion of the population over age 65 is about 15 % and is growing with an accelerating pace - 2.5 times faster than the whole population. Moreover within this group is a shift towards very old age - over 85 years. The corresponding increase in the need for medical services as well as long-term care was recognized already 40 years ago and gave rise to two medical disciplines. **Gerontology** is a scientific discipline searching the biochemical and biological background of the aging process and **geriatrics** deals with the practical medical problems of the old people.

According to the WHO the adult and old age can be divided into 4 groups:

* **middle age (45 - 59 years);**
* **presenium - the age preceding old age (60 - 74 years);**
* **senium - old age (75 - 89 years);**
* **very old age (90 and more years).**

These dividing lines are arbitrary and in the practice as old are usually considered people over 65 years and as very old people over 85 years of age.

The main characteristics of aging (or **senescence**) from the medical point of view are as follows:

* **Increased mortality with age after maturation**
* **Changes in biochemical composition in tissues with age**
* **A broad spectrum of progressive deteriorative physiological changes with age**
* **Decreased ability to respond adaptively to environmen-**

tal changes with age.

* **Increased vulnerability to many diseases with age**

Despite the cumulation of diseases (multimorbidity), decreased reserves and diminished adaptability leading to activity limitations (Tab. 6.6) the general health status of older persons is better than is often assumed - old age is not inevitably coupled with diseases and disability. Elderly people living in appropriate social and economic conditions can retain their physical and mental functions intact to surprisingly old age. The main target of geriatrics is therefore not the bare prolongation of human life but to achieve an improvement in the quality of life of old people.

Tab. 6.6. Proportion of people needing permanent help in different age groups

GROUP years	DISABILITY %
65 - 74	≈ 5
75 - 84	≈ 10
> 85	≈ 35

BASIC CONCEPTS

Death is the inevitable end (and not the opposite) of life. In medical statistics **mortality** is the number of deaths in the course of 1 year from 1000 people.

The **cumulative mortality** (or survivorship) curve of a population follows an S-like path, termed the **Gompertz curve*** (Fig. 6.5). From this curve two important variables can be estimated:

---

* The mathematical equation of the S-shaped or **logistical** curve is $R = \beta e^{at} + A$ where R is the mortality at age "t" and α, β and A are constants. The model fits well the human mortlity between 35 - 80 years of age

1. The **median life span** - the age at which 50 % of a given population dies.

2. The **maximum life span potential (MLSP)**. which represents the longest-living individuals in a population.

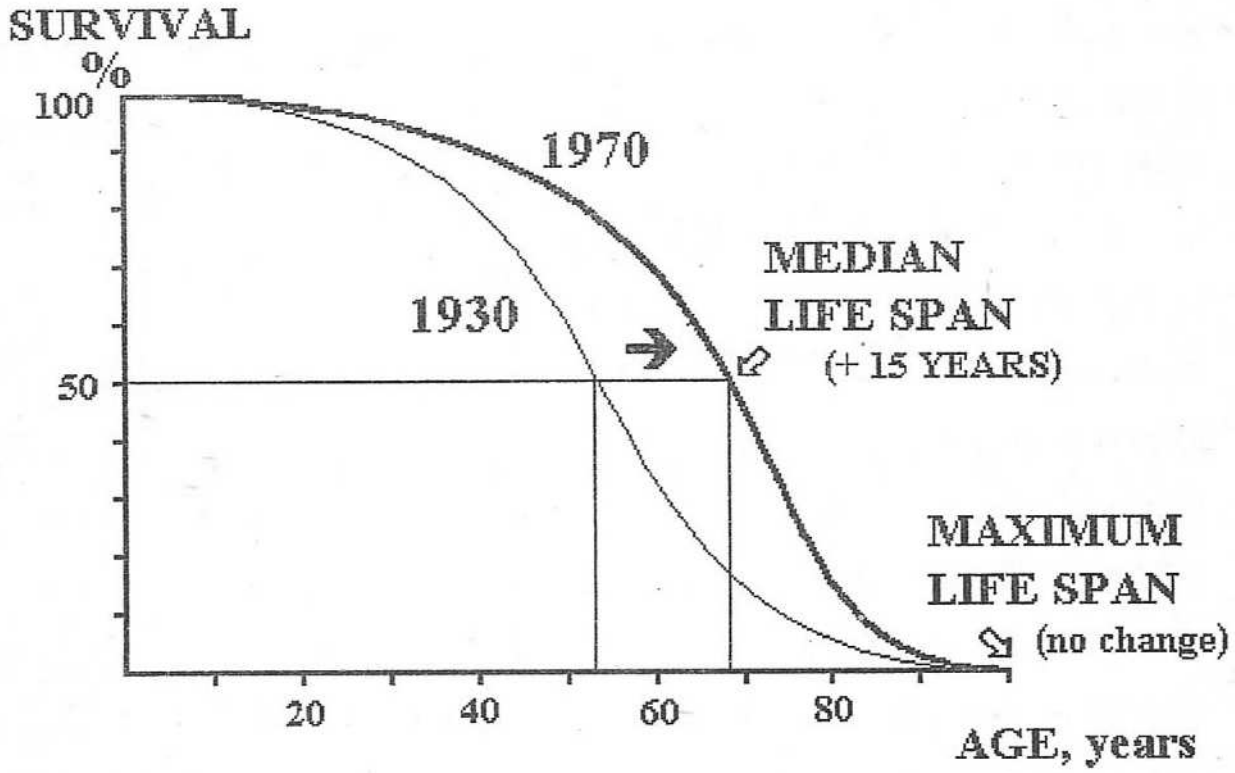


Fig. 6.5. The Gompertz curve of survivorship in a population.

The median life span is equal to the statistical **life expectancy at birth**. Statistical methods enable to calculate other variables as for example **life expectancy at a certain age** or **life expectancy** for different groups of people.

Life expecancy at a certain age is of usually lower than life expectancy at birth but the sum of the actual age and the life expectancy at this age is higher than the life expectancy at birth. For example in a country if life expectan-

cy at birth is 70 years 65 years old people have a life expectancy about 12 - 18 years.

Life expectancy of various groups reveal hidden biological, medical or social (economical and ecological) effects. For example women outlive men in all parts of the world (probably a genetically determined biological phenomenon), smokers live shorter than nonsmokers (mainly for lung cancer) and people in poor countries and in countries with heavy ecological damage have usual shorter life expectancy than citizens of rich and ecologically intact countries.

Life expectancy rose slowly in the past centuries and rapidly in the 20th century because early causes of mortality were excluded. The highest life expectancy in the world is in Japan and exceeds 75 years for men and 80 years for women. Despite this dramatic change the maximal life span of man (MLSP) does not change and its value is about 115 years.

Man and mammals of the animal kingdom have principially the same genetic code, the same enzymes, metabolic pathways, cell organelles, tissue and organ structure and despite huge differences in MLSP exist between species (e.g. mouse - 3 years; cat - 20 years; horse 50 years; man and elephant over 100 years) and the differences are even more striking considering not only mammals. This difference may be of genetic origin but another explanation is possible as well.

The aging process is a biologically (and perhaps genetically) determined phenomenon (**primary aging**) influenced by hostile environmental factors (diseases, trauma, socioeconomical state - **secondary aging**). The speed of aging discloses great individual variations and therefore **chronological age** is not a measure of physical or intellectual (**functional**)

age. In some pathological states (m. Down, m. Werner, m. Alzheimer and others) an acceleration of the aging process takes place, and this is termed **progeria** (Fig. 6.6).

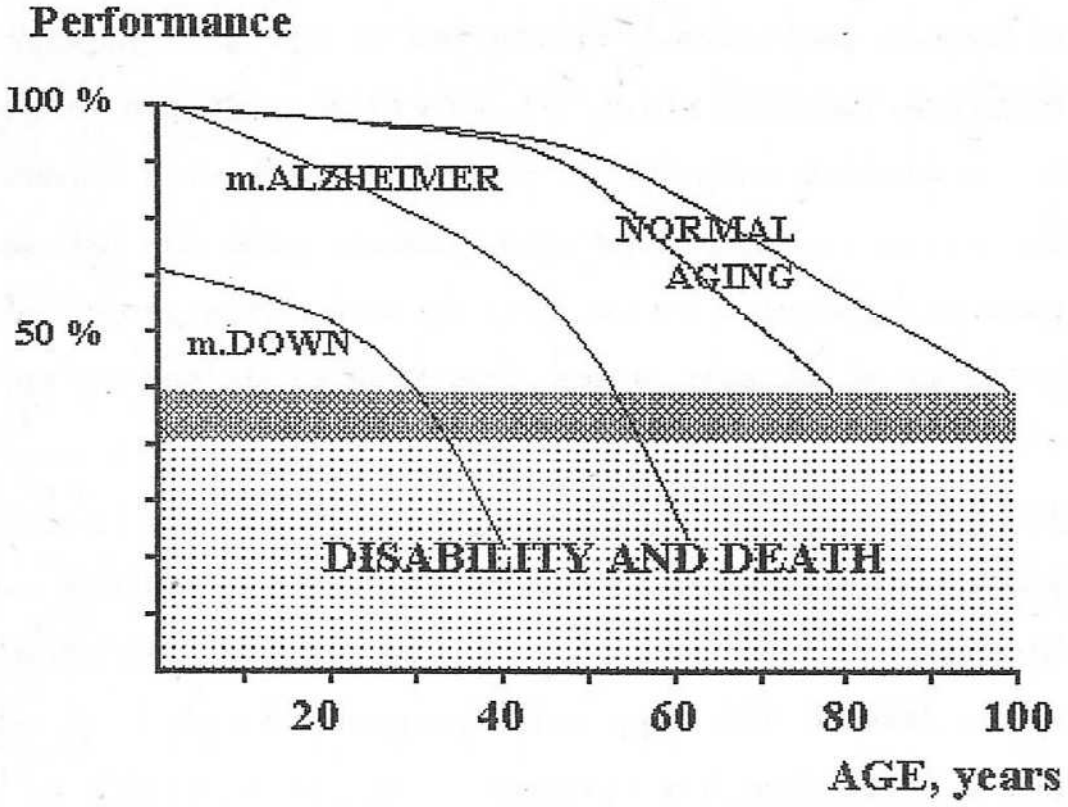


Fig. 6.6. Different patterns of cerebral aging.

According to another view the aging process and the diseases which appear in most old people are indistinguishable and no "pure" aging exists. The tear-and-wear process of the tissues and organs should sooner or later manifest as a disease. It is only a matter of chance, conditions and previous damage whether it would be the brain (dementia), the vessels (atherosclerosis), the locomotor system (rheuma), the eye (cataract) or something else. Despite these differences of views from practical point of view one can divide the aging of an individual into **normal** (primary aging prevails) and **pathological** (age-related diseases prevail) aging or into **successful** and **unsuccessful** aging.

6.3. THEORIES OF AGING

The aging process is an extremely complex biological phenomenon. Its ways are different at molecular, subcellular, cellular and organ level and furthermore different tissues or organs may reveal their own trajectories of aging.

The numerous theories which try to explain aging at these levels can be divided into two groups. The **stochastic** theories consider aging as a tear and wear process, and the **pacemaker** (or **genetic**) theories claim the existence of a genetically encoded clock which determines the MLSP of different species.

STOCHASTIC THEORIES

Stochastic theories should answer two basic questions:

1/ Which are the weakest point of the living systems determining the rate of the tear and wear process and

2/ what are the damaging agents.

To the first question the most plausible answer is the genetic code and to the second the reactive oxygen species described in the Chapter 6.1 but in actual fact the answers are far more complicated and far from being unambiguous.

Somatic mutation theory and **failure of DNA repair theory.** One possible cause of aging is genetic damage (e.g. from background radiation. The mutations accumulate in time and lead to deterioration of cell function. A more sophisticated version of the same theory seeks the cause of the aging not in mutations themselves but in the diminishing ability of repair systems to correct them. Although elevated radiation exposure shortens life and the failure of DNA repair cause diseases, these theories as the basic cause of aging are not verified experimentally.

A very intersting theory is the **error catastrophe theory** first proposed by Orgel in 1963. According to this theory mutations of the common protein encoding genes do not exert any dramatic effect on the cell. (Mutation of a certain structural gene leads to synthesis of one faulty enzyme - the cell may or may not survive this mistake.) Crucial are, however, mutations of genes included in proteosynthesis - that is genes for ribosome proteins, enzymes that take part in RNA processing, couple aminoacids together and control the fidelity of translation. Mutations in these genes should lead to overall deterioration of the precision of protein synthesis (faulty sequences of all enzymes) and therefore should have catastrophic consequences to the cell. Again, strong experimental evidence of decreased fidelity of protein synthesis in aging tissues is lacking.

Genes for some key enzymes of the terminal oxidation are located in the mitochondrial DNA. The mutation rate of DNA in the mitochondria is much higher than in the nucleus because mitochondria lack DNA repair mechanisms. It is known that some rare inherited diseases (mitochondrial myopathies) are caused by mutations of the mitochondrial DNA. The **OXPHOS (oxidative phosphorylation)** theory claims that error accumulation in mitochondrial DNA, in the weakest part of the whole human genome, is the clue of the aging process and many common diseases as well.

The fact, that different mammals with principially identical cell, tissue and organ structure and function and with very similar methabolic pathways have very different MLSP at first glance favours the genetic theories. However one of the oldest stochastic theories - the **rate of living theory**

- claims that MLSP is in inverse relationship to the rate of metabolism, that is the amount of oxygen metabolised not by the whole animal but by one unit (gram) of his body. An elephant needs much more oxygen (or energy) than a mouse but mice have higher rate of metabolism per gram tissue and therefore they "burn" more rapidly than the big but slowly metabolizing animals. This is rather a hypothesis than a theory and there are too many exceptions from this rule. Nevertheless it can be considered as the forerunner of the more elaborated and with biochemical facts more underpinned **theory of random postsynthetic modifications.**

This is actually an attempt for a unifying theory because it couples the role of bioreactive forms of oxygen, nonenzymatic glycation and other random postsynthetic modifications of biological macromolecules as the common case of the aging at molecular and subcellular level. At cell and tissue level key importance should be probably assigned to the ability of defense mechanism to prevent and repair random postsynthetic damage (antioxidant enzymes, repair systems) because these in a normal cell or tissue do not allow the accumulation of faulty molecules. The attempts to prolong life according the postulates of this theory are, however controversial. Transgenic animals with high activity of antioxidant enzymes had only marginally prolonged MLSP and exogenous antioxidants were useful in some, but not in all experiments. An interesting but for possible human use dubious positive result was achieved through caloric restricition (with adequate vitamin and mineral supply) which prolonged the life of rats and mice by 50 %. As a matter of fact these animals had a lowered metabolic rate as well.

DEVELOPMENTAL-GENETIC OR PACEMAKER THEORIES

These theories consider aging as continuation of the development and maturation. Early development is clearly genetically programmed, maturation is a cooperation between genes and environment, hence, aging and death might also be programmed by a genetic clock.

The responsible genes are not known but there are some facts supporting this class of theories:

* Maximum life span is species specific and the rate of living theory does not explain these differences completely.

* The life span of monozygotic twins is similar, whereas that of dizygotic twins and nontwin siblings is not.

* In humans women possesing two X chromosomes outlive males who have only one of it.

* Two rare diseases displaying accelerated aging are genetic in their origin (Hutchinson-Guilford's and Werner's syndrome). Down's syndrome due to trisomy of chromosome 21 also exhibits some features of progeria. Of course, the existence of faulty genes leading to accelerated aging do not mean that the same genes in their undamaged form are the pacemakers of aging.

* Mutation in a gene of *Caenorhabditis elegans,* a nematode prolongs its MLSP by 50 %.

In addition to the proofs seen at the level of whole body and genetic code, there are numerous processes of programmed "aging" at the tissue and cell level. One of the most convincing proof was discovered by Hayflick and Moorhead in 1961. Normal cells growing in tissue culture are not able to divide indefinitely and their mitotic capacity decreases with the age of the donor. Fibroblasts isolated from young people are

able to undergo more (between 40 and 50) divisions as the same cells of old donors. Furthermore there is a correlation between dividing capacity of fibroblasts and life span of different animals and the mitotic capacity of cells of patients with progeria is considerably reduced (Fig. 6.7).

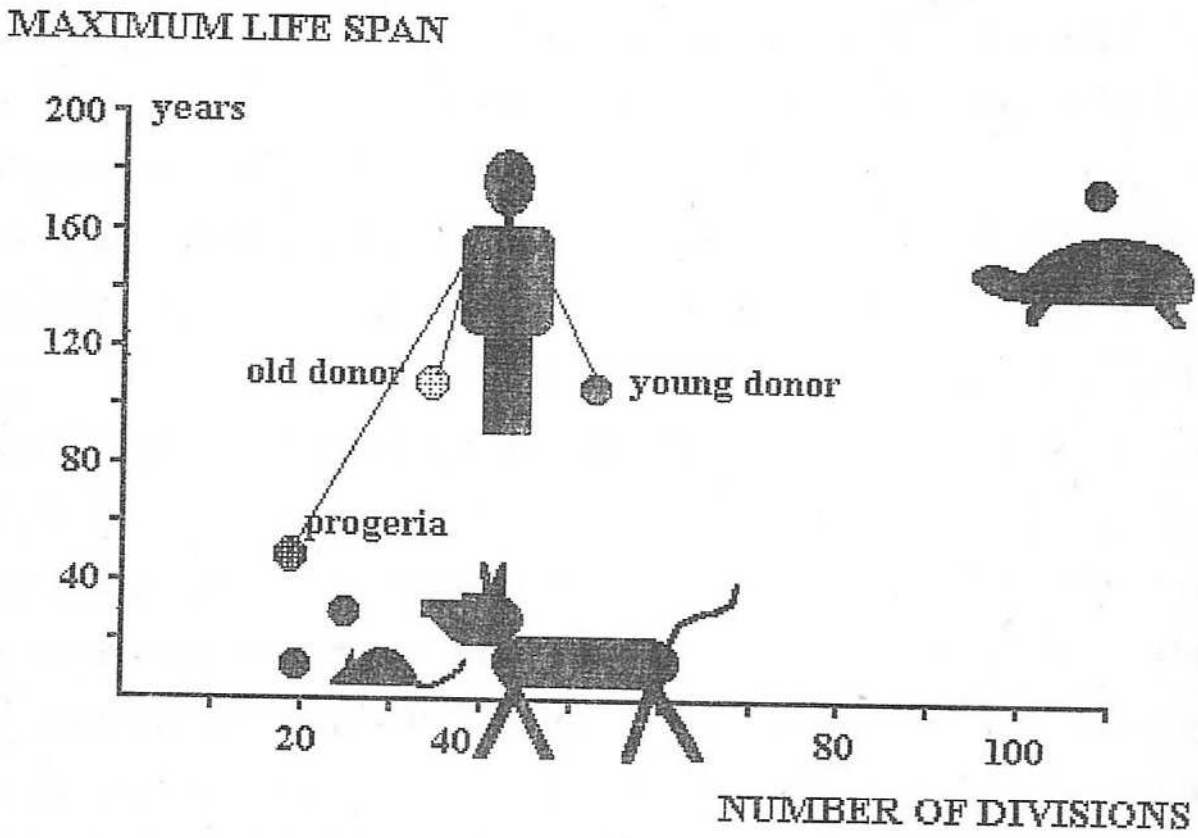


Fig. 6.7. Correlation between maximum life span potential and mitotic capacity of fibroblasts.

Not every cell death is due to aging. Cell death may occur physiologically, through a strictly regulated (and hence genetically determined) way called **apoptosis**. This pathway is necessary to remove cells that are no longer needed (e.g. in the process of brain development) or function abnormally. The involution of thymus after puberty often mentioned as an example of programmed aging is clearly not a stochastic event but it is probably a genetically defined event not resembling aging at the level of whole organism.

Two versions of the developmental theories, the neuroendocrine and the immunological theory, place the pacemaker of the aging not in the individual somatic cells but into specific systems.

The **neuroendocrine** theory claims that the hypothalamo-pituitary-adrenal axis is the main regulator of the aging process. It governs growth and development, controls the maturation and function of the reproductive system and regulates metabolism. Functional changes of the neuroendocrine system may cause aging of the whole body. The decline in female reproductive ability in relatively young age is obviously a process of this type.

The **immunologic** theory is based on two main observations:

* The functional capacity of the immune system declines with age and

* autoimmune phenomena increase with age.

Although both the neuroendocrine and the immune system play important role in adaptation, health maintenance and survival, the above mentioned age-related events in their function might be also secondary processes and not the primary causes of the aging.

RECONCILIATION OF THE STOCHASTIC AND GENETIC THEORIES

Although contradictory at first sight, these two classes of theories are not mutually exclusive. The actual damage due to stochastic events depends to a great extent on the integrity and ability of the defense and repair mechanisms described in Chapter 6.1. Most of the defense and repair mechanisms are genetically coded and regulated (e.g. antioxidant enzyme systems, DNA repair processes, structure of mitochondria). The better and more sophisticated these processes are the

longer can the given species or individual cope with the dmaging forces.

Damaged molecules and faulty cells are quickly removed and destroyed. If possible, these structures are replaced by new ones but in some, for the survival crucial tissues regeneration does not take place. Based on this process the stochastic and genetic theories can be united in a hypothesis of **security measures**. The regulating systems carefully survey the integrity of the organism and if repair or replacement is not possible, the removal of the slightly damaged structures is considered the lesser of two evils compared with the possibility of gross deterioration of its function. An example of a preventive measure may be the removal of the 120 day old human red cells in the spleen. Despite the fact that these old cells are able to carry oxygen they are removed for the circulation and replaced by young ones.

A very interesting aspect on the basic cause of aging is presented in the **disposable soma** theory of Kirkwood and Holliday. From the point of view of species survival the most important period of life is early adulthood ensuring reproduction. Up to this period it is extremely important to maintain every biochemical, cellular and organ function at the maximal level of precision. In the course of evolution the complexity of the living organisms obviously rose parallel with the complexity of the maintenance systems. The maintenance mechanisms should be (and in actual fact are) more efficient in long-living species, usually with long individual development and low reproduction rate (e.g. humans). On the other side these highly sophisticated systems cost a lot of energy and despite their complexity they sometimes fail. The-

refore it is plausible to keep them at full vigilance only until the period of reproductive age. After this period the survival of the species is already ensured and the individual can begin to age. The accelerated aging and death of salmons after breeding fits into the after-reproduction-disposable body theory very well. Another proof of this theory is the observation of M. Nakano - lipofuscin, the age pigment begins to accumulate in cells of different species shortly after they reach reproductive age.

6.4. CHANGES IN MAIN PHYSIOLOGICAL FUNCTIONS DURING NORMAL AGING AND THE MOST FREQUENT HEALTH PROBLEMS IN ELDERLY PATIENTS

It would be very useful to establish the physiological ranges of basic variables in the elderly but it is an almost impossible task due to two factors:

1. If the value of a physiological or biochemical variable changes (e.g. blood glucose after meal) in a group of people during aging, it may be a general (true age-dependent) shift in the whole population or it may be a consequence of occurence of abnormal values only in a subgroup of people with latent or nondiagnosed disease.

2. The population of very old and healthy people is probably a highly selected one. They survive because their adaptive forces are the best. The values of their physiological and biochemical variables may be better than those of a non-selected group (who already died and therefore their values were not involved).

The best solution to avoid these biases is to carry out longitudinal studies (follow-up of the same group from middle age) but they last very long.

In addition to the above mentioned uncertainities the significance of numerical values of biochemical and physiological functions may be questionable because all organs posses remarkable functional reserves. The numerical changes of individual variables (e.g. the decrease of glomerular filtration rate or the number of cells in the brain) do not mean unambiguously the physiological disability of the particular system. The rate of decrease of some physiological functions is depicted in Fig. 6.8.

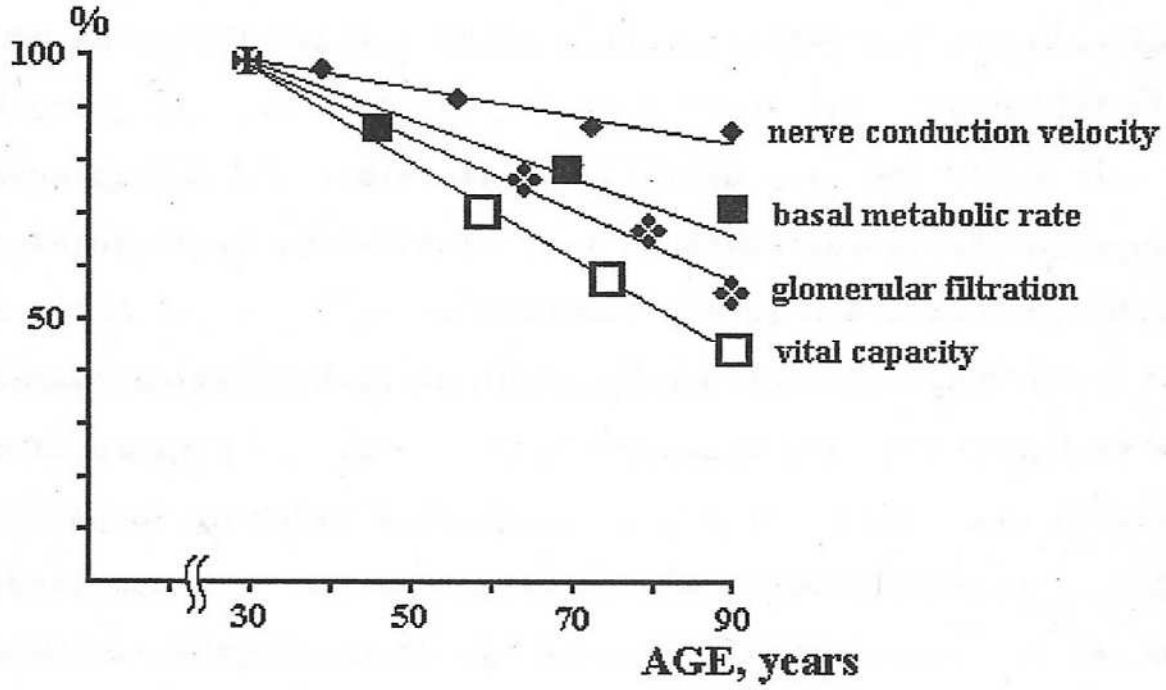


Fig. 6.8. The decrease of some physiological functions with age.

Mutual interactions between systems further complicate the picture. For example aging of the brain may impair the neural regulation of the cardiovascular system but one of the main factors of brain aging may be the sclerosis of its arteries.

SKIN, BONES AND MUSCULATURE

The age of a person can be estimated quite well according the appearance of his skin. The skin of the old people is wrinkled and dry, atrophic and dotted with senile purpura. The number of elastic fibers is decreased. Graying of the hair is common an has an earlier onset in people with light skin and light hair. Balding also advances with age but it is mostly an inherited trait.

Osteoporosis, a pathological condition characterized by decrease in total bone mass, leads to loss of height, to pain in the limbs and even to hump (due to collapse of vertebrae) and to fractures of the femur and other bones. The osteoporosis of the old age is a multifactorial process but can be successfully prevented by regular exercise, calcium tablets, low doses of fluoride, vitamin D and calcitonin and in postmenopausal women with estrogen treatment.

In old people muscles are weaker (the muscle fibers are replaced by connective tissue) and slower than in the young.

CARDIOVASCULAR SYSTEM, VESSEL WALL AND BLOOD PRESSURE

In old age the isometric relaxation and the contraction of the heart muscle are impaired. It is probably due to increased passive permeability and decreased active transport of calcium through biomembranes of the heart muscle cells. The activity of the calcium dependent myosin ATP-ase is decreased as well. The number of myocardiocytes decrease but the remaining increase their volume and in healthy old people the the basal cardiac output remains constant. The heart rate is usually slightly decreased but within the normal range (58 - 65/min).

The chronotropic and inotropic response to load (due to

diminished reaction to β-adrenergic stimulation) is impaired as well as the vasodilatation response.

The elasticity of great arteries diminishes and the systolic blood pressure raises slowly with a concomitant mild left heart hypertrophy (1 - 1.5 g in a year between age 30 - 90). Atherosclerotic plaques of the vessel walls are common already in relatively young age but they pure occurence does not mean inevitably impaired tissue perfusion. The basal oxygen demand of the body is diminished in old age. Fewer cells (atrophy of muscles, organs) need less oxygen and perhaps the oxygen consumption of the individual remaining cells is diminished as well.

The age-related elevated occurence of hypertension is a well-known phenomenon but it is probably not part of normal aging because it does not appear in groups of people who do not consume salt.

In contrast to often elevated blood pressure orthostatic hypotension with or without collapse is common in old people. It is hard to distinguish between the possible causes - impaired cardiovascular regulation, antihypertensive treatment, sclerosis of the arteries or long stay in bed due to diseases.

RESPIRATORY SYSTEM

The vital capacity decreases considerably with age, but this is partly due to diminished strength of respiratory muscles and stifness of the ribs. The elasticity of the lung decreases with age and in exspirium the small airways often collapse. The residual volume of the lung increases. The basal parts of the lungs are well perfused but their ventillation is impaired and therefore a slight drop in the oxygen

saturation of the blood can occur.

BLOOD

Healthy old people should have normal red cell count, normal concentration of haemoglobin and normal hematocrit. The concept of "anemia of the old age" is misleading because this conditions always has its specific cause. The same is true for white cell and platelet count.

DIGESTION

A common cause of digestive problems in elderly is the loss of teeth. However this is not a part of the normal aging but a consequence of pathological processes of the parodontium.

The excretion of gastric acid and digestive juices is decreased. The decreased motility of the guts is partly responsible for obstipation, another common complaint of old people.

The overall metabolic activity of the liver is impaired and can lead to dangerous changes in drug metabolism.

EXCRETION

Renal blood flow and glomerular filtration decrease with age. As the creatinin synthesis is decreased as well, its concentration in healthy old people remains in the normal range. In men the prostatic hypertrophy may cause difficulties with urination and the retention of urine can lead to infections and damage of the kidneys.

ENDOCRINE SYSTEM

According to some researchers changes in the neuroendocrine relations (namely in the hypothalamo-hypophyseal axis) act as a pacemaker of the aging.

The concentration of hormones do not decrease uniquely

with age. On the contrary the concentration of somatotropin, corticotropin and gonadotropins are usually increased. It may be a consequence of feedback effort due to the atrophy and diminshed hormone release of the target glands.

The decreased excretion of thyroid hormones cause a drop in the basal metabolic rate.

The concentration of insulin is often elevated but its efficiency is usually low and this points to a very important phenomenon, namely that the concentration of a certain hormone is often not decisive because:

* it reveals very little about the dynamics (secretion rate and turnover) of the hormone;

* the effect of a hormone depends strongly on the number and affinity of the specific hormone receptors and on the postreceptor events triggered by the hormone binding to the receptor.

Probably the second possibility is the cause of the elevated insulin concentration. The primary age-related event is a disturbance at the receptor or postreceptor level and the rise of insulin is a compensatory process to maintain blood glucose value in the normal range.

REPRODUCTION

Reproduction is closely related to the function of hypothalamus, hypophysis and the gonads which are endocrine glands and gamete producing organs at the same time. In women climacterium and menopause is a relative early and probably programmed event. In men spermatogenesis decreases after the age of 50 but it may be intensive enough to beget children at advanced age.

FLUID, ELECTROLYTE AND ACID-BASE BALANCE

Healthy old people do not reveal any apparent disturbance in the fluid, electrolyte and acid-base balance, but the range of adaptation of these systems is considerably diminished. This may manifest after bleeding, burns, diarrhea and other pathological conditions as fast and unexpected metabolic derangement. The danger of metabolic decompensation is more pronounced if heart or kidney failure, diabetes and other diseases are present.

THERMOREGULATION

One important consequence of the aging is the impairment of the thermoregulatory adaptability. In old people both hypo- and hypertermia can easily develop. Old people in addition have impaired sense of thermal comfort - they wear warm suits even during summer and complain on cold in well-tempered rooms.

SENSES

Hearing loss is common in old age and is usually more pronounced in men than in women. **Tinnitus** (buzzing in the ears) is also a very frequent and annoying symptom of aging.

Diminished ability of accomodation (**presbyopia**) begins usually already at age of 40 - 45 years. In advanced age to this opacity of the lens (**cataract**) can join.

AGING BRAIN, SENILE DEMENTIA AND PSEUDODEMENTIA

Physiologic brain aging

Although the neurons are not replaceable and from birth a steady decrease of the cells take place, the enormous plasticity of the nervous system allows to maintain all basic functions of the brain up to old age. Old neurons retain they ability to form and use synapses.

Age influences intelligence tests and performance of cognitive skills and behavioral tasks. However, the view that intelligence and creativity peaks in young adulthood and decreases thereafter is probably not true. Between 60 and 70 there is a decline of some abilities (mostly in tasks involving speed component) but the interindividual variation is very wide. Beyond this age the decline is obvious. Crystallized intelligence (based more on experience) is better preserved than the fluid intelligence. The reaction time in unexpected situation is getting longer. A very important finding is that between intellectual performance and life expectation is a positive correlation.

Normal aging is accompanied by changes in sleep pattern. On the average, elderly subjects require less total sleep time than young adults. There is a reduction in the REM stage and wakenings during the night are more frequent. Sleep disorders may be also of organic etiology and connected with dementia or cardiovascular, respiratory and other diseases. On the other hand **sleep apnoea** (cessation of breathing for more than 10 second, usually connected with heavy snoring) is present in 30% of old people may cause serious hypoxia of the brain and heart.

One of the most serious problem connected with aging is the **deterioration of the memory** (about 25 % loss by age of 75).

A very important and up to date not fully solved problem is where to draw the dividing line (if there is any) between normal brain aging and senile dementia. The rate of decline of brain performance displays wide range of variation (Fig. 6.6). Besides deterioriation due to loss of neurons **underuse**,

organic diseases and very frequently social and economical problems can mimic dementia. These conditions are, however, reversible under if the underlying cause is treated properly. Despite these uncertainities any intellectual decrement before the age of 50 must be considered as pathological.

Senile dementia

Many old people suffer from mental disturbances which are beyond the range considered as a component of normal aging process. The symptoms of **senile dementia** include

* **intellectual dysfunction:** severe memory impairment, absentmindedness, impaired orientation in space and time;

* **altered mood:** lack of interest, blunting of affect, anxiety, tendency to depression;

* **changes of behavior:** apathy, irritabillity, aggressiveness.

According to present knowledge there are two basic types of senile dementia:

Primary degenerative dementia is the commonest type, accounting for more than half of all cases (Tab. 6.7). The intellectual deterioration is gradual, slowly progressive and irreversible. After the initial 2 - 3 years of memory impairment and disturbances of orientation severe cognitive disturbances follow and in the terminal phase the patient is immobile and incontinent. Death ensues after 4 - 12 years of duration. According to recent research **Alzheimer's disease** which is the most frequent cause of the primary degenerative dementia, is not a simple wear and tear process but a specific disease with defined genetic, biochemical and histological features. (These are described in chapter on Pathophysiology of Nervous System.) Under age 65 **(presenile dementia)** it

occurs in 1 individual out of 1000, between 65 and 70 years already in 1 out of 50 and above 80 in every fifth. This represents an epidemic affecting only in the USA 4 million people and due to the increasing percentage of old people this number can reach 20 million in the next 25 - 30 years.

Tab. 6.7. Prevalence of forms of senile dementia

Primary degenerative dementia Mostly senile dementia of the Alzheimer type	> 50 %
Multi-infarct or vascular dementia	> 20 %
Mixed types	≈ 20 %
Other, rare types of dementia, associated with different diseases of the nervous system	REMAINDER

Multi-infarct dementia. This type of mental deterioration develops as a result of sclerotic changes of the vessels of the brain. The symptoms appear abruptly and sometimes signs of small strokes are present. With proper treatment some of the symptoms (slight paralyses, disturbances of speech) are at least partly reversible.

In the differential diagnosis of senile mental decline the possibility of **acute or chronic depression** and of **confusional states associated with physical illness** (e.g. decompensated diabetes, hypertension, thyroid disease) or **inappropriate use of drugs** (benzodiazepines, antihypertensives) should be always considered.

SOMATIC DISEASES IN THE OLD AGE

The diseases occuring frequently in old subjects can be divided into three categories:

* **Diseases occuring in all old people**, atherosclerosis beeing the best example. Despite developing at various pace after 75 years of age atherosclerotic changes are universal, progressive and irreverible.

* **Diseases which are more frequent in old age than in young.** Due to decreased immune function the overall rate of malignancies is higher on old people than in young. The prevalence of diabetes mellitus, hypertension and many other diseases is also higher in old age than in young but they do not occur universally.

* **Diseases which are not age dependent, but their prognosis is worse in old people than in young**, for example pneuomonia, flu and other infections, burns, bone fractures.

The symptomatology od diseases in elderly is often altered (e.g. myocardial infarction without pain, asymptomatic hypothyreosis and diabetes, etc.) and therefore their accurate diagnosis is more diffcult than in young or middle age.

A very important feature of every almost disease contracted in old age is that they usually accelerate the process of aging despite succesfull treatment.

The most frequent age dependent diseases and health problems are listed on Fig. 6.9. They occur already in the period of presenium but later they tend to cluster and manifest as **multimorbidity.** The presence of different cardiovascular, urogenital, respiratory and other diseases confuse the symptomatology, accelerate the development of each other, lead to frequent complications and render the treatment more difficult.

In addition to pure pathophysiological events the **socioeconomic status** of the old people is often decisive for the

development of complaints and diseases. Poverty, low level of education, problems arising from retirement, loss of partner and friends, isolation and loneliness influence badly the mental state of old individuals and in turn accelerate the development of many diseases, aggravate their course and prognosis and render treatment inefficient.

The clinical pictures arising as a combination of somatic, mental and socioeconomic factors led to defining some diseases termed as **complex geriatric syndromes**, for example the **Diogenes syndrome** old men living in complete social isolation careless of his own hygiene or the syndrome **Philemon and Baucis** (two old people neglected by children living in social isolation.

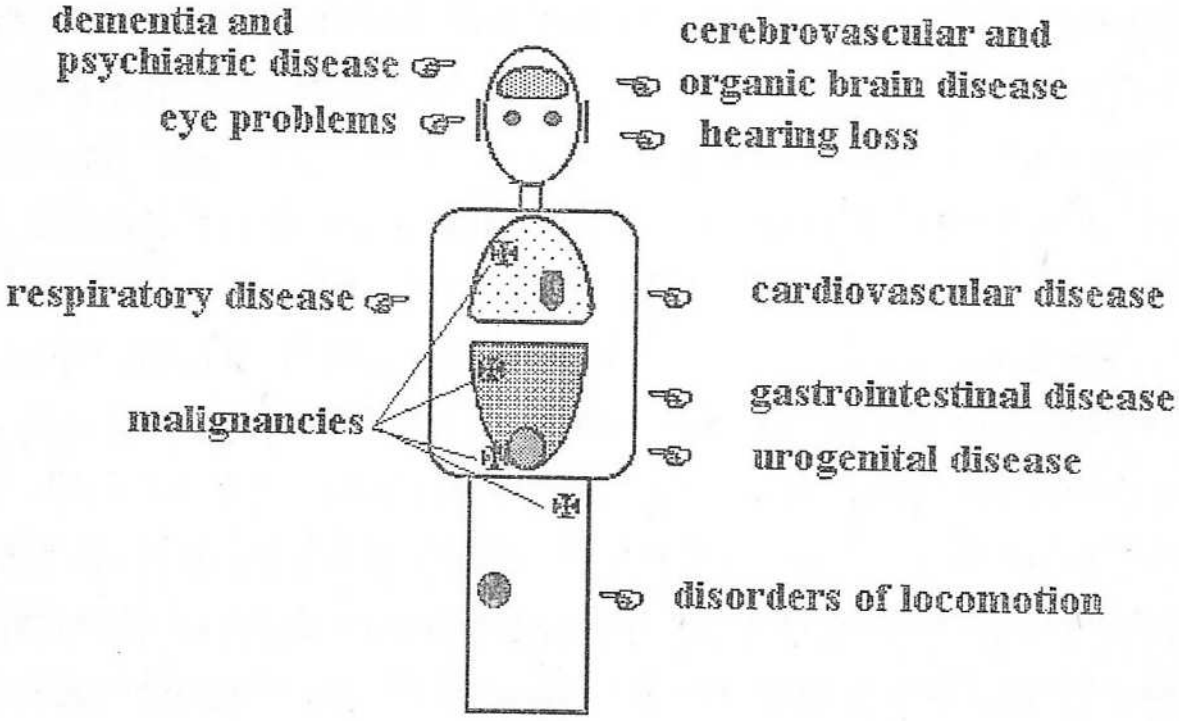


Fig. 6.9. The most frequent health problems affecting old people.

7. TERMINAL STATES AND CARDIO-PULMONARY-CEREBRAL RESUSCITATION

7.1. TERMINAL STATES

Tanatology is a science studying the mechanism of dying resulting in irreversible disintegration of the organism as a whole. **Reanimatology** studies various specific and nonspecific changes in vital organs and systems such as respiratory, cardiovascular are central nervous systems (CNS) in order to prevent or reverse them. Application of various methods to restore consciousness, life or a seriously disordered function is called **resuscitation**. Basic pathophysiological concepts and new resuscitation methods were developed especially by V.A. Negovsky (Moscow) and P. Safar (Pittsburgh).

In chronic diseases, irreversible pathologic changes in various organs and systems may cause multiorgan or multisystemic failure resulting in unavoidable death. About 25% of all deaths occur because of rapid unexpected dying in the absence of incurable disease or senility. Therefore, pathophysiological research and resuscitation oriented studies are very important. Terminal states may develop progressively as an acute exacerbation or complication of a chronic pathologic process such as respiratory insufficiency complicated by an acute infection or cardiac decompensation resulting in pulmonary oedema. Nevertheless, acute or peracute development of terminal states are more frequent and important, i.e. suffocation, drowning, asphyxia neonati, severe haemorrhage, myocardial infarction, etc.

There are several stages in the development of **terminal states**:

1. **Preagonal stage** is characterized by interaction of two

antagonistic tendencies, such as a) tendency to damage and even kill the organism resulting from sudden pathological situation, i.e. excessive bleeding and ischemia, severe hypoxia and acidosis, developing especially in the central nervous system, etc, and b) defensive and compensatory reactions of the organism, such as tachypnoea, tachycardia, general vasoconstriction, hypertensive reaction, and so on, tending to counterbalance and compensate the impaired functions and to prevent death. With both very excessive damage and extensive prolongation of its action, the compensatory reserves of the organism may be exhausted. In such cases the breathing may stop - preterminal apnoea and the EEG activity disappears. Similarly, the partial atrioventricular (A-V) blockade initially tending to protect the ventricles from overirritation, during progressive hypoxia changes to A-V dissociation resulting in a preautomatic pause followed by appearance of ventricular extrasystoles and bradyarrhythmia, ventricular tachycaria or fibrillation with a progressive decrease in blood pressure and tissue perfusion (including CNS).

2. **Agonal stage** is an expression of chaotic function of various systems escaped from cortical control and being altered by phylogenetically older subcortical regulatory centres and reflex mechanisms. Typical example is the **gasping type of breathing** representing a periodic but maximal activation of all inspiratory muscles including the auxiliary ones from a medullary centre. This native and extremly strong but still physiological process represents the last attempt to reactivate the dying subcortical centres and the cortex by spreading of excitation through the reticular activating system and the sympat-

hetic nervous system. This may result in periodic but transient improvement of various vital functions appearing as Cheyne-Stokes breathing, Adams-Stokes syndrome, phasic changes in CNS activity characterized by sopor, stupor and even transient consciousness alternating with coma. In young mammals and under optimal conditions even spontan revival can occur - self-resuscitation by gasping. Selfresuscitation has been fostered by evolution, which has given animals and humans the diving reflex, the sympathetic discharge in response to trauma and blood loss, agonal gasping and blood pressure surge at the start of clinical death and the "neuroendocrine switch" from flight or fight to giving up - fostering a painless death with equanimity when survival seems impossible.

3. **Clinical death** is the period of unconsciousness, apnoea and pulselessness, i.e. (cardiac arrest) during which prompt resuscitation attempts can sometimes result in full recovery, even of the brain. Unconsciousness alone, i.e. without apnoea and asystolia, can often be observed in severe diabetes, as well as in liver and renal diseases (coma diabeticum, hepaticum, uremicum, traumaticum, etc). The absence of all these three basic vital functions results in progressive damage to most organs and systems. These changes are, at the beginning only functional and reversible based on physico-chemical modifications only. Later they become irreversible and can be manifested by severe morphological alterations. These changes aggravate gradually the functions of other important organs resulting in hepatal, renal and gastrointestinal failure, alteration of the clotting and fibrinolytic mechanisms in the blood, etc - multi-organ and polysystemic failure. These changes can be reversed

by applying appropriate resuscitation techniques until they become irreversible. The outcome of resuscitation is determined by the intensity and quality of the changes in vital organs and the duration of clinical death on one side, and by the compensatory reserves of the organism and the effectiveness of the resuscitation methods used, on the other side.

4. **Biological death**. The development of the pathophysiological changes, both reversible and irreversible, depends on the sensitivity to the lack of both oxygen and blood supply in the tissues concerned which determines the onset of their biological death. The brain displays the highest sensitivity to lack of oxygen and/or blood supply determining the upper limit for complete revival of the organism. The survival time without long-term neurological consequences, may be prolonged in patients in deep anaesthesia and hypothermia to 12 min. and even more (young children were resuscitated even after 40 min. of submersion in ice-cold water). Irreversible damage of various tissues develops in the following order: cerebral cortex (5 min.), subcortical structures (30 min.), brainstem and heart (45 min.). spinal cord (60 min.), kidneys (120 min.), liver (180 min.), skin (days) and bone (weeks). These time delays are important for both reversal of extinct functions and organ donation as well as transplantation.

7.2. BRAIN DEATH

Brain death. Dying is a longer-lasting process but the onset of death must be precisely defined for various social, ethico-legal and practical reasons such as organ transplantation, etc.

According to Pittsburgh declaration, brain death must be declared in writing by two specialists (anaesthesiologist and neurologist or cardiologist) evaluating the results of complex clinical and laboratory examinations repeated at intervals of 12-48 hours. Among the most important clinical signs of brain death belong: absence of both the spontaneous breathing for 15 min. and the voluntary and involuntary movements, loss of brain reflexes (spinal reflexes may be present), absence of cortical and brainstem evoked potentials, permanently nonfunctioning brain or destroyed brain (are better terms than permanent coma), and extreme mydriasis with non-reacting pupils. The most important laboratory findings are: isoelectric EEG, stop of brain perfusion proved by angiography of both internal carotid and vertebral arteries, increase in intracranial pressure above 50 tor (often resulting in development of cerebral oedema) and decrease in arteriovenous difference in O_2 in the brain circulation.

Determination and certification of brain death, followed by discontinuance of artificial ventilation does not present dilemmas. Since 1962, discontinuance of all treatment in the brain death (i.e. dead.) heart-beating organism can be considered as an ethical requirement, irrespective of organ donation. In 1966, the conditions for permission from relatives for organ donation by brain-dead heart-beating donors has been defined. In 1968, a Harward panel published brain death criteria for organ donation and a multidisciplinary panel in Pittsburgh developed guidelines for brain death determination and certification.

Vegetative state or apallic syndrome is persistent state of

cerebral death (supratentorial), without destruction of the medulla, i.e., with continued spontaneous breathing and reflex swallowing. After cardiac arrest, no purposeful response to stimuli (in the absence of hypotension, hypothermia or CNS depressants or relaxants) for 1-2 weeks has newer been followed by good cerebral outcome in this "decorticated subject". Although there is no 100% certainty, the discontinuance of all life support, including artificial airway, ventilation, feeding, and hydratation as well as emergency surgery, is ethically justified.

Brainstem paralysis results from a selective damage caused by local ischemic, anoxic or degenerative processes abolishing the function of automatic centres in the brainstem (i.e. breathing in poliomyelitis) without massive damage to the higher brain functions. Transient replacement of the failing automatic breathing by a newly developed equipment - "iron lungs" in the acute phase of the disease saved thousands of lives during a pandemy of poliomyelitis occuring in Scandinavian countries in 1950s.

Locked in syndrome or state of deefferentation is characterized by loss of all somatomotoric activities (as in amyotropic lateral sclerosis) with the persistence of sensory functions and consciousness . Such patients need very intensive permanent care.

7.3. POSTRESUSCITATION DISEASE

Postresuscitation disease is a state characterized by various neurological and psychosomatic symptoms developed after successful resuscitation. It has usually four stages:

a) **hyperdynamic stage**, occuring 20-60 min. after the resuscitation is manifested by acidosis and increased secretion of catecholamines resulting in tachycardia, hyperventilation, hypovolemia and decrease in blood pressure;

b) **hypodynamic stage** occuring 4-6 hours after the resuscitation is characterised by progressive decrease in both cardiac output and tissue perfusion accompanied by increased extraction of O_2 in tissues. Severe acidosis with development of both coagulopathies and brain and lung oedeamas, may often result;

c) due to still effective compensatory mechanisms **stabilisation of some functions** such as acidobasic balance, blood pressure etc, develops in 10-12 hours after the resuscitation. In spite of this relative stabilisation there may be a progressive deterioration of peripheral circulation and severe hypoxia in various tissues;

d) after 1-2 days there is either a **general deterioration** or **an improvement** according to the compensatory reserves of the organism and the effectiveness of both the resuscitation methods and the intensive care measures used.

The general state and the outcome of both the resuscitation and the intensive care could be evaluated by using various scoring systems such as Glasgow-Pittsburgh categories, Apgar scores, etc.

Cerebral and Overall Performance Categories - Glasgow - Pittsburgh 1978.

CPC 1: Good cerebral performance: conscious, alert, mild neuro-psychologic deficit.

CPC 2: Moderate cerebral disability: sufficient function for work in sheltered environment.

CPC 3: Severe cerebral disability: conscious but need daily support for impared brain function (ranges from ambulatory care to dementia).

CPC 4: Coma or vegetative state: Unavereness and cerebral unresponsiveness without interaction with environment.

CPC 5: Brain death: apnoea, areflexia, EEG silence.

APGAR-scoring system is used for evaluating newborn infants (1-5 min. after delivery). Zero, 1 or 2 points could be ascribed for the following five basic parameters: A = Appearance (color: blue-pink), P = pulse (0->100), G = grimace (reflex irritability: 0-cry), A = Activity (limpness - active movement), R = respiration (absent-good). Score 10 - optimal condition, Score 6 or less - depression, resuscitation measures required.

7.4. CARDIOPULMONARY - CEREBRAL RESUSCITATION - CPCR

CPCR frequently used from 1950s has 3 stages:

I. - First aid: oxygenate the brain immediately (Basic Life Support - accessible also for laic).

II. - Start spontaneous circulation (Advanced Life Support - accessible also for paramedicals).

III. - Support recovery (Prolonged Life Support - accessible for profesionals).

Each stage consists of three steps, thus creating altogether 9 steps (with several tasks) arranged in alphabetic order indicating at the same time the sequence of importance:

A - Airway control: neck left, head tilt, jaw thrust,

B - Breathing support: mouth-to-mouth ventilation, manual bag-mask ventilation, mechanical ventilation (IPPV),

C - Circulation support: control of pulse and ext. haemorrhage, position for shock, precardial thump and cardiac compression. Cardiac compression: Ventilation ratios of 15:2 for one operator and 5:1 for two operators are considered standard.

D - Drugs i.v.: sodium bicarbonate (anti-acidosis), adrenalin (cardiotonic and vasoconstrictor), lidocaine (anti- arrhythmic), atropine and calcium chlorate,

E - EKG monitoring: diagnosis of lethal arrhythmias, propranolol for ventricular fibrillation and defibrillation (discharge 200 J, applied up to four times in intervals of 2-3 minutes),

F - Fluids: plasma, dextran, saline and glucose,

G - Gauge (assessment): evaluation of overall performance, treatening the cause of demise, determining salvageability,

H - Human mentation: case oriented cerebral resuscitation,

I - Intensive care: multiple organ support on intensive care unit.

The algorithm for basic urgent resuscitation is indicated in a Fig. 7.1 (modified from Gordon A. S. In: Supplement to JAMA vol. 227, No. 7, 1974). The last three steps (H - I) representing prolonged life support concentrate mostly on cerebral resuscitation completing the previous cardiopulmonary resuscitation - CPR to CPCR. In animal experiments high doses of barbiturates, adrenergic drugs (adrenalin) and calcium entry blockers as well as cardiopulmonary bypass have been succesfuly tested. Clinical trials of brain resuscitation, however, have

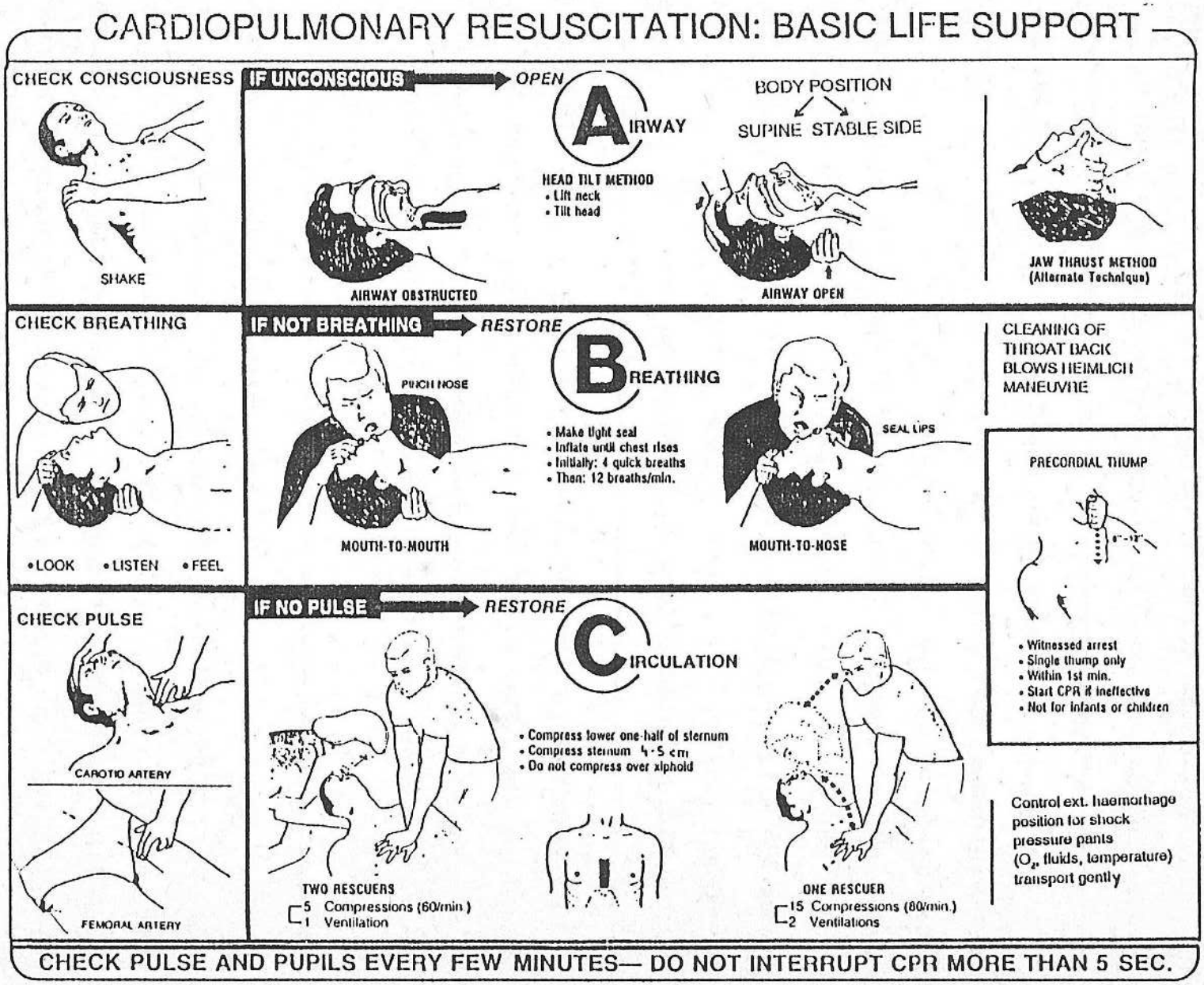


Fig. 7.1. Cardiopulmonary resuscitation.

thus far not confirmed the brain benefitting effects of these promising therapies demonstrated in the laboratory.

Before the 1950s, complete airway obstruction , apnoea, and pulselessness outside the hospital, and pulselessness within the hospital but outside the operating room, resulted in death. In contrast, in recent years CPCR attempts in hospital operating rooms and special care units are 50 to 100 percent successful in restoring circulation, at least temporarily. Out-of-hospital CPCR attempts after sudden cardiac death, when started immediately, have achieved consciousness and discharge from the hospital in up to 40 percent of patients. Prehospital sudden cardiac death is often caused by ventricular fibrillation, which can be reversed by antiarrhythmics and defibrillation.

Over the past 20 years, more than 20 million people in the United States have had some training in CPCR steps A, B and C. Use of manequins improved performance rates of mouth-to-mouth ventilation and CPR. In addition to such large scale organisation of CPR courses, there were many international symposia, workshops and panel discussions devoted to preparation of guidelines for uniform application of new techniques in the practice.

There are several important **goals for optimalization of the resuscitation results** in the future:

1. to minimize the response time with improved delivery of current knowledge and skills, to promote rapid and effective initiation of basic and advanced life support and to improve resuscitation methods,

2. to maximize the reversible period of terminal states and clinical death using animal models and clinical trials,

3. to link resuscitation with other fields of medicine, including transplantation,

4. to evaluate benefits and costs and foster a continuing dialogue on ethical dilemmas.

There are at least five **levels of care** and the appropriate level should be chosen during the prolonged life support at intensive care unit:

1. emergency resuscitation,

2. intensive therapy,

3. general medical care, including antibiotics, drugs, chemotherapy, surgery and artificial hydratation and nutrition,

4. general nursing care, including pain relief, hydratation and nutrition,

5. terminal care.

In the end stage of incurable disease various interventions have to prevent or control pain, convulsions, pulmonary oedema, vomiting, etc. If at any time before the onset of severe senility a sudden terminal state or clinical death occurs, emergency resuscitation should be applied. This should be extended into a prolonged life support, however, only if the mind can be recovered into a near pre-arest level. If soon after the start of the prolonged life support there is no chance to restore human mentation, continuance of prolonged life support is not justified. One should then allow the person to die. For similar reason, no resuscitation measures have to be applied in end stages of incurable diseases and in some extraordinary cases with entirely hopeless outcome where the conditions exclude the possibility to restore life and human mentation, e.g. in extremly severe brain and whole-body injuries, progressive sta-

ges of extensive intoxication, etc.

Research on humans can not be performed without informed consent (CPCR studies on comatose victims by consent of relatives). Animal research is regulated. Pain can and must be prevented. Both research and effective application of new resuscitation methods have to contribute to save the highest valus in the world - the human life.

COMPENDIUM OF GENERAL PATHOLOGICAL PHYSIOLOGY - Vol. 1
Autori: doc. MUDr. Oliver Rácz, CSc., MUDr. Jozef Kolenič, CSc.,
prof. MUDr. Rudolf Korec, DrSc., MVDr. František Ništiar, CSc.,
RNDr. Anna Šipulová, doc. MUDr. Anna Šofranková, CSc.,
prof. MUDr. Zoltán Tomori, DrSc.
Rozsah: 240 strán
Náklad: 120 výtlačkov
Vydanie prvé
Vydavateľ: Lekárska fakulta Univerzity P. J. Šafárika v Košiciach
Tlač: Edičné stredisko VVŠL gen. M. R. Štefánika v Košiciach
Vytlačené: február 1995