CLINIC AND PRACTICE

Cellular defects as guiding principle of the therapy

Diagnosis and therapy in medicine have been and are reflexions of the momentary state of knowledge. The diagnosis, in fact, keeps better up with the theoretical knowledge than the therapy, which must usually, with difficulty and often over generations, fight for the practical consequences of really progressive knowledge.

The historic metamorphosis of occidental medicine ranges from the supernatural abilities (loans) of Cheiron and Asklepios to the molecular-biological details of our days – or from the God-priest medicine of the inconceivable in antiquity to the biology of atoms and molecules in the area of the no longer visible and no longer imaginable dimensions. Medical diagnosis approaches this field reluctantly, and the principles of therapy are still based upon the dimensions of the visible, controllable, objectively demonstrable, if possible measurable. The clinical findings on the body, on the organs, on parts of organs (tissues) or products of organs (secretions), which must be rendered visible, constitute the outlines of therapy.

These comparatively rough proportions necessarily make the therapy symptomatic rather than causal. The last sequelae of the long chain of causes are followed up so as to eliminate them if possible, and the beginnings and connecting links are often difficult to trace by scientific parameters and thus ill-suited to a therapy relying on control and objectivity.

We measure the immunoglobulins and divide the states of a disease by these final products of a long process of cellular synthesis, and observe the retarded sequelae, not the causes. The metabolic diseases are divided by groups of material, metabolic disturbances of proteins, lipoids, carbohydrates, instead of finding out whether the metabolism is disturbed in the mitochondria or ill-regulated in the ribosomes, inhibited in the cytomembranes or misprogrammed already in the nucleus.

If one submits to the cogent logic that every control or miscontrol in the body must originate from a biochemical reaction from cells or cell organelles, this origin of disease should be made the ther-

apeutic leitmotif where the origin is known. Possibilities and realities of a causal therapy make the subject of the considerations given hereafter.

The diseases of the blood-forming system

are usually divided under quantitative viewpoints – anemia/hyperglobulinemia; leukopenia/leukocytosis – which direct the therapeutic tendencies automatically to the quantitative deviation; substitutions and destruction take place. As for anemia, a cogent relation to cellular and subcellular structures results here already.

The globin of the *hemoglobin molecule* shows characteristic innate abnormalities:

1. Deviations within the rate of synthesis in one of the polypeptide chains of the hemoglobin molecule provoke *thalassemia*.
2. Tissue defective through amino-acid, with an amino-acid substituted by another in the alpha-, beta-, gamma- or delta-chains (e.g. in *sickle-cell anemia*/fig. 297) or with an amino-acid lacking without substitution (e.g. in the *hemoglobin M-Freiburg*).
3. Disturbed sequence of amino-acids in the beta- and delta-chains provoking *lepore hemoglobins* and *thalassemia-like diseases*. 13 abnormalities in alpha-chains, 23 abnormalities in beta-chains have been differentiated, 2 dozen are not yet differentiable.

Anemia is the common result of the much differentiated abnormalities; in part of the cases, the changed sequence of amino-acids reduces the stability of the hem-group of iron. Hemoglobin S and hemoglobin C in a reduced condition are less soluble than hemoglobin A_1; when the oxygen saturation declines, crystals of hemoglobin will form, the shape of the erythrocytes changes to the sickle-cell phenomenon. The dispersion of the hemoglobin in the erythrocytes is disturbed in carriers of the hemoglobins C, E and in thalassemia; hemoglobin occurs chiefly in the center and periphery of the erythrocytes. The morphological outcome is the target cells, the clinical result is a reduced survival of the erythrocytes, hemolytic anemia.

Innate or acquired insufficiencies or depressions of the hematopoietic tissues – *thrombocytopenia, leukopenia, anemia, panmyelopathia* – have for decades come under the therapeutic axiom of substitution. Here, too, it is advisable though only in part of the cases possible, to implant or transplant bone-marrow for causal stimulation instead of symptomatic substitution at the end of the chain.

Immun-insufficiency – immun-depression

Insufficient immunity is identified serologically and immunochemically i.e. diagnosed by secondary findings (immunoglobulins in the serum) or tertiary mechanisms (method of precipitation, stimulation test). Of the division of primary immunoinsufficiencies established by the WHO-committee, all are of cellular origin (tab. 13, 14).

Whereas the therapy has hitherto been based upon the idea of substituting lacking products of synthesis, the causal attack on the sites of cellular origin is more logic and more promising. Since

insufficiencies of tissue and organs are in question, a biological stimulation of the insufficient cellular units ought to be tried. Effective ways to the not tissue-identical implantations of fetal liver or thymus tissues via the HLA-identical transplantations of bone-marrow are approached just reluctantly (tab. 14, fig. 205, 206).

The neuralgic point of these insufficiencies declared as cellular lies in the ribosomes of the endoplasmatic reticulum. The cause may be alone a false information of DNA – like in the hereditary and sex-linked forms – or originate on the way: r-RNA → m-RNA → transfer RNA, or in the final processing of the protein structure.

As to the therapy, success can be anticipated for these ailments only if one does not rely on a substitution of the final products IgA, IgM and IgG but tries to repair the «manufacturing base».

Equal origin – different sequences

Let us consider the problems from another perspective. The manuals of medicine aiming at a systematizing order include clinical aspects as e. g.

enchondral dysostosis,
mucopolysaccharidosis,
sphingolipidosis,
disturbances of the glycoprotein metabolism,

i. e. groups of ailments comprising a total of 22 well defined nosologic pathological units in quite different chapters: disorders of the skeleton, metabolic diseases, affections of the central nervous system. The symptomatological variety can be brought to a common denominator: lysosomal defects (see tab. 22).

The *lysosomes* are cellular organelles serving with their oxyreductases and differentiated hydrolases for the rapid rebuilding and disintegration of superfluous structures; they play an important part in the quickly changing formations of embryonic and fetal life. As substrate is dammed up, storage cells with an extended cytoplasma space such as in Morbus Gaucher (fig. 209) grow, because the enzyme gluco-cerebroside-beta-glucosidase is lacking.

In mucopolysaccharidosis, the sulphatases, iduronidases and glucoronidases of the lysosomes (see tab. 22) are deficient.

The example of the relations between lysosomes and circumscribed aspects explains the causal nexus between cell organelles, their contents and the somatic and spiritual influences (tab. 22, lysosomal diseases). It appears that quite different clinical aspects have a common topographic denominator, the lysosomes, and that the therapy must centre on this conditions. Similar statements apply also to other cell organelles, especially to the large number of membraneous diseases. The clinical aspects, however, ought to be treated in the clinical chapters because only the correlation-principle has to be shown. The Fabry syndrome alone has been picked out for an example.

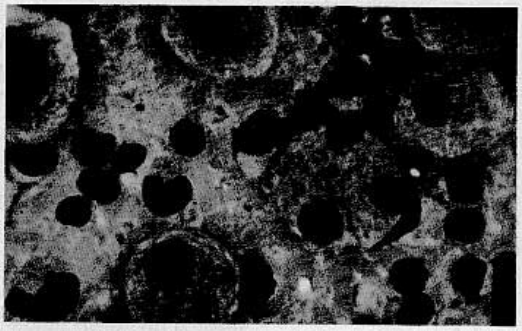

Fig. 209: Gaucher cells: spleen

Tab. 22: **Lysosomal diseases (genetic defects of lysosomal enzymes)**

Mucopolysaccharidoses

• = *Leading clinical symptoms*

Disease (syndrome)	Enzyme defect	Metabolic disorder (affected substrate)
Mucopolysaccharidosis I (Pfaundler-Hurler-S., Dysotosis multiplex, Gargoylism)	α-L-iduronidase	Dermatan-sulphate Heparan sulphate
• *Skeleton symptoms – Storage symptoms – Mental retardation. Disproportionate nanism, thoracolumbal gibbus, macrocephalic dyscephalia, typical physiognomy («gargoyle face») hepatosplenomegalia, opacity of the cornea, steadily increasing backwardness of mental development*		
Mucopolysaccharidosis II (Hunter's syndrome)	Iduronate-sulphatase	Dermatan-sulphate Heparan-sulphate
• *Symptoms similar to I, but milder. Skeleton changes and mental development impaired. Hepatosplenomegaly, no opacity of the cornea, defective hearing. Only male sex afflicted.*		
Mucopolysaccharidosis III (Sanfillipo-syndrome, Oligophrenia-polydystrophica) Subtype A Subtype B	Heparan N-sulphatase (Heparan-sulphamidase) α-N-acetylglucosaminidase	Heparan-sulphate
• *Progressive mental reduction with disturbed behaviour, aggressivity Hypertrichosis; enlargement of the liver, no splenomegaly.*		
Mucopolysaccharidosis IV (Morquio-Brailsford-S)	N-acetylhexosamin-6 sulphatase	Keratan-sulphate Chondroitin-6-sulphate
• *Disproportionate nanism due to platyspondyly. Projecting sternum. Angular knees. Normal mental development. Slight opacity of cornea, sometimes hepatomegaly.*		
Mucopolysaccharidosis V (Ullrich-Scheie's disease)	α-L-iduronidase	Dermatan-sulphate Heparan-sulphate
• *Moderate skeleton changes like type I and slighter hepatosplenomegaly. Dense opacity of the cornea; normal mental development. Multiple articular contractions*		
Mucopolysaccharidosis VI (Maroteaux-Lamy's s.) Syndrome of lacking β-glucuronidase Chondroitin-IV-sulphate mucopolysaccharidosis	N-acetyl-galactosamin-4-sulphatase (arylsulphatase B) β-glucuronidase	Dermatan-sulphate Heparan-sulphate Chondroitin-VI-sulphate
• *Intense nanism with chondrodysplasia-like proportions and, in certain circumstances, morquio-like changes of the spinal column. Hard features, hepatosplenomegaly, opacity of the cornea; normal intelligence.*		

Sphingolipidosis

GM_1-gangliosidosis (generalised gangliosidosis; pseudo-Hurler's disease; Landing syndrome)	Galactosidase	GM_1-gangliosides Glycopeptides Keratan-sulphate
• *Hypotonia of muscles, motor regression, neurological deficiencies, skeleton changes, in case distended abdomen.*		

Disease (syndrome)	Enzyme defect	Metabolic disorder (affected substrate)
GM_2-gangliosidosis (Tay-Sachs' disease, juvenile form)	β-N-acetylhexosaminidase A	AGM_2-gangliosides
• *Psychomotor retardation. limited motility of joints. Hepatosplenomegaly; red macular spots (50 % of the cases) Macroglossy, gingivahyperplasia; coarse physiognomy. Vacuolised lymphocytes.*		
Sanhoff's syndrome (Tay-Sachs'-O-variant)	β-N-acetylhexosaminidase	GM_2-ganglioside Globosides
• *Storage of gangliosides in the brain with progredient deficiencies.*		
AB-variant	GM_2-ganglioside-β-N-acetylgalactosidase	GM_2-gangliosides
Morbus KRABBE	Galacto-cerebroside β-galactosidase	Galactosylceramide; galactosylsphingosin monogalactosyl-diglyceride
«Slowly progredient encephalitis»		
• *Cerebral-degenerative symptoms with seizures. «Slowly progredient encephalitis». Beginning in the early infancy.*		
Morbus GAUCHER	Gluco-cerebroside-β-glucosidase	Glucosylceramide
• *Two forms: Infantile form with moderate hepatosplenomegaly, increasing bulbar deficiencies (dysphagia, strabism, opisthotonus); normal fundi Adult form: splenomegaly more distinct than hepatomegaly. «Hypersplenism»: leukopenia, haemorrhages. Changes of bones (Perthes' necrosis), articular disorders.*		
Morbus FABRY	α-galactosidase (ceramide-trihexosidase)	Trihexosylceramide; digalactosylceramide
• *Angiokeratoma corporis diffusum; cornea-dystrophy; cardiovascular, renal degeneration.*		
Metachromatic leukodystrophy	Cerebroside-sulphatase (arylsulphatase A)	Sulphatides
• *Steadily increasing mental retardation. Death mostly till the 10th year. Disturbance of the statomotor development in early infancy with muscular hypertonia, hyperreflexia. Muscular atrophy with growing involvement of peripheral nerves, specially in the lower extremities.*		
Lack of polysulphatase	Arylsulphatases A, B, C Sterol-sulphatases Mucopolysaccharide sulph.	Sulphatides Mucopoly-saccharides Sterol-sulphates
Morbus NIEMANN-PICK	Sphingomyelinase	Sphingomyelin
• *4 clinical variants:* *A. Serious retardation of development, considerable hepatosplenomegaly, macula degeneration to blindness. Death in the first two years.* *B. Storage without involvement of ZNS.* *C. Most frequent form, manifestation in late infancy, survival 3 – 6 years. Progredient statomotor and mental deficiencies.* *D. Manifestation in mid-childhood, survival till 2nd decade of life*		
Morbus FARBER	Ceramidase	Ceramides
• *Reddened cutaneous nodes to plaques, swelling and rigidity of the extremities. Dysphonia. Rise in temperature. Articular, cerebral and cardiopulmonal symptoms possible.*		

Disease (syndrome)	Enzyme defect	Metabolic disorder (affected substrate)

Disorders of the glycoprotein metabolism

Fucosidosis	α-L-fucosidase	Glycoprotein fragments Glycolipids

- *Hypotonia, resulting in spastic tetraplegia and growing decerebration rigidity. Frequent infections of the respiratory passages, hyperhidrosis, cardiomegaly. Hurler-like phenotype, death mostly before the 6th year.*

Mannosidosis	α-mannosidase	Glycoprotein fragments

- *Muscular hypotonia, hepatosplenomegaly, opacity of the lens, abnormal bone-structure, vacuolised lymphocytes, accumulated infections of the respiratory passages, Hurler-like phenotype.*

Aspartylglycosaminuria	Aspartylglucosylaminase	Aspartyl-2-deoxy-2-acetamido-glucosylamin

- *Mental retardation, opacity of the lens, hepatomegaly Changes of bones like in mucopolysaccharidosis.*

Lack of β-xylosidase	β-xylosidase	Xylose

- *Mental retardation, spasm, vomiting, recurrent infections of the respiratory passages.*

Further lysosomal enzymatic defects

Pompe's disease	α-glucosidase	Glycogen

- *2 forms: infantile and adult forms Generalised glycogenosis; vomiting, anorexia, dystrophy, cardiomegaly with dyspnoea and cyanosis. Storage mostly in muscles, liver and nervous system. Infantile form: death within the 1st year*

Morbus WOLMAN	Acid lipase	Cholesterol-ester Triglycerides
Lack of acid phosphatase	Acid phosphatase	

- *Hepatosplenomegaly, blown-out abdomen, anaemia, vacuolisation of lymphocytes; no ZNS-symptoms! Vomiting, diarrhea. Adrenal calcination. Death from inanition within the first 4 years.*

Fabry's disease

(Angiokeratoma corporis diffusum universale, FABRY, 1898; referred to also as RUITER-POMPEN-WYERS syndrome (1939) after the discoverers of the relations to participations of inner organs.)

The X-chromosomal inheritable enzymopathy of lysosomal localisation is accompanied by storage of trihexosylceramide through lack of alpha-galactosidase. Intarsia-like deposits of livid to blackish colour occur in the skin and mucosae. Paraesthesia, rheumatoid pain, subsidence of mental power, cardiovaso-renal symptoms (edema, dilatation of the heart, renal insufficiency) and ocular symptoms (ampoule-like conjunctival

veins, Tortuositas vasorum retinae, spot-like opacity of the cornea) indicate the extended deposits. This ailment occurs chiefly in the male sex.

The prognosis, serious especially if kidneys and eyes are involved, seems to be influenced with a longer lasting effect by implantation of fetal liver cells (TOURAINE I. L. et al., 1979) than by other measures such as transplantation of kidneys, steroid hormones or azothioprines. The authors discuss a «colonization» of lysosomal enzymes.

Membrane dysfunctions

Membranes are cell organelles separating ecological spaces, on the one hand, and assuring the necessary exchange of material and fluids, on the other hand. This is effected by a structure of 3 lipophile and hydrophile layers, an accordion-like elasticity, a special outfit of enzymes and the apparatus for the transport of ions, with calcium/magnesium and sodium/potassium taking a key-position.

Membrane defects and dysfunctions include pathological units of all age groups:

1. Innate metabolic disturbances;
2. Acquired membrane dysfunctions;
3. Responsibility for the control of immunological identity.

Any body-cell can have membrane dysfunctions if it is supposed that the erythrocytes without nucleus have the properties of blood-groups in their membranes. In pathology, the membranes in the kidneys, in the lungs and in the gastrointestinal tract are of greater importance because metabolic processes essential for the continuance in life take place.

The innate defects of the *renal-tubulus epithelia* cause aspects characterized by an increased loss of substrate through the urine, on the one hand, and by a corresponding lack of substrates in the body, on the other hand: amino-acids are secreted in the urine selectively or generally, the excretion of protein and sugar increases. The organism lacks these substances specially in the period of growth, which causes delays of growth and partly serious rickets-like changes of the skeleton.

Acquired nephrosis is accounted for by a similar loss of membrane function. In most of the chronic renal disorders, the changes of the basal membrane and of the tubulus apparatus are the essential pathological deviations.

An improper outfit of enzymes in the intestinal epithelia same as cases of lacking disaccharase or of intolerance to fructose cause delay of growth and emaciation just as immunological alterations of the intestinal epithelia in allergies to cow's milk, egg, fish and other nutritive allergens.

A decisive part in the aging process of the tissues is ascribed also to the rigidity, thickening and loss of functions of the cell membranes connected therewith.