Genetic aberrations

The genetic i.e. hereditary illnesses and abnormalities comprise nosological units under the mode of inheritance. According to this individual criterium, dominant, recessive and sex-linked hereditary diseases are comprised. The cellular primary defect and the clinical symptoms give heterogeneous and heteromorphous pictures.

On principle, *enzymes or substrates* or both metabolic components can be affected. The connection between these biochemical constituents is outlined in fig. 256 a, b. Enzymes are pilots catalyzing the transformation of biochemical substances without being part of the balance of this process. Normally, a substrate (1) is conveyed into another substrate (2) by an enzyme (alpha) (fig. 256 a).

The damming up overcharges the cell with undigested metabolites, disturbances of the cellular metabolism, inflation of the cytoplasm, storage.

The absence or want of substrate 2 causes the interruption of the metabolic chain at this point, from which disturbances of growth and development, dystrophy, skeletal abnormalities result.

These then are the two cardinal processes in innate metabolic disturbances, and the important clinical aspects have been compiled in Tab. 22, 30, 31. This survey of a group of more than 400 known metabolic abnormalities, seen from the genetic and the clinical point of view, shows that the enzymopathies prevail, followed by the metabolic tissular systems mesenchyme (skeleton) and the central nervous system.

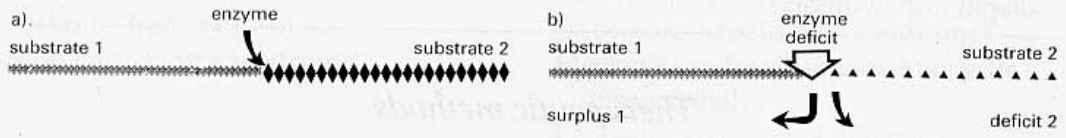

Fig. 256 a, b:
Principle of the metabolic disorders. A chemical substrate is changed into a substrate 2 by the pilot-function of an enzyme (a). The enzyme does not go into the bilance of the process. If the (b) enzyme is insufficient or lacks, a surplus of substrate 1 (= storage, intracellular poisoning), on the one hand, and a lack of substrate 2 (= interruption of the metabolic chain, dysfunction or failure, disturbed development) will take place.

So if this enzyme lacks or is reduced, the substrate 2 cannot or not sufficiently be formed. The two resulting biological consequences are

a) excess (damming up, storage) of substrate 1 because it cannot be metabolisized further;
b) lack of the substrate 2 because it is not synthetized, which means metabolic insufficiency on this level.

More important for clinic and therapy than the adjectives «dominant» and «recessive» is knowledge of the subcellular localisation of the disorder and the affected biochemical substances: enzymes, substrates or both. Sticking to the hereditary adjectives favours the therapeutic nihilism, the knowledge of the origin and of the substances in question provokes action.

Tab. 30: **Genetic development disorders**

A. **Dominant**	B. **Sex-linked – hereditary**
tuberous cerebral sclerosis (Bourneville-Pringle's syndrome)	Mucopolysaccharidosis (Pf.-Hurler's syndr.)
H.-Lindau's syndrome	gangliosidosis
neurofibromatosis	progressive muscular dystrophy
chorea huntington	Lowe's syndrome (oculo-cerebro-renal syndrome)
dystrophia myotonica	Lesch-Nyhan's syndrome
Moebius's syndrome (diplegia facialis cong.)	incontinentia pigmenti (Bloch-Sulzberger's syndrome)
Sturge-Weber's syndrome	Norrie-Warburg's syndrome
Oxycephaly (due premature suture-synostosis)	resistance to vasopressin
dysostosis craniofacialis (Crouzon)	familial hyperuricalmia
Apert's syndrome (acrocephalo-syndactyly, type I, II)	C. **Recessive-hereditary (significant or probable)**
Goldenhar's syndrome (oculo-auriculo-vertebral dysplasia)	Amaurotic idiocy (gangliosidosis)
Treacher-Collins's syndrome (dysostosis mandibulo-facialis)	phenylketonuria
Franceschetti's syndrome	galactosaemia
Noonan's syndrome	endemic struma
Christ-Siemens-Tourraine's syndrome (hypohidrotical ectodermal dysplasia maxillary hypoplasia)	maple-sirup disease
Engelmann's disease (progressive diaphysical dysplasia)	homocystinuria
	hyperhistidinaemia

Therapeutic methods

The so far scarce therapeutic methods rely on two principles, namely the elimination of the dammed up substances by withdrawal (e. g. food poor in phenylalanin in cases of phenylketonuria) or the substitution of the lacking enzyme (e. g. digestive enzymes in cystic pancreatic fibrosis). A reasonable treatment of the innate metabolic diseases, therefore, is restricted to a few forms because the pathological chain is virtually not changed.

It would be more promising to try and influence the subcellular source of the aberrations by cellular organelles (mitochondria, lysosomes, membranes) but the necessary preparations are not available in an adequate concentration. Only tissues and cellular suspensions can be supplied for practical use so that the proportion between the active ingredients and ballast substances for cellular injections is not favourable.

Reproduceable effects were meanwhile demonstrated for a considerable number of metabolic diseases but the therapeutic action is limited as to time and quality. Observations have been made for:

mucopolysaccharidosis (fig. 310);
gangliosidosis;
Noonan's syndrome;
hyperammonaemia;
cystinosis;

Familial dysautonomy (Riley-Day-syndrome)
alkaptonuria
albinism
Hartnup's syndrome
cystathionurie
arginin-succinic-acid imbecility
citrullinuria
hyperammonemia
cystinosis
gluco-amino-phosphat-diabetes
hyperglycemia
histidinemia
imidazolaciduria
hyperprolinemia
hydroxyprolinemia
Joseph's syndrome
Oasthouse-urine syndrome
familial genetic microcephaly
Grigler-Najjar syndrome
porphyria erythropoetica
hypophosphatasia

Neuro-ectodermal symptom prevalence

Ataxia teleangiektatica (Louis-Bar's syndrome)
Sjörgen-Larson's syndrome
Cockayne-Neil's syndrome (nanism)
pigmentxerodermia
Rothmund's syndrome (congen. poikilodermia)
Friedreichs-ataxia
Canavan's disease (spongy degeneration of the central nervous system)
Alexander's disease (megencephalia and hyaline panneuropathia)

Mesenchymal or polytope symptoms

Craniostenoses (premature suture-synostosis)
acrocephalo-syndactyly
osteopetrosis (infantile form)
pyknodysostosis
Laurence-Moon-Biedl-Bardet's syndrome
Conradi-Huenermann's syndrome (chondroangiopathia calc.)
Ellis-van-Creveld's syndrome (chondroektodermal dysplasia)
Smith-Lemli-Opitz's syndrome
Zellweger's syndrome (cerebro-hepatorenal syndrome)
Meckel's syndrome (splanchnocystic dysencephaly)
Fanconi's syndrome (anaemia)

gluco-amino-phosphate diabetes;
Grigler-Najjar's syndrome (fig. 257);
tuberous cerebral sclerosis (fig. 275);
Christ-Siemens-Tourraine's syndrome (fig. 290);
progressive muscular dystrophy;
Louis-Bar's syndrome (fig. 206);
Rothmund's syndrome (fig. 289);
Friedreichs's ataxia (fig. 275);
Ellis-van-Creveld's syndrome;
Fanconi's syndrome (fig. 322).

In cellular therapy, one should rely on the clinical guiding symptoms, the supposed or statistically established localisation in the organs, cells or cellular organelles. Irrespective of these special requirements as appearing from the synoptic Tab. 30, the doses of fetal liver (150 mg of the lyophilisate) and sex-specific placenta (150 mg of lyophilisate) seem to exert generally the most favourable effect of innate metabolic diseases. Examples are shown in the fig. 206, 257, 274, 275, 276, 277, 278, 289, 290, 310. Special attention should be paid to a reasonable medication and dietetic concomitant therapy for innate metabolic disorders.

Fig. 257:
Grigler-Najjar's syndrome. At 6 years (a) icterus, serum-bilirubin values between 25–35 mg%, reduction of speech, increasing ataxia; at 10 years (b) bilirubin about 25 mg%, scanning and distinct speech, ataxia remedied.

As far as multiple disabilities with symptoms centred in the central nervous system are in question, the synoptic concept of an integral medical treatment will be discussed in detail hereafter.

Tab. 31: **Metabolic disorders**

Of the more than 400 known metabolic disorders, those of importance have been listed in a synopsis by R. G. SCHMID (1979). It has been divided into classes of matter in metabolic disturbances of carbohydrates, fat, amino-acids, porphyrin, plasma-protein, metals, vitamins and purin. The table, intended to be used as a guide in the practice, comprises definitions of the basic disturbances, clinical guiding symptoms, frequency and age-disposition and diagnostic proofs. The data have been taken from: H. OPITZ and F. SCHMID, 1965; U. STEININGER and H. THEILE, 1974; H. MEHNERT, 1975; K. SCHREIER, 1979. ▶

Carbohydrate metabolism disorders

A. Enteral **1. Disaccharidmalabsorption:** Lactose/Saccharose/Isomaltose Primary/secondary forms **2. Monosaccharidmalabsorption:** glucose/galaktose	Diarrhea, dehydratation, dystrophia. In time of first milk meals, but various forms also at higher age. Diarrhea – dehydratation when supplies of milk are initiated.	H: dependent on type A: from birth H: rare A: from birth	test for lactose tolerance test f. sacch. tol. biopsy of small intestine test for glucose tolerance test for galactose tolerance
B. Intermediary metabolism **Metabolic disturbances of galactose:** galactosaemia lack of galactokinase	Hyperbilirubinaemia, non appetite for drinking, vomiting, dystrophia, hepatomegalia, cataracts, spasm	H: 2–10 A: 0–18 M.	reduction samples + clinistix – enzymes in erythrocytes
2. Metabolic disturbances of fructose: intolerance to fructose Benign fructosuria Fructose 1,6 diphosphatase	vomiting, hypoglycaemia, hepatomegalia, laktatacidose, spasm. After beginning of fruit feeding.	H: 1–5 A: fruit feeding	reduction samples + clinistix – test for fructose tolerance
3. Glycogen storage disease: type I–X (Gierke, Pompe, Cori, Forbes)	Diabetes mellitus with frequent hypoglycaemia, hyperlipaemia, laktatacidose, cardiomegalia, hepatosplenomegalia	H: up to 0.5	sugar after fasting – fat values + test for glucagon + test for adrenalin +
C. Diabetes mellitus **1. Diabetes mellitus:**	acetonaemic vomiting, dyspepsia loss of weight, hypo/hyperglycaemia	H: 3000 A: old age	acetone-glucosuria blood sugar daily prof. test for fructose tolerance

H = frequency on 100.000; A = age in days, months (M) years (J.) any age (old age)

Disorders of complex carbohydrates

1. Mucopolysaccharidoses: type I–VII Pfaundler-Hurler. Hunter. Sanfilippo, Morquio. Lamy.	facial dysmorphie, progressive dementia, nanism, convulsions, dysostosis multiplex, corneal disorders, hepatosplenomegalia	H: 1 A: 1–2–6 Y.	test for toluidin + urine of heparansulfat urine of keratansulfat urine of dermatansulfat prove in leukocytes
2. Mucosulfatidosis	like mucopolysaccharidosis + leukodystrophia	A: 1–3 Y.	prove in leukocytes
3. Mucolipidoses type I–III (I also sialidose)	like mucopolysaccharidosis	A: 0–4 Y.	prove in leukocytes prove in fibroblasts
4. Fucosidosis I + II:	like mucopolysaccharidosis	A: 4–12 M	prove in fibroplasts
5. Mannosidosis:	like mucopolysaccharidosis	A: 1–3 Y.	prove in serum
6. Aspartylglucosaminuria:	like mucopolysaccharidosis, speech-disorder	A: 1–5 Y.	prove in urine

Fat-metabolism-disorders

A. Enteral **1. Cöliakia:**	Anorexia, vomiting, period. diarrhea, fatty stools, dystrophia, blown-out belly, steathorrhea	H: 100 A: 5 M–3 Y.	test for xylose 80 % + (blood) fats test for gluten-tolerance sucking biopsy small intestine
2. Mucoviscidosis	Mekoniumileus, pancr. insuff., offensive fatty stools, diarrhea and obstipation in menopause, dystrophia, chronic emphysembronchitis	A: 10–100 A: 0–2 Y.	test for sweat steathorrhoea + trypsin activity – iontophoresis
3. Enteritis: Gastroenteritis, colitis. Morbus Crohn, enterocolitis	gripes, nausea, muco-bleeding diarrhoea, obstipation possible, vomiting	H: 100 000 A: 0–old	test for morbific agents in stools fats in serum protein in serum – BSG + stom. – intest. – passage
B. Changed lipoprotein **1. Hyperlipoproteinaemia:** type I–V	nausea, vomiting, atherosclerosis, xanthoma hepatosplenomegalia, colic in the upper abdomen	H: up to 3000 A: 0 – old	blood fats unchanged lipidelectrophoresis
2. Hypolipoproteinaemia: blood fats lipidelectrophoresis unchanged	ataxia neuropathia, avitaminosis	H: rare A: 0 – old	

C. lipidosis **1. Niemann-pick:** type A – E	refusal of food, vomiting, hepatosplenomegaly, psychomotor retardation, red retina spot, hypotonic – ICP, idiocy	H: rare A: 6 m – 50 y	hypertriglyceriaemia hypercholesterinaemia osteomalacia thrombocytopenia
2. Morbus Gaucher: type I (adults) type II (infantile) type III (juvenile)	indigestion, (Hepato-)splenomegalia, hypertone ICP (type 1), kachexie, idiocy night-blindness	H: till 50 A: 3 m – 20 y	Acid phosphatase pelvic osteolysis bone-marrow: Gaucher cells
3. Refsum's disease	night-blindness, paraesthesia, ataxia, paresis, attacks of pain	H: rare A: 2 – 20 y	Triglycerides + (in liver, kidney, muscle) liver biopsy protein + – liquor
4. Glycosphingolipidosis: Fabry	teleangiectasia, diarrhea, leg oedema, burning in fingers and toes	H: rare A: 10–20–30	proteinuria, haematuria opacity of the cornea
5. gangliosidosis (amaurotic idiocy) GM – 1 (type O, A, B) GM – 2 (type I, II, III) GM – 3	psychomotor- regression, amaurosis, nystagm, decerebration rigidity, idiocy, megalencephaly with «hydrocephalus» paroxysm	H: 0,25 A: 6 m – 6 y type 15 y	fovea centralis red EEG leukocyte enzymes biopsy of the rectal mucosa
6. leukodystrophies: metachromatic leukodystrophy Pelizaeus-Merzbacher's syndrome Schilder's disease, spongy degeneration, morbus Krabbe	muscular hypotony, weakness, psychomotoric retardation, spasm, tetraplegia, paroxysm, opticus atrophy	H: rare A: 0–1–19 y	liquor protein + EEG arylsulfatase urine + histology

Disorders of amino-acid metabolism

1. Alcaptonuria	Black-brown staining of napkins, skin pigmentation in old age	H: 0,1 A: from 0	FeCl 3 green Fehling + urine deposit black osteoarthrosis paperchromatography
2. Albinism: yellow, black, white, ocular	White (in case with black spots) pigmented skin, red iris, photophobia	H: 0,3 A: from 0	Ophthalmology
3. Phenylketonuria:	Smell of mouse urine, dermatosis (eczema) paroxysm, psychointellectual retardation	H: 10–15 A: 0–5 M	FeCl 3 deep greenish-blue phenistix-test, guthrie-test, EEG
4. Disturbed tyrosin metabolism tyrosinaemia (three arts)	Vomiting, diarrhea, dyspnea, cataracts, hepatosplenomegaly, hypophosphataemic rachitis, retardation, blisters on feet and fingers	H: rare A: 1 W – 8 M	hypophosphataemia, glucosuria, proteinuric/leuko/thrombo-cytopenia, aminoacid-chromatogram, hypoglyaemia
5. Histidiaemia:	Disturbed articulation, reduced hearing	H: 6–8 A: 0–5 J	FeCl 3 green (from 2. week)
6. Maple-syrup disease:	Refuse of food, apathy, moro + apnoe, paroxysm, Maggi-like smell from 6th day)	H: 1 A: 3–4 T	FeCl 3 greyish-green chromatography, EEG
7. Homocystinuria:	Tallness, longfingers, lens ectopy, suited to thrombosis, reduced intelligence, changes of vertebral column, paroxysm	H: 0,3–1 A: 2–30 Y.	nitroprusside test + chromatography
8. Cystinosis:	Polydipsia, polyuria, anorexia, obstipation, vomiting, photophobia, rachitoid osteopathy	H: 1 A: 6–12 M	glucosuria, erythrocyturia, slit-lamp examination
9. Hyperammonaemia I + II	vomiting, spasm, lethargy	H: rare A: from 0	serum-ammoniak +
10. Citrullinuria:	cerebral lesions with fits	H: rare A: 0–30 Y.	serum-ammoniak + Ehrlich Reganz yellow chromatogram-blood
11. Argininsuccinicacid disease	paroxysm, ataxia, reduced intelligence	H: 0,25 A: 0–old	Ammoniak in the serum + GOT Arg. succ. acid-secretion

Porphyrin metabolism disorders

1. Porphyria several types and courses	Red urine, blisters in irradiated skin, photomatosis, polyneuritis, psychoneurological syndrome	H: rare-D A: 0–20 years	test for aldehyde + uroporphyrin + koproporphyrin +

Anomalies of plasmaproteins

1. Plasmaproteinemia: group of diseases	Bleedings at intervals, relapsing fever, emphysembronchitis, diarrhea, vomiting, dystrophy, neuropathy, oedema, hypotonia, hepatosplenomegaly with cholostasis up to hepatic coma. Accord. to disease very different courses	H: accord. type A: 0 – old	electrophoresis path. lipidelectrophoresis path. tranferrin path. alpha 1 antitrypsin path. fibrinogen + HLA system

Disturbed metallic metabolism

1. Haemosiderosis primary/secondary form	loss of weight and thirst, weakness, hepatosplenomegaly, diabetes mellitus, bronced skin	H: pri-sec! A: 0 – old	serum iron exceed. 200 µg Desferal test path.
2. Wilson's disease	hepatosplenomegaly, ascites, «parkinsonism»	H: 1 A: 11 – 25 years	proteinuria, Kaiser-Fleischer's corneal ring (ophthalm.)

Hereditary disturbances of vitamin metabolism

1. Disturbances of pyridoxin	Shrieking, tonic-clonic spasm, restlessness, tremor anaemia	H: rare A: 0–2 M	B 6 i. v. under EEG B 6 substitution
2. Vitamin B-12 malabsorption: familial/primary-secondary	anorexia, megaloblastanaemia, inflammations, pernicious anaemia	H: rare-p. A: 2 – 5 M	proteinuria blood-count
3. pseudo-vit. D defiency rachitis:	rachitis	H: rare	alkaline phosph. parathormone + calcium

Purine metabolism disorders

1. gout	Podagra, pellagra, painful inflammatory articular swellings	H: 2500 A: 20 – 40 years	BSG +, leukocytosis urea exceedting 6 mg%