Pathological physiology as a science

30.9.2004

General teaching on diseases

Pathological anatomy | Pathobiochemistry | Pathological physiology

P.P. is a teaching on diseased functions, i.e. on etiology and pathogenesis of diseases based on experimenting and clinical observations incl. functional diagnostic

Methods: biophysical-physiological, mathematical (modelling)

Connection between a premorbid organism and a disease

Pathological physiology

- **Experimental**
- **Clinical = Clinical Physiology**:

Human person represents a complex „system“, „composed“ of hierarchically ordered „subsystems“ → hierarchical levels of study (e.g., of hypertension):

- Pathological Physiology
- Psychosomatics
- Social Medicine

Medical practice leans on scientific experience *and* medical experience

Etiology

Etiology – is the assignment of causes or reasons for phenomena. A description of the cause of a disease includes the identification of those factors that provoke the particular disease.

e.g. tuberculosis

In the etiology of particular disease, a range of extrinsic or exogenous factors in the environment must be considered along with a variety of intrinsic or endogenous characteristics of the individual.

Pathogenesis

Pathogenesis of a disease refers to the development or evolution of the disease.

To continue with the above mentioned example, the pathogenesis of tuberculosis would include the mechanisms whereby the invasion of the body by the tubercle bacillus ultimately leads to the observed abnormalities.

A given disease is not static, but it is a dynamic phenomenon with a rhythm and natural history of its own.

It is essential to keep in mind this concept of natural history and the range of variation among different diseases with respect to their natural history.

General pathophysiology

A. Health and disease.

- 1. Definition of health and disease
- 2. Pathogenic factors (physical, chemical and biological) and response of organism for them (adaptation, dysadaptation).
- 3. Types and degree of disease.
- 4. Death (clinical, biological, cerebral).

General pathophysiology

B: Cellular mechanisms in pathological stages

C. Reaction on damage of tissue integrity and infection.

- 1. Non-specific (innate) immunity: inflammation
- 2. Specific (acquire) immunity, acquire immune diseases (immunodeficiency, hypersensitivity and autoimmunity)

General pathophysiology

D: Growth and proliferation

- 1. Induction of proliferation and wound healing
- 2. Malignant proliferation
- 3. Tumour growth

E: Genetic background in etiopathogenesis of disease

monogenic diseases

polygenic disease (multifactorial)

Special pathophysiology

- Pathophysiology of organ systems
- Pathophysiology of organs

Definition of health

- Health – is a component of a general quality of life
- To declare a person or a group diseased ⇒ fateful consequences, broad social effects
- Law presupposes a definition of health

Concept of normality

- Most people have some notion of normal and would define disease or illness as a deviation from or an absence of that normal state.
- However, on closer scrutiny, the concept of normality turns out to be complex and cannot be defined succinctly, correspondingly, the concept of disease is farfrom simple.

Normality as health may be defined on various levels:

- *Biological (physical) normality:* A whole of undisturbed functions. There are, however, non-reflected presumptions: it is not said what is the aim of an organism. A "humanistic" definition must precede.
- *Psychological normality:* A well balanced result of an adequate self-esteem (self-confidence), of spontaneity and excitability Realistic attitude towards the aims of life and realistic individual desires, an ability to draw lessons from experience, sociability
- *Sociological normality:* An ability to fulfill expectations and roles in the frame of the existing social system
- *Normality of mind (spiritual):* An advancement of objectivity and reason, independency and finding ones identity, ability to love and creativity

Normality as viewed by law (juridical): Ability to work, lack of the necessity to be cared for.

„Ecological" defintion of WHO: State of perfect physical, psychical and social wellbeing, not only an absence of disease and infirmity.

Critique: The definition is an utopian one, it suggests omnipotency of a doctor and elicites an ungrounded expectation that such total subjective and objective wellbeing is realizable in a long run, definitely. It inspires to setting unrealizable, not to be fulfilled, demands on medicine: in the sense of maximum spending of resources and in the sense of competency in all problems of life – each form of neediness of help is regarded as disease. The health becomes a social norm which should be warranded by the state, possibly also forced out.

Physical health: functional vs. normative definition

Functional (descriptive) definition:

Positivists try to define disease as a disturbance of a function typical for the human species, ascertainable in a purely descriptive way (statistically). However, commonness is not identical with health and rareness with disease. Moreover, „the species-typical function" need not be desirable to a human subject under circumstances (e.g., fertility).

Normative (humanistic) definition:

Health is a bodily condition in which man is not limited in attaining his/her goals.

"Healthy is a man who – may be with objectivizable deficiencies or only with those which are patent to him alone – or without them; may be alone or with the help of others – finds, develops and maintains balance which enables him to live meaningfull life, focused on the development of his personal gifts and of his life disposition and attaining life goals within certain limits."

Summarily, the „functional" definitions of health are descriptive, explaining and value neutral;

„humanistic" definitions of diseases are normative, value-laden and inciting to act

The functional definition leans necessarily on a value definition, e.g. with the selection of individuals in the control (reference) sets.

A sober look – conditional health: Health is nothing ideal mostly. It rather encompasses the ability to live with disturbances and complaints which do not surpass some degree, individually and socioculturally conditioned and variable. Conflicts and small physical disturbances (e.g., small injuries) are almost obligatorily present in the life of man and animals. Health is not a point biological optimum, but rather a whole area of homeostasis. Everybody has several „week points" representing dispositions to various diseases

Definition of disease

Disease can be defined as a contradiction to health = „alternative model"

Or only as a contrary term – than, there is a whole array of intermediate steps:
- ideal health
- reasonably acceptable health
- predispositions
- feeling not well
- subclinical forms
- clinical forms
- foudroyant and fatal courses of disease

Normal and abnormal processes represent different points on the same continuous spectrum.

Definition of disease (BUCHBORN

- Feeling of bad health as a result of subjective and/or objective somato-psychical derangement, with/without subjective, medical or social need for help, as a result of disturbances in harmonic cooperation of individual functional parts and subsystems of an organism

A superposition of three aspects of a disease in medical practice (together: "morbus")

- a patient's point of view (aegritudo, illness)
- a doctor's point of view – objective in a medical description (nosos, disease)
- a point of view of the social milieu (a state of need and deficiency)

The concepts of health and disease relate to both natural and cultural phenomena

Stages of disease development

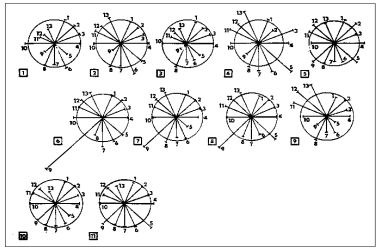
- Symptoms (prodromal stage)
- Acute disease (1-21 days)
- Chronic disease (above 40 days):
  - following after acute disease (chronic bronchitis in smokers)
  - primary chronic (e.g. Wegener´s granulomatosis)

A complication of a disease – is a new or separate process that may arise secondarily because of some change produced by the original entity

Resolution
Remision
Exacerbation

Identification of health and disease

- Interindividual variability → health and disease are probabilistic, not strictly deterministic phenomena;
- a diagnosis is a task of a statistical type.



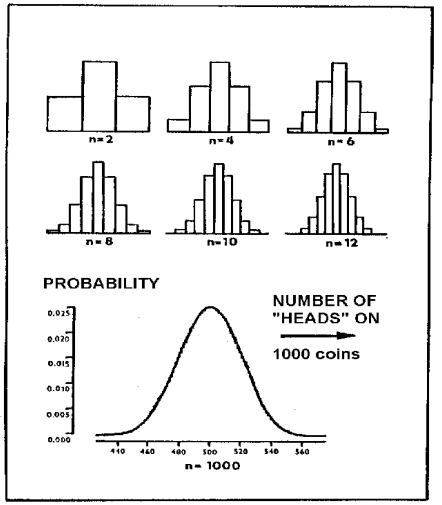
If only because of diagnostic aims, we must be well aware of the enormous extent of the interindividual variability among people and we must be able to work with it in our scientific methodology

Qualitative and quantitative characters in population

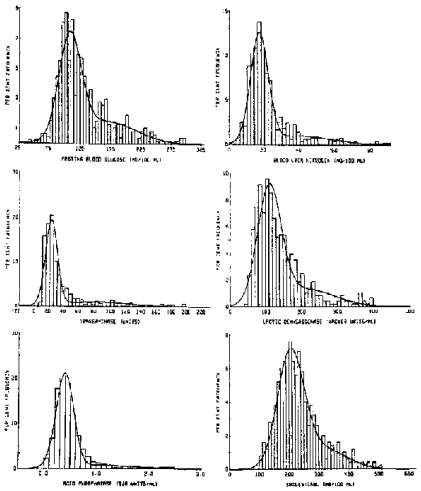
Characters
- qualitative
- quantitative
  - countable
  - metrical

We are interested in frequency distributions of quantitative characters – a starting point for determining s.c. normal (= reference) values

The simplest (binomial) model of the origin of a bell shaped, possibly „normal“ distribution. Normal distribution origins when the effects of infinitely many infinitely small factors composing a variable (body height, longevity etc.) are added

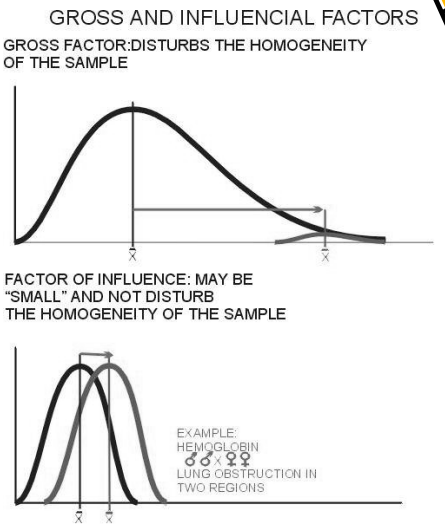


Empirical frequency distributions of metrical, diagnostically used (biochemical, „functional“ etc.) characters are bell-shaped generally, but mostly positively asymmetrical (correspondir more or less to the log-normal distribution)



Large and small factors, influential and non-influential factors, homogeneity of samples.

If only small factors are at play, one can speak on a homogeneous set. The difference between „large“ and „small“ factors is only relative, depending on the total number of the factors involved



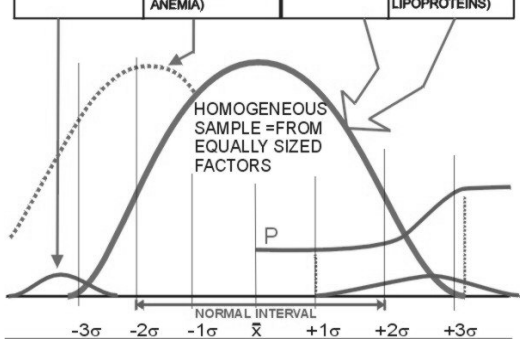
It is advisable to distinguish *large* and *small* factors creating the distributions.

A large (gross) factor is something what acts beyond the mechanism of the origin of a normal distribution. It disturbes the homogeneity of factors prescribed by this mechanism. One of the levels of the large factor must have a gross effect upon the trait, it must "move" the position of the trait in the affected individual strongly "to the right" or "to the left". Now, because of the blurring effect of the other factors, the result is as if the large factor created "its own" distribution, sometimes hidden in the general population.

Small factors correspond roughly to the prescription for the normal distribution. Their set creates something as a *homogeneous set* and correspondingly a homogeneous distribution arises

FACTORS

LARGE		SMALL	
RARE (NON-INFLUENTIAL)	COMMON (VERY INFLUENTIAL)	RARE (NEGLIGIBLE)	COMMON (INFLUENTIAL)
RARE SERIOUS TRAUMAS INTOXICATIONS INFECTIONS	HARMFUL INFLUENCES ON LARGE POPULATION SEGMENTS	NOT INTERESTING	COMMON INFLUENCES OF ENVIRONMENT, FOOD, MUSCLE ACTIVITY
RARE ALLELES ↓ MONOGENIC DISEASES	(COMMON ALLELES) ↓ SERIOUS DISEASE (SICKLE CELL ANEMIA)	NOT INTERESTING	COMMON ALLELES NEUTRAL (SEX, BLOOD GROUPS, PLASMA LIPOPROTEINS)



Large rare factors form small distributions on the sides of the general distribution, a large common factor would strongly „move“ a large segment of the population (a rare situation – e.g., G6PD polymorphisms); small factors produce by their combinations a homogeneous subset of the whole population. A „philosophy“ of the normal = reference interval of the diagnostic signs leans on an idea that the given disease acts as a large factor producing its own subdistribution. Ideally, we should know a probability (P) with which a specific level of a sign falls into „healthy“ or „pathological“ distribution

We may distinguish between *factors of influence* and *noninfluential factors*.

An influential factor need not be large: its effect regarding the position of an individual on the trait axis may be small, but its influence on the overall variance of a trait is large because the frequency of the variant of the factor is high and therefore its share in the overall variance of a trait is high as well.
The share in the variance is given as a product of the size of the effect and the relative variant frequency of the trait. It would be easy to present algebraic evidence that the contribution of a gene to the variance of a trait increases with the frequency of the two alleles when they approach 0.5, and an analogous consideration applies in cases involving more alleles.

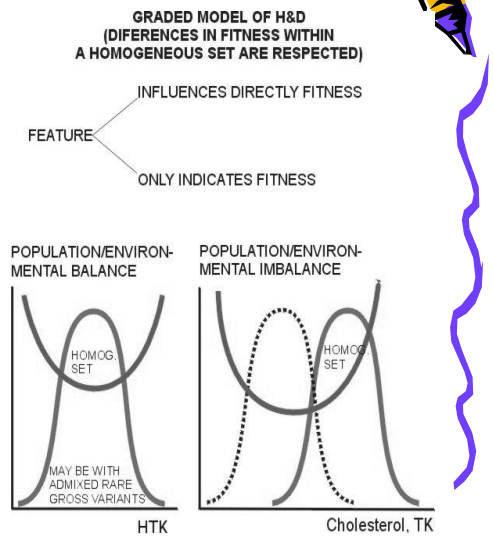
Example: sex as a factor of the hemoglobin concentration in the blood, or: the dynamic resistence of the airways in the polluted and non-polluted areas of comparable magnitude. Sometimes it is advisable to separate the variants of a trait according to even a small but influential factor, say, according to the sex, as in the example above.

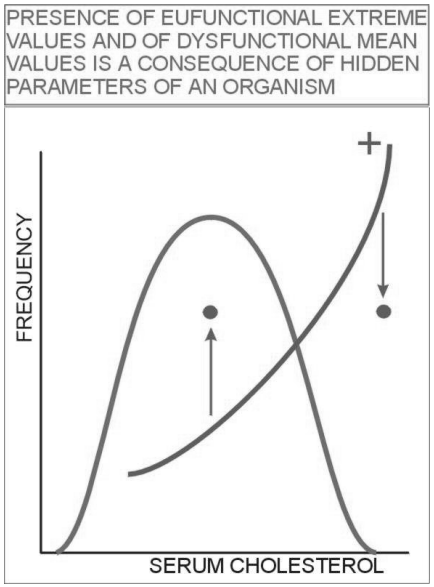
All realizable combinations of gross/small and influential/ noninfluential factors are exemplifiable both in genetic and environmental factors. Small factors create homogeneous sets of values (individuals, from the point of view of the trait). The influential small factors are much more important than the more or less negligible small rare factors. A large factor creates "its own" distribution, shifted by a step aside. Large factors are important even if rare, for the affected individuals at least. The most important - from the point of view of public health - are, however, the common large factors. They represent large genetic or environmental burden posed on the population. A large factor may not be connected with any pathology: sex in relation to the sexual traits, some blood group polymorphisms, skin colour according to the geographical differences etc. But some of them produce pathology, i.e., they are connected with states evaluated as undesirable, limitig our freedom etc. Examples are innumberable: all alleles producing serious Mendelian diseases, influence of high concentrated poisons, virulent bacteria, high radiation doses etc.

We may speak about a disease (intoxication, trauma) as an *alternative to health* when the difference is large and the step between them is rather steep. Of course, what is large and what small cannot be said or defined absolutely. Sometimes it is a matter of operational easiness or suitability: preventive medicine may regard infarction of a myocardium as a last step in a smoothly graded array of risks and intermediate traits, the emergency unit doctor will divide his patients in those having IM and those not having it.
From the diagnostic point of view, it is important to realize that if we subscribe to the alternative model of health and disease (for the particular case at least) the differences of the trait inside the "normal", control or healthy sample are usually regarded unimportant, uninteresting and they are often neglected. We will come later to the question how the diagnostic problem arising here is solved in the clinical practice by means of the so called normal (reference) intervals.

Features relevant from the point of view of health/adaptation are exposed to selection pressures.
A population may get beyond the adaptation optimum after the conditions have changed – typically in s.c. civilization diseases

As far as the population is not too far from the optimum (of the feature given), typical U-curves may take place:
either symmetrical around the population modal value (e.g., mortality as dependent on hematocrit),
or shifted beyond the modal value (a genotyp in imbalance with the environment in civilization diseases – blood pressure, plasma cholesterol etc.)

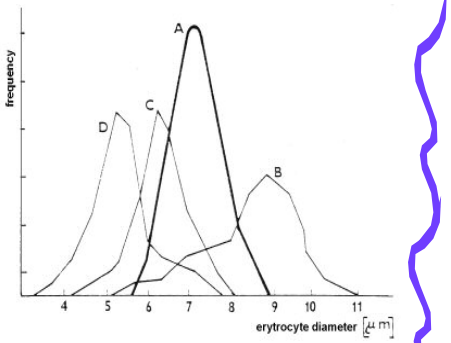




Comparing the alternative vs. continuous (graded) model of disease

Alternative model

- "All or none" rule
- Effect of a large factor ⇔ heterogeneity of a set of causes
- Detached distributions of quantitative traits
  (Fig. – RBC diameter)
- Curative medicine interested



Comparing the alternative vs. continuous (graded) model of disease

Continuous:

- Smooth transitions
- Homogeneous set of causes
- Single distribution
- Preventive medicine interested

Normality conception and its role in diagnostics

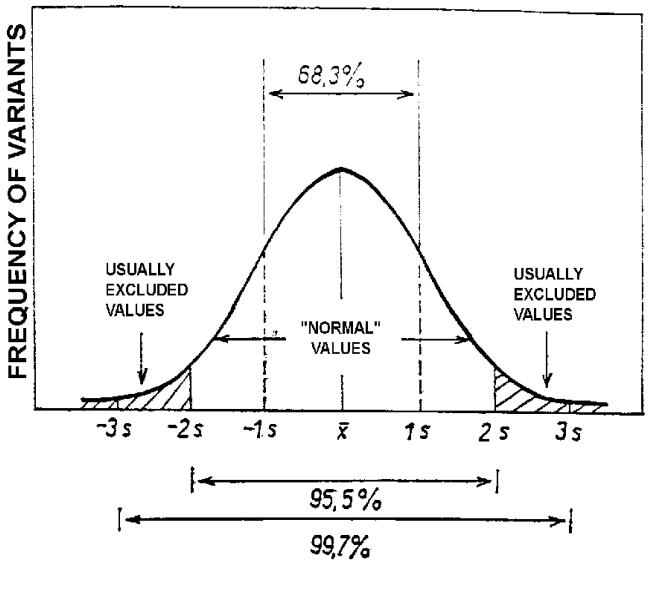
„Normal“ is currently a condensed term for „common and therefore healthy“: it is used so when we try to define health in a descriptive-statistical way. Those who derive health according to value criteria could do without it easily, using independently terms „healthy“ and „common“ according to the circumstances.

Statistical norms for health are set according to the value criteria valid in the particular time and place; it is a secondary step following the value decision.

There is some arbitrariness in the normative definition, namely according to the shared *interesses* prevailing in the particular era and place, and according to different viewpoints:

of insurence medicine (expected life span)
of preventive medicine (profylaxis of complications)
of epidemiology (weighting of risk factors) etc.

Fig.: A way of determining reference („normal“) interval



The reference interval is of use only in the alternative model; even here it does not say too much without knowing the positions of the alternatives. The term „normal“ itself in the sense of „common“ (and not perhaps „optimum“) coud be applied only on alternative situations

How can a position of a patient in an edge of a reference interval (or beyond the interval at all) be interpreted:

-Preinstrumental error (e.g., a way of blood withdrawal)
-Instrumental error (dispersion of readings and/or systematic error, e.g.,
with a spectrofotometric determining of stuff concentrations)
-Intraindividual fluctuations of the variable measured
-The person counts to the 5% of healthy individuals who are used to be
excluded from the reference interval definitorically
-Eufunctional extreme (individual norm is not severed)
-A real pathology – we mostly do not know, however, with what probability

A problem evoked by not-demanded information: the not-demanded readings could be (under circumstances):

-repeated, may be monitored in a long run (lowering of the preinstrumental and instrumental error, intraindividual fluctuations)

-supplemented by anamnestic data and further findings (enhancement or lowering of probability that they form a component of some broader syndrom or disease)

-ignore in the end

Recommended textbooks of pathophysiology

Kaufman C.E. and McKee, P.A.: Essentials of Pathophysiology.
Little, Brown and Company, Boston, 1996, ISBN 0-316-48405-9
(high pregradual standard, but no general pathophysiology)

Nowak T.J. and Handford A.G.: Essentials of Pathophysiology.
Wm. C. Brown Publishers, Dubuque, Iowa, 1994.
ISBN 0-697-133314-1
(for paramedical professionals only, but with good drawings and some chapters on general pathophysiology)

Essential pathophysiology questions

- How?
- Why???
- You can find the lectures on:

  http://www.med.muni.cz/patfyz/patfyzc.html
  Výuka
  Prof. MUDr. Anna Vašků
  Doc. MUDr. Lydie Izakovičová Hollá