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)

1 Pathological Physiology as a science

General teaching on diseases s.s
- 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 diagnostics.
Methods: biophysical-physiological, mathematical (modelling)
Connections between a premorbid organism and a disease

Pathological Physiology
- Experimental
- Clinical = Clinical Physiology: works under clinical conditions
  methods: - functional diagnostics
  - clinical diagnostics
  - epidemiological methods

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

2 Definition of health

Philosophy of prosperity is interested in definitions of health and disease

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

Pathology must define its realm of activity

E.g., understanding of homosexuality:
crime - developmental redardation of personality – dropping from the list of diseases 1973 in the USA (→ minority variant, "anomaly")

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: „descriptive", „functional", and „value", „humanistic", „normative" definition

Descriptive, „functional" 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)
„Value", „humanistic", „normative" 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 ceratin 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

3 Definition of disease

Disease could be grasped 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
A 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

A definition of a disability and of a handicap
NORDENFELT is right when he suggests that disabilities and handicaps should be determined in relation to the individual's own vital goals. *A vital goal* is a state of affairs that is a necessary condition for the realization of a persons's at least minimal happiness in the long run. Everything that is necessary for survival belongs to the vital goals of a person. Most people consider marrying and establishing a family to be a vital goal, too, but this is not universally so. The individual's own vital goals are certainly partly influenced by cultural norms and cultural demands, but they are not completely determined by them
Disability is a non-ability to perform a *basic action*, i.e., simple intentional movements of one's limbs or other parts of the body.
Handicap is a non-ability to perform a *generated action*, i.e., an action caused by the performance of some other action, for instance, a non-ability to perform one's work properly. Handicap is therefore conditioned by disability and disability is produced by some disease.

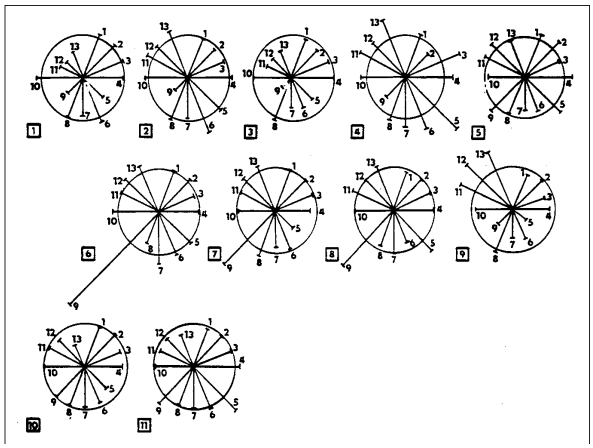
S.c. theories of disease are only hypotheses (VIRCHOV´s cellular pathology, SPERANSKY´s and PAVLOV´s nervism, SELYE´s stress theory etc.)

A disease and the purposefulness of the body

A teleonomic principle, i.e. focusing on an aim, is not valid absolutely in the body, but only in a particular context. It may even become a pathogenetic principle, as in the case of autoimmune diseases. The body as a whole as well its individual organs and functions cannot be optimalized under all aspects at the same time (s.c. constraints)

4 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. A diagnosis is a pattern recognition task:
A, A, *A*, A, △...



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Pathological states display some form of regularity, of course, and follow certain patterns in a typical case. Now, making a diagnose could be understood as a patttern recognition. It means, we have some typical pathological pictures, patterns, in our mind (or in our computer databases), we compare the individual patients staying in front of us with these patterns and we try to subsume the individual pathological picture under some general pattern of a disease. The general pathological patterns are not sharp, however. They represent a sediment of an experience of generations of doctors, destilled as if from a vast number of individual cases. The variability among individuals, the interindividual variability, differences among both healthy and deseased people, blur these patterns, make all those textbook pathological "nosological units" out of focus. As with other general concepts describing the real world, we speak about *family resemblance* only, not about exactly defined entities. Now, the task is to make a diagnose in spite of the presence of this blurring interindividual variability

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

Fig. 1 "Profiles" of individuals regarding their physiological and biochemical traits. Paralelly in the 60ies, a gene polymorfism has been studied by electrophoretic methods. Currently - polymorphisms on the DNA level: exon mutations, mutations in regulatory sequences, composed alleles
We are interested in frequency distributions of quantitative characters – a starting point for determining s.c. normal (= reference) values

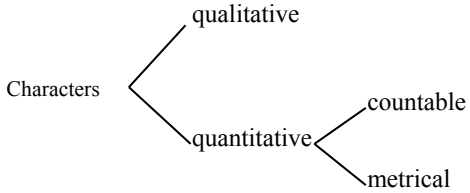

Fig. 2 Empirical frequency distributions of metrical, diagnostically used (biochemical, „functional“ etc.) characters are bell-shaped generally, but mostly positively asymmetrical (corresponding more or less to the log-normal distribution)

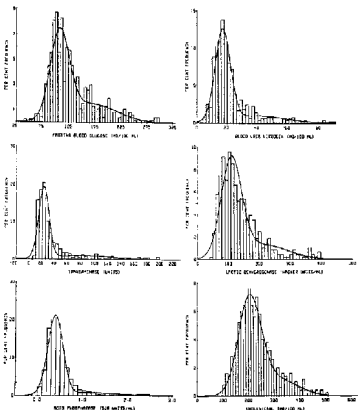

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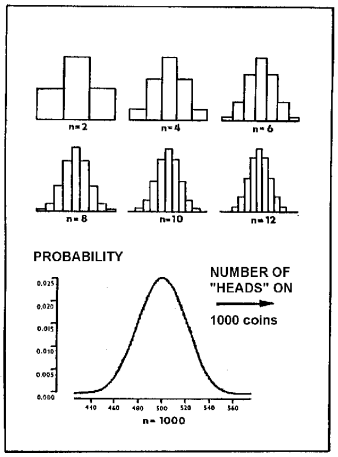
Fig.3. The simplest (binomial) model of the origin of a bell-shaped, possibly „normal“ distribution. Normal distribution origins when the effects of infinitely many infinitely small factors composing a variable (body height, longevity etc.) are added



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The origin of the binomial distribution can be conceived in the following way: Let us toss a coin and record the outcome, i.e. the side on which the coin landed. Conventionally, one of the outcomes is assigned the score 1 (success), the other zero (failure). The terms of success and failure are not quite fortunate, because they may not have anything in common with biological reality. The coin may be equilibrated, making the probability *p* of a success equal to the probability (1-p) = *q* of a failure, but in case of unbalanced coin p ≠ q.

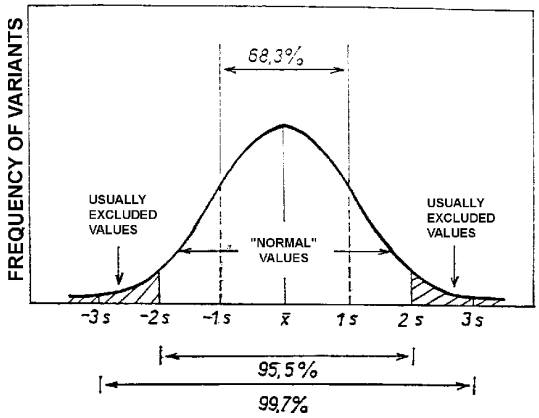
Most actual experiments are not comprised of isolated trials, but groups of them. When two or more coins are tossed simultaneously - or one coin is tossed n-times - and the successes and failures are summed up (the zeros and the ones), the sum represents one of the variants of the variable (trait) X, i.e., one numerical value, and this may be put on the X-axis

If we carry out the whole procedure several times (N-times) and put the frequences of the individual sums (variants) on the Y-axis, we get an empirical distribution which approaches the binomial distribution with growing N. The number of coins tossed in parallel determines the order of the distribution and is designated as *n*

Pure intuition makes it clear that on tossing 5 coins where *p*=0.4 the most uncommon situations will be those where all the 5 coins will land mutually independently on the same sides, making the score of successes for all the coins equal to either 0 or 5. On the other hand, the most common variants will be those where 3 coins will score 0 and two will score 1 each (or vice versa)

From the viewpoint of the analysis of the genetic architecture of the intermediate traits, the binomial distribution needs to be interpreted in the following way: One trial (a toss of one coin) corresponds to one locus/gene, the two possible outcomes of the trial represent two variants of the gene (its alleles), probabilities *p* and *q* correspond to the probabilities of these alleles occurring in the population, score 0 corresponds to the low-level allele (a failure) and score 1 corresponds to the high-level allele (a success). The X-axis, i.e. the sum of the successes, corresponds to the size of the trait. The set of parallel trials with one sum of outcomes (a point on the X-axis) corresponds to the value of the trait in a single person. The whole binomial distribution corresponds to the distribution of the trait in the population. Apparently, for the purpose of solving our problem, the binomial model will have to be substituted with a much more universal model, even though the binomial model offers a powerfull means for the solution of simple situations

Fig. 4: A way of determining reference („normal“) interval



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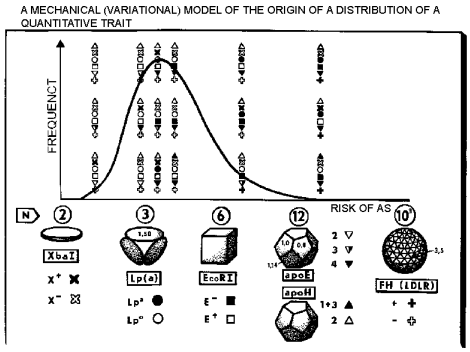

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Fig. 5: As a first approximation, dispositions to common diseases are transmitted according to combinatorial rules. „Binomial process“ should be generalized for general number of variants, general probabilities general effects. Besides, synergistic effects („nonlinear interactions“ etc.) fall beyond the scope of combinatorics

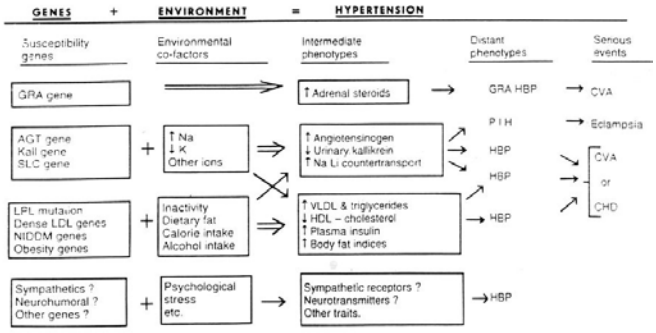

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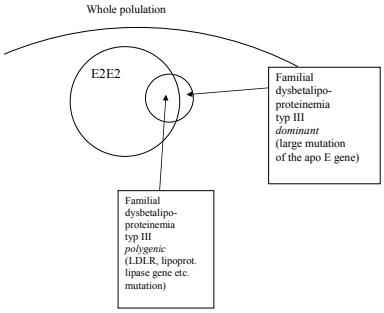
Fig. 6: Genetic architecture of a common, „civilization“ disease like essential hypertension

GRA = glucocorticoid remediable aldosteronism
AGT = angiotensinogen
Kal = kallikrein
SLC = sodium-lithium carrier
EH = esential hypertension
PIH = pregnancy induced hypertension
CV = cerebrovascular accidents

An organism behaves as a system, and the theory of dynamic systems is undoubtedly its legitimate model. However, this theory operates with such terms as "peculiar attractors", "disasters", "bifurcations", "saddles", "limiting cycles", etc. which mainly express "unexpectable" modes of behaviour of the dynamic systems under specified circumstances. For the sake of brevity, we shall speak of "non-linear interactions" to describe situations where the effects of the factors are not just added or multiplied

Examples of „non-linear“ interactions

Example1. The apo E polymorfism and the mutations in lipoproteine lipase:



The mutations of the second gene in the polygenic form → marked hypercholesterolemia much higher than should correspond to the effects of both components alone (E2E2 + e.g., LDLR)

EXAMPLE OF A „NONLINEAR“ GENETIC INTERACTION

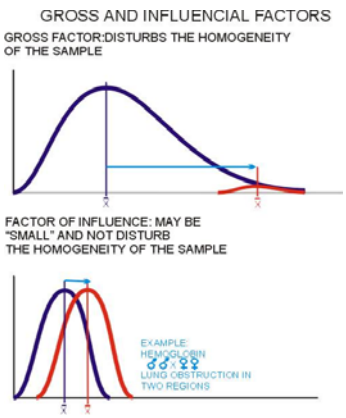
RECEPTOR FOR AT II

ACE	AA	AC	CC
II			
ID			
DD	1,05	IM 1,52	3,95
DD	1,64	7,03	13,3

Example 2. Fig. 7 Probability of the origin of IM rises according to the genotype of the angiotensin II receptor, but only in the carriers of DD genotype of the angiotensin convertase. The phenomenon is especially well expressed in the group of patients without the classical risiko factors for IM (bottom row)

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

Fig. 8 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



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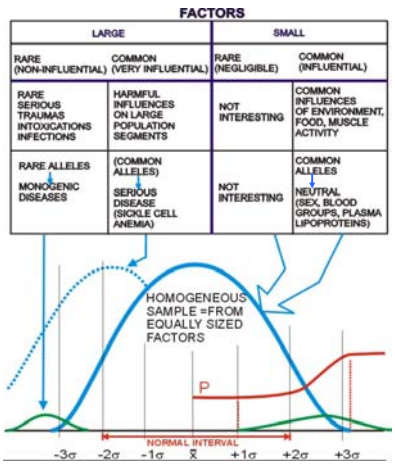
It is advisable to distinguish *large* and *small* factors creating the distributions. *A large (gross)* factor is something what acts beyond the mechanism of the origin of a normal distribution. It disturbes the homogeneity of factors prescribed by this mechanism. One of the levels of the large factor 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



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Alternative model of health and disease

Fig. 9 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.

5 Pathology may origin just inside a homogeneous set

A feature of any origin may correlate with the health status, therefore also a feature conditioned by a homogeneous set of factors → graded model of health and disease

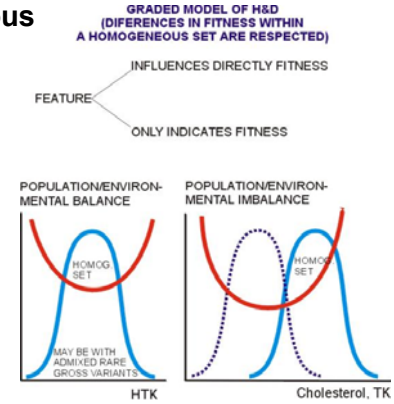
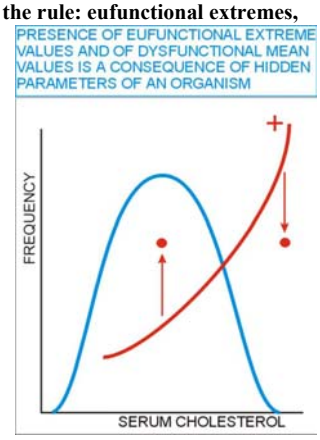


Fig. 10 Features relevant from the point of view of health/adaptation are exposed to selection pressures.
A population may get beyond the adaptation optimum after the conditions have changed – typically in s.c. civilization diseases
As far as the population is not too far from the optimum (of the feature 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.)

An important exception from the rule: eufunctional extremes, dysfunctional mean values.

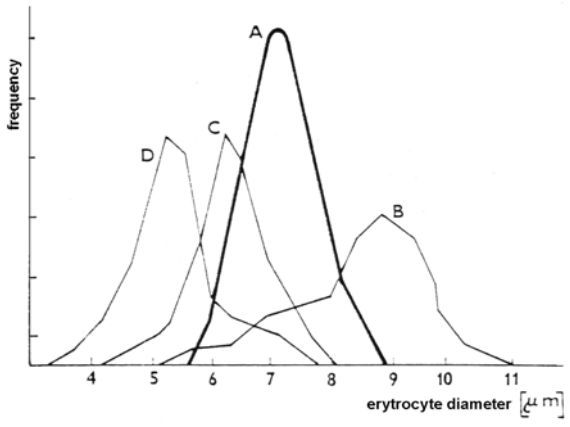
Fig. 11 Hidden parameters may cause deviations from the „mean" courses of the curves. Knowing a patient´s premorbid values would be the best solution



6 Comparing the alternative and 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. 12 – RBC diameter)
- Curative medicine interested

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



7 Normality conception and its role in diagnostics

Fig. 4 – definition of the normal or reference interval

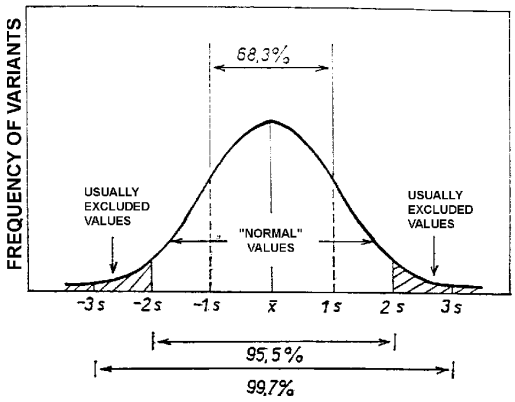
„Normal“ is currently a condensed term for „common and therefore healthy“: it is used so when we try to define health in a descriptive-statistical way. Those who derive health according to value criteria could do without it easily, using independently terms „healthy“ and „common“ according to the circumstances.

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



A history of the normality concept:

In Classical times and in Renaissance, „Normal“ often in a sense of "naturalis", and this again in the sense of „mean“, but *at the same time* in a sense of „healthy“, therefore ambiguity. The 18. and 19. century: the concept of health substituted by the concept of normality (normalcy) –Science became positivist and got rid of evaluative elements

Anomalous is derived from the Greek ANOMALÓS = unequal, it is a descriptive term, meaning a *functionally irrelevant deviation* from the species type, basis of individual distinctiveness

Anormal is a sonsequence of an erroneous derivation of the term „anomal“ from the Greek NÓMOS = norma in Latin, whereby a descriptive term has been converted into a normative one. "Anormal" means *pathological* in this way

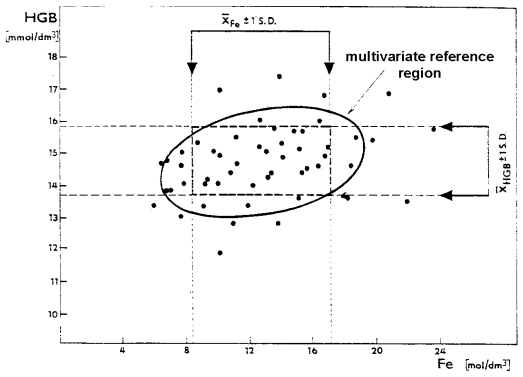
The reference interval is of use only in the alternative model; even here it does not say too much without knowing the positions of the alternatives. The term „normal“ itself in the sense of „common“ (and not perhaps „optimum“) coud be applied only on alternative situations

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



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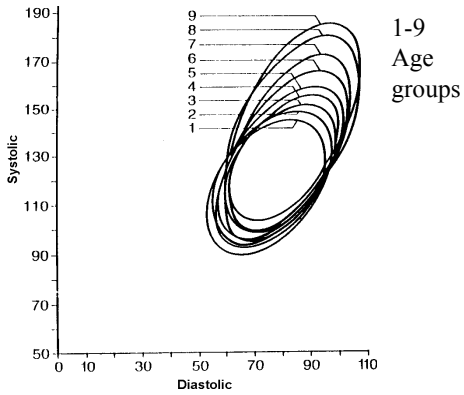

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Multivariational norm: Fig. 13 and 14

In the backgroud, there is an idea of an abstract optimum relational structure (of an „invariant“), examples: a constancy of the dimensionless relationships in the circulatory system of mammals, a constancy of the degree of V´/Q´ heterogeneity in the lungs of various classes of Vertebrates