Neurocrine-endocrine synopsis

Neurosecretion means the production and output of hormones and their prophases by nerve cells of the diencephalon. As these synthesis products of the nerve cells are secreted direct into the portal circulation of the hypophyseal stalk, this function of certain areas of the central nervous system is also called *«neurocrinia»*, its products are referred to as *«neurincretes»*. The regular and very narrow connections between the central nervous and endocrine systems have so far been chiefly the subject of studies by anatomists, histochemists and endocrinologists, but their importance for the clinic has not yet been sufficiently appreciated. The following synopsis of the organismic connections is based upon data by SCHALLY and KASTIN; BARGMANN; HAGER; NOETZEL as well as E. L. SCHÄFER.

The *diencephalon* regulates a number of vital functions such as body-temperature, blood-pressure, rhythm of sleep and awakeness, balances of water and electrolytes. In particular, the *hypothalamus* is the central switch-board for the coordination of the endogenic regulatory mechanisms and for the processing of environmental influences. Whereas the latter are led to the central nervous system through afferent nerves (fig. 280), the endocrine and metabolic processes are regulated by reactive mechanisms. The system seems to be secure enough in many respects to reduce clinically relevant real «dyscrinia» to a minimum, provided that the central nervous system is intact.

The many symptoms of innate dysplasia and metabolic disturbances of the development of the central nervous sys-

tem, however, indicate considerable relations between the disturbed development of the brain, the endocrine regulation with its somatic influences on the growing organism. They become perceivable in the area of the glandotropic hormones (fig. 282); the growth hormone (GH = growth hormone; STH = somatropic hormone), the thyroid hormones and sex hormones are of primary interest.

The tubular survey is to show by simple data the interrelations between the central nervous system and the endocrinium (fig. 280–282) and gives an outline of the clinical main effects (fig. 282). Under these aspects, somatic influences and functional disorders as part of disturbed cerebral development cannot be understood unless the connections are clear. They include all symptoms that can occur only through the endocrine system i.e. not direct but indirect are consequences of the disturbed cerebral function:

nanism; high growth; aberrations of growth proportions (e.g. acromegaly, acromicria).

«Diencephalic symptoms»: erethism, disturbed rhythm of sleep and awakeness; lability of the water-electrolyte balance; circulatory lability with reduced compensation; tendency to salivation, alopecia, cushingoid cheek-erythema (cheeks of a clown), abnormal ossification: disturbed sequence, asymetry, accelerated differentiation, and the like.

«Thyroid symptoms»: clumsy lineaments, thick skin; hoarse voice; large tongue; tendency to constipation; dry, strawy hair; retarded ossification.

«Sex-gland symptoms»: general infantilism; hypogenitalism (penis, scrotum, labia); absence of sexual characterization and of puberty.

Neurincretions

The 7 incretory glands (epiphysis, hypophysis, thyroid gland, parathyroid gland, adrenal glands, male and female sex-glands, pancreas) produce increts, which are divided into 4 biochemical groups:

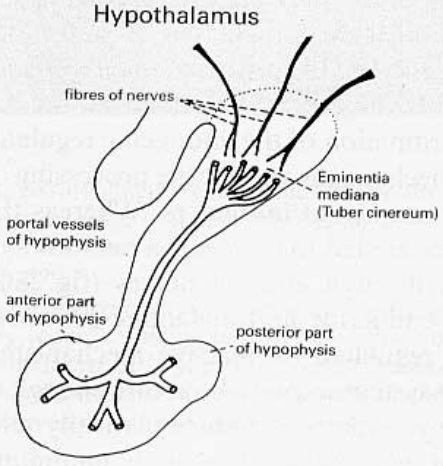

Fig. 280:
Functional connection between nerve fibres of hypothalamus and portal vessels of hypophysis into which the secretory products of the nerve-cells (neurosecretions are ingested direct, thus becoming neurincretes.

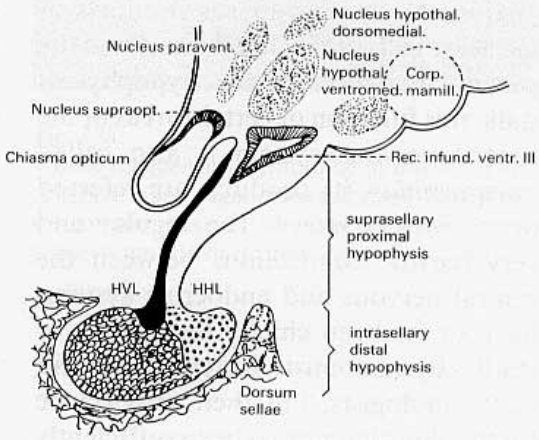

Fig. 281:
Diencephalic and hypothalamic centres. Hypophyseal stalk and hypophysis.

Neurotransmitters

Monoamines
- Dopamin
- Noradrenalin
- Serotonin
- Acetylcholin
- Histamin

Aminoacids
- Gamma-aminobutylacid
- Glycin
- Taurin ?

Neuropeptides
- Carnosin
- TRH (Thyreotropin-releasing-hormone)
- Methionin-Enkephalin
- Leucin-Enkephalin
- Angiotensin II
- cholecystokinin-like Peptid
- Oxytocin
- LHRH (Lutein.-hormon-releasing-hormone)
- P-substance
- Neurotensin
- Bombesin
- Somatostatin
- Vasoactive intestinal polypeptide (VIP)
- β-Endorphine
- ACTH (adreno-corticotrope hormone)

Derivatives of amino-acids (adrenalin, noradrenalin; thyroxin, triiodothyronin – as thyreoglobulin bound secondarily to protein).

Polypeptide hormones (oxytocin; ACTH; most of the hypothalamic neurohormones, so-called releasing factors).

Proteohormones (prolactin; choriongonadotropin; somatotropic hormone; insulin, glucagon; parat-hormone).

Steroid hormones (hormones of adrenal cortex: hydrocortisone, corticosterone, aldosterone, hydroxyandrostendione, sex hormones: testosteron, oestron, oestriol, oestradiol, progesteron).

The neurincretions originating from the hypothalamus are, as shown by recent analyses (SCHALLY and KASTIN), not only releasing factors but real hormones or their prophases. They belong to the group of polypeptide hormones and have very low molecular weights.

These hormones regulate the function of hypophysis, which therefore can no longer be regarded as the endocrine «control room» but as a «relay station» between impulses of the central nervous system and metabolism.

Endocrine disorders

Implantation of *calf's hypophysis* for nanism belong undoubtedly to the oldest methods of cell-therapy using xenogenous tissues. Looked upon as the hour of birth of cell therapy is that dramatic occasion when P. NIEHANS (1931) implanted dissected tissue of parathyroid gland under the abdominal skin of a woman writhing in tetanic spasm immediately after strumectomy whereupon spasms subsided before long. Meanwhile, comprehensive experience and documentation in many fields of endocrine disorders and diseases involving endocrine organs are available (STEIN, J. 1982).

Nanism

Nanism (more than 10% below average) and dwarfishness (more than 20% below average) are clinical collective names for stature deficits of various causes. The most important forms have

been compiled in Tab. 41 (after O. MARGRAF, 1979). The forms of endocrine nanism are disorders of the axis: hypothalamus – hypophysis – thyroid gland – adrenal gland – gonads. Forms of endocrine nanism use to be less proportionate than constitutional or metabolic forms, but better proportionate than most of the skeletal forms of nanism. Enchondral dysplasia and dysostosis call for other therapies and are treated separately (Tab. 49–50).

The *hypophyseal nanism* is caused by lack of STH (somatotropic hormone = growth hormone). The standard therapy consists in a permanent parenteral application of this hormone. It is doubtful whether the results of this expensive con-

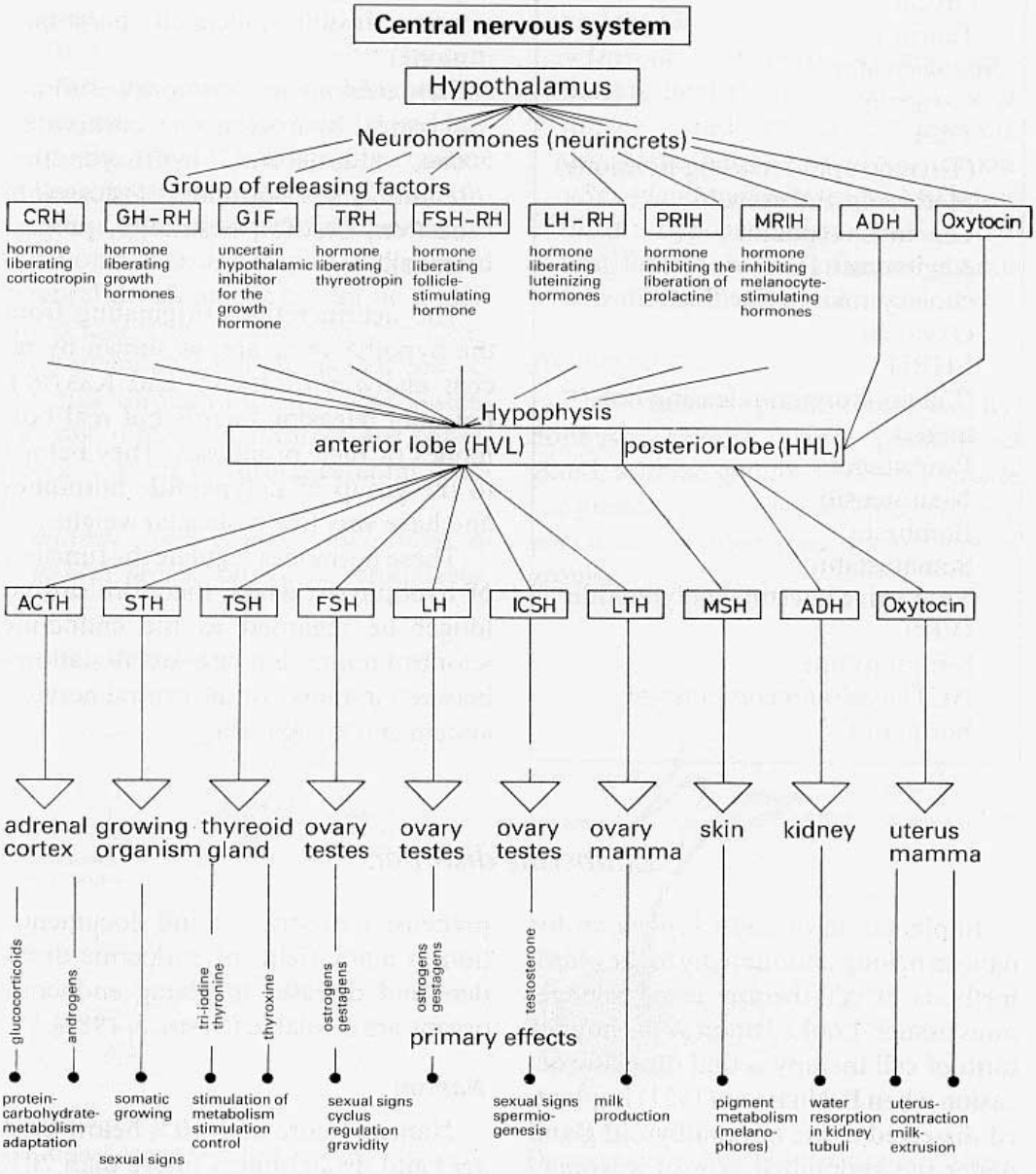

Fig. 282:
Synopsis of neurocrinia and of the endocrine system and glandotropic glands; relay stations, substrates, target organs and primary effects.

Tab. 41: **Survey of nanism** (after O. MARGRAF, 1979) (= etiologically different clinical forms of the symptom «nanism»)

hereditary factors	**neuro-endocrine nanism**	**metabolic nanism**	**Ossary nanism (defective bone growth)**	**N. with chromosomal aberrations and genopathies**
Familial nanism Constitutional retardation of development Primordial nanism Hereditary, brachy-meta-carpal nanism (Pseudo-Hypo-Parathyreoi-dism) Progeria (= hered. const. **nanism** defective growth potency of bones)	**dycerebral nanism** innate or acquired brain defects mongolism microcephaly cerebral, malformation Laurence.-Moon-Biedel-S. **hypophyseal nanism** isolated lack of growth hormon nanism in partial growth hormon deficiency Somatomedin-deficiency lack of ACTH combined hormon deficiencies **Hypothyreotic nanism** precipitation of TSH **nanism in Hypopara-thyreoidismus** **Adrenal nanism** M. Cushing **Dysgenital nanism** Pubertas praecox Pseudo-P. p. Ulrich-Turner-S. Hanhart-S. (hereditary nan. with lack of STH and retarded ripening) **Pancreas** ill controlled diabetes with lack of insulin	**Renal nanism** deformities congenital tubular nephropathies Phosphat-Diabetes (Vit.-D-Def. Rachitis) Vit.-D-resist. Rachitis Debré-de-Toni-Fanconi-S. serious chron. nephritis **Intestinal nanism** Coeliakia, Megacolon Pancreasfibroses Kwaschiorkor-S. Andersen-S. **Hepatic nanism** Starage disease Glykogenosis Lipoidosis Mucopolysaccharidosis Cystinosis **An-or hypaxemic nanism** cardial nanism pulmonal nanism. anaemic nanism rachitic nanism **Alimentary** Hypocaloric hanism (prot. vit. trace elements)	= congen. skeletal dysplasia with short limbs Chondrodystrophy = Achondroplasia hereditary dysostosis diastr. nanism chondroectoderm. dysplasia metaphys. dysostosis Osteogenesis imperfecta dyschond. nanism **Nanism with prevailing shortening of trunk** Spondyloepiphys. Dysplasia Morquio-disease **Further dysprop. dysost. nanism** Pfaundler-Hurler-disease Hunter's disease Sanfilippo disease (all mucopolysacch.) **Proport. dysostot. nanism** marble bones Dysostosis cleidocranial. **Nan. with multiple varieties** Laurence-Moon-Biedel-S. Männl.-Turner-S. Pseudo-Hypoparathyreoi-dism. **Pseudoforms** (= false nanism) phocomelia rachitic curvetures	the most monosomies trisomies and chromosomal deletions

tinuous therapy are better than the former implantations of calf's hypophysis and oral substitution because immunological reduced effects bring about less convincing growth rates in later years.

The evaluation of 14 own cases treated with subcutaneous implantations of calf's hypophysis under the skin of the abdomen revealed rather different results. Apart from non-reactions with growth rates of 2–3 cm per year, some cases showed enormous growth impulses of 11–18 cm per year. As regards the concomitant oral substitution-therapy or cell-therapeutic concomitant therapy, it must be taken into consideration that hypothalamus and hypophysis have leading conductor's functions in the finely coordinated symphony of endocrine glands. From this it appears that

the effects on the secondary glands must be tested and disorders be included in the therapeutic conception. The use of thyroid gland, adrenal glands, gonadal tissue justifies these considerations by the demonstrable effect where implantations of hypophysis alone failed to bring about the growth impulse desired.

Hypophyseal – hypothalamic disorders

The axis of hypophysis – adrenal glands – gonads plays in adults a part that often escapes the doctor's notice. RÜMELIN (1970) demonstrated the effect of implantation therapy in 2 filigree-like analysed cases of post-partal *Sheehan syndrome.* The part of the hypophysis-hypothalamic system in the loss of weight during puberty – socalled *anorexia nervosa* – and various forms of *obesity* is surely less circumscribed. It is advisable to consider the use of hypothalamus, diencephalon, hypophysis, adrenal gland and gonadal tissue when the «classical» i. e. customary methods fail. A. C. GIANOLI (1968) reported on the combined treatment of obesity with diet-choriongonadotropin-cell therapy. According to recommendations by SIMEONS, the best results were obtained after 21–30 days of treatment with a 500 cal.diet, 125 int.units of human choriongonadotropin i. m. and implantations of hypothalamus or diencephalon. This study relies on 165 observations. The implantations are said to have a long-term effect regulating the metabolism.

Furthermore, articles on cell therapy in diseases of hypothalamus/hypophysis were written by: G. DÖDERLEIN, (1953); MAISCHEIN (1955); JANSON 1955); F. E. BIRCHER (1953); BLUME (1957); EHNI and DUDE (1957).

A. KMENT (1968) and J. BABILLOTTE (1979) dealt specially with the central position of hypothalamus in the endocrine system, F. G. SULMAN (1975) with the neurohormones.

In *Diabetes insipidus,* the balance of water and electrolytes is disturbed owing to dysregulations of the posterior part of the hypophysis and hypothalamic centres. No verified reports on cell-therapeutic treatments of human patients are available so far because the nasal substitution makes usually adequate permanent treatments possible. K. ULRICH (1960) reported on the successful implantations of diencephalon in 7 dogs; the substitution of hormones of the posterior part of the hypophysis alone was not sufficient.

Irrespective of the classical diseases with constellations of distinctive symptoms, the diencephalon-hypothalamus system is involved in many disturbances of growth, cerebral affections, forms of obesity and loss of weight, and can characterize the secondary and concomitant symptoms. The inclusion of these tissues into the therapeutic conception should be taken into consideration wherever the symptoms seem to suggest so (e. g. Down's syndrome).

Thyroid insufficiencies

constitute, primarily as athyreosis or hypothyreosis with a frequency of 1 : 4000 new-born, a numerically minor problem, which however is significant from the sociological point of view. Still more important is a mostly unrecognized secondary dysfunction of the thyroid gland among the cerebral diseases, namely the *secondary hypothyreosis.*

Hypothyreosis manifests itself ac-

cording to the functionary deficit of the thyroid gland during the first weeks of age – in athyreosis – or are detected in infancy. The early diagnosis for the new-born adopted in many countries is likely to reduce henceforth the number of cases recognized later. Of course, the diagnostic safety of the TSH-determinations leaves doubts, which often are covered with the mantle of «transient hypothyreosis», probably however imply wrongly positive diagnoses. The determination of the bone-age should be included in the diagnosis, in new-born the degree of the ossification of the talus, calcaneus, distal femur – and proximal tibiaepiphysis. These are found in a mature new-born.

Hypothyreosis is a classical indication for the substitution-therapy with thyroid-hormone preparations. The fractions T3 and T4 are used more frequently nowadays as integral preparations on a base of thyreoidea sicca; the correctness of this method ist doubtful. If the thyreoid substitution is applied too late or by inadequate doses, the whole organism is affected, especially the development of the brain. The forebrain is the part to suffer most, which can often be noticed alone by the narrow, flat forehead, a low-descending growth of hair and a narrowed bitemporal diameter of the skull. The individuality lacks chiefly initiative and the capacity of abstracting and combining. Increases of the thyroid substitution cannot neutralize these effects on the brain; frontal brain, temporal brain, thalamus, hypothalamus, possibly combined with thyroid implantations, in total doses of 200–300 mg of lyophilisate per series of implantations bring about effects that cannot be obtained with any other therapy. The substitution therapy and the implantations should be completed by long-term medications with vitamin-B complexes and trace elements, especially as long as macroglossia and thickenings of the skin as clinical symptoms indicate this deficiency.

Research workers dealing specially with the cell-therapeutic problems of thyroid disorders are H. KURTZAHN and H. HÜBENER (1927) as well as A. STURM (1955).

Parathyroid insufficiency

Although the implantation of parathyroid tissue by P. NIEHANS in 1931 for a dysfunction of this organ is a spectacular individual case at the beginning of modern « cell therapy», only little substantiated reports such as by A. STURM (1955) and A.C. GIANOLI (1971) were added. The small number of cases may be accounted for by the fact that the substitution-therapy is easier to apply in practice. A.C. GIANOLI describes the case of a 53-year-old woman, who suffered from postoperative hypoparathyroidism with tetanic syndrome, trophic disorders and vegetative symptoms. In spite of many years of intense and careful treatments with AT10, vitamin D and calcium, the condition grew worse into incapability for work. Already the first cell treatment with parathyroid gland, thyroid gland, hypothalamus and placenta provoked soon a marked improvement; the tetanic attacks did not occur any more. After another two treatments at intervals of 13 and 12 months, no complaints were seen during an observation of 3 years.

Diabetes mellitus

Diabetes mellitus (= diabetes, from Greek «sweet honey passing through») constitutes a first-class sociologico-medical problem, with respect to its frequency and therapeutic problems. Although the therapeutic conception with the two columns « diet» and «insulin substitution» appears well-founded theoretically, every clinician knows the practical difficulties of the long-term treatments, the shortcomings of which are readily imputed to a defective diet discipline of the patients. Diabetes is generally looked upon as «a factor of risk» for many other diseases because the vascular and circulatory lesions predispose the organism to other serious affections:

circulatory dysregulations; hypertonia, vascular occlusions;
infarctions; apoplexia; ophthalmological lesions to the retina, lens and iris;
degenerative lesions of liver and kidneys; disturbed gastric, intestinal, vesical and sexual functions;
degenerative lesions of the skeleton and joints, and trophic discorders.

Diabetes is believed to be caused by a genetical disposition. Accumulations of the tissular antigens HLA-B8 and HLA-DM3 were found in diabetics with organo-specific autoantibodies (GROMET et al., 1974). Diabetics needing insulin have antibodies against parietal cells of the gastric mucosa and against thyreocytes more frequently than diabetics independent of insulin. When diabetes manifests itself, autoantibodies against islet-cells will appear, but persist only in 20% of the cases, especially in patients depending primarily on insulin (R. LENDRUM et al., 1976). This has caused suggestions that the diabetes type I, which depends on insulin, should be classified among autoimmune diseases and be divided into the types I a and I b. To the type I a belongs the diabetes developing in infancy and which needs insulin at once; perhaps viruses (mumps?) react with HLA-specific areas of the B-cell cytomembrane and lead to immuno-cytotoxic cellular lesions. Whereas the autoantibodies against islet-cells disappear here, they persist in type I b; accumulations in families, predisposition in women and occurrence of other organospecific autoantibodies indicate a «primary» autoantibody disease.

Even if the main function of the insulin is to infiltrate glucose through the cytoplasma membranes into the interior of cells, it must be realized that the transporting and intermediary metabolism is also affected in the area of the electrolytes (potassium, sodium, magnesium, phosphorus, zinc), the proteins and lipids.

The inadequately solved problems called for methods constituting a causal principle against the symptomatic substitution (insulin) and the restriction therapy (diet). Though this way has been taken experimentally and clinically, it is not yet generally practicable.

Casuistical reports on cell-therapeutic treatments of Diabetes mellitus are available already from the period of 1950–1960 (NIEHANS; RIETSCHEL; SPRADO; FELDWEG; UHLENBRUCK; SCHENCK). They were insufficiently substantiated and recorded. NIEHANS himself was nearly possessed by the cell therapy of Diabetes mellitus and sacrificed large sums for the experimental research in order to reach the therapeutic use of «isolated B-cells». Recently overviews were given by STEIN, J. (1982) and NEUBERT, H. (1982).

The first experimental studies by DUBOIS and GONET (1961) proved that in-

jected pancreatic cells can produce in subtotally pancreatectomised rats sufficient insulin to normalize the blood-sugar. Remarkable in this case and for alloxane diabetes was the intensive proliferation of the remaining B-cell areas. These first results have been confirmed widely as an effective principle in many variations these last few years (FEDERLIN et al. 1978; RUMPF et al., 1977, 1978; W. MEYER, 1979; W. KÖSTERS, 1979).

The following results must be emphasized:

1. Intraperitoneal and intraportal injections of islet-cells work better than subcutaneous or intramuscular transplants.
2. Fetal, juvenile and adult tissues develop heterotopically in the organism of the receiver into areas of fully functioning islet-cells.
3. Isogenous implants (of inbreeding strains) function for months, allogenous (homologous) implants are disintegrated.
4. An immunosuppressive therapy can keep allogenous implants functioning for months. How far diabetic secondary changes can be remedied by transplantations of islet-cells, appears from the detailed studies by KÖSTERS on changes of glomeruli.

Genetically isologous male Lewis-albino-inbreeding rats were used to produce diabetes through want of insulin by intraperitoneal injections of acqueous solution of streptozotocin (65 mg/kg of body-weight). Part of the animals got intraportal transplantations of isologous pancreatic islet-cells 7 months after the onset of diabetes. The islet-cells were isolated manually with a stereomicroscope following the methods described by LACY and KOSTIANOVSKY (P. E. LACY and M. KOSTIANOVSKY: Method for the isolation of intact islets of Langerhans from rat pancreas, Diabetes 16, 35 (1967) and SHIBATA et al. ; (A. SHIBATA, C. W. LUDVIGSEN, St. P. NEBER, M. L. MCDANIEL: Standardization of a digestion-filtration method for isolation of pancreatic islets, Diabetes 25, 667, 1976). The parameters for the clinical assessment were: weekly determinations of the blood-sugar, tests for the tolerance to glucose, body-weight, quantities of beverages, volumes of urine, secretion of glucose in the urine. Ten months after the beginning of the tests, renal tissue was taken from healthy and diabetic animals and such treated with transplantations for the light- and fluorescence-microscopic studies. Seven months after producing the diabetes, 34 of the 35 diabetic animals tested had a diabetic glomerular sclerosis, and incorporations of pathognomonic nodular mesangium were traced in 13 animals. Immuno-histologically, IgG, complement beta 1 c fibrinogen and albumin were detected in the mesangium and along the basal membrane in nearly all diabetic animals.

Already 2 days after successful transplantations of islet-cells, the level of the blood-sugar was normalized. The increase in weight corresponded for the animals treated with transplantations to the physiological course in healthy animals. Ten weeks after the implantation of islet-cells, a distinct regression of the histological glomerular changes was observed. Impressive was the regression of the immuno-histological changes: only a third of the animals treated showed minor, mostly fine-grained deposits of protein of the categories described above. The mean width of mesangium in the animals treated with transplantations came to 9.18%, in the diabetic animals to 13.38%.

Compared with these broadly founded experiments, the clinic lags behind. The most comprehensive studies in this field were submitted by H. NEUBERT (1978, 1982), J. STEIN (1982). Of 179 diabetics that got cell theryps in 1977, 94 (61 women, 33 men) were evaluated catamnestically. Their ages varied from 14 to over 80 years, most of the patients i. e 75 were 60–79 years old. In 38 cases (= 40% of the patients) an improvement of the carbohydrate metabolism was observed. It ranged from the stabilization of the blood-sugar with equal medication, through the reduction of the tablets to the reduction of the dose of insulin (in 3 cases).

The favourable influence on diabetes as part of the so-called revitalizing treatments has been confirmed repeatedly.

More difficult are the problems with the insulin-depending diabetes in children and adolescents.

The author's own experience in this respect is restricted to individual cases of instable diabetes difficult to treat in the first five years. The metabolism is stabilized (blood-sugar, acetone, exretion of sugar). The requirements of insulin may increase in the first days after the implantation, to drop in the 2nd to 3rd week below the initial requirements before the implantation. This calls for an exact – preferably clinical – observation in order to conform to these changes pending the stabilization.

For the old-age diabetes, the following viewpoint is noteworthy: if trophic disorders and serious changes of vessels are in question, the conditions of absorption for the implantation are often unfavourable so that a broad, deeply subcutaneous injection is advisable.

Treatments of Diabetes mellitus with xenogenous tissues cannot be recommended generally for the following still not yet sufficiently cleared up reasons:

1. The instability of metabolism in the insulin-dependent diabetes of children in the stress-phases after the implantation must be analyzed thoroughly and regularly.
2. The therapy with pancreas or pancreas-hypothalamic tissue is not extensive enough as the gastric mucosa, liver and adrenal gland must be included into the clinical aspect.
3. Careful attention should be paid to the reduced absorption in advanced diabetes of old age.

However, a cell-therapy prepared by an experienced expert according to individual symptoms of a diabetic cannot only stabilisize the metabolism but also influence heterotopic symptoms (fig. 291).

Adrenal insufficiency

The adrenal cortex with its cortical hormones constitutes an important switch point in the endocrine system. The isolation and therapeutic use of corticosteroids belong to the greatest medical progress of the last decades – with many draw-backs. The adrenocortical hormones stimulate the gonads so that the third (= puberal) phase of growth is initiated and controlled by the adrenal and sexual hormones. The retarded appearance of the secondary sex characteristics (beyond the 16th year in boys, beyond the 15th year in girls) is due to an insufficiency of this part of the endocrine chain in the majority of cases.

Primary and secondary hypogonadism justify the use of endocrine glandular tissue; the organs must be selected in accordance with the diagnostic results incl. the analyses of hormones and the clinical outfall symptoms. The earlier in the hypophyseal phase of growth (between the 3rd and 10th years) the outfall symptoms manifest themselves, the more hypothalamus-diencephalon-hypophysis must be involved. If the development of stature and genitals is not retarded before the prepuberty and puberty, the adrenal glands (of the same sex), ovaries, testicles should preferably be used, along with homosexual placenta.

General medical treatments are recommended especially for complex aspects. For the *Prader-Willi-syndrome* (fig. 283), the absence of the secondary sex characteristics is the main criterion, though obesity and retarded mental development are not less important. The observation shown in fig. 283 demonstrates, how astonishing effects a complex long-time treatment may have (and

cell therapy as central point cannot be replaced by anything); this case is one of 7 treated so far, which had different initial situations and different therapeutic results.

The *secondary lesions* of the adrenal glands are more frequent nowadays than the innate hypofunctions. The broad therapeutic spectrum of the corticosteroids in inflammation, allergies, as cytostatics and externals has augmented the atrophies of the adrenal cortex due to therapeutic measures; they are referred to as *hypercorticism, secondary Cushing's syndrome, cushingoids*, etc. The basic process is the functional immobilization of the adrenal glands by hormones supplied from outside for some time, with higher doses and unfavourable intervals between the (daily) applications. The functional non-use is followed by the morphological atrophy of structures so that, from a certain time, the adrenal glands can no longer produce sufficient quantities of their own hormones. This situation is also of major importance for many prolonged allergies so that the application of adrenal tissue should be taken into consideration, in spite of contraindications.

Prolonged therapies with corticoids in allergies, asthma and generalized neoplasms (leukemia) cause this secondary adrenal insufficiency; its treatment involves serious practical problems, more so if it is accompanied by leukopenia or even panmyelopathies. Implantations of adrenal, hepatic, splenic and bone-marrow tissues may bring about remarkable changes (fig. 306), though the risk of the stress phase after the implantation must be taken into consideration.

A relative indication for a combination of thymus and adrenal gland is the *deficient resistance to infection* and *severe allergic conditions* including *autoimmun diseases*, which can be mastered neither with biological nor with antibiotic remedies.

Puberty

is the third phase of growth after the genetic and hypophyseal phases; it is controlled by the adrenal-sex hormones. Accordingly, the sex characteristics are the main point of the puberty, besides the dimensions and proportions of the body.

The medical problems of the puberty have been characterized largely by the secular process of acceleration these last decades. The beginning and end of puberty have considerably moved to younger ages in the course of the last hundred years. According to the exact criterium «Menarche», the mean values have been shifted from a mean age of $16\frac{1}{2}$ years to $12\frac{1}{2}$ years. The earlier onset of puberty proceeded with an acceleration. This means it is now more difficult to overcome the changes of the pubertising body as puberty manifests itself earlier and proceeds faster than in former generations.

Somatic-physiological problems of puberty

The commencing function of the sexual glands promotes the growth unharmoniously, often impetuously. This process is identical with the so-called «change of stature» after W. ZELLER. During the second half of puberty, the arms and legs, especially the hands and and feet grow faster than the body. Legs and arms are relatively longest at the beginning of menstruation in girls, at the first production of semen in boys (H. R. STOLZ and L. M. STOLZ). Adolescents of

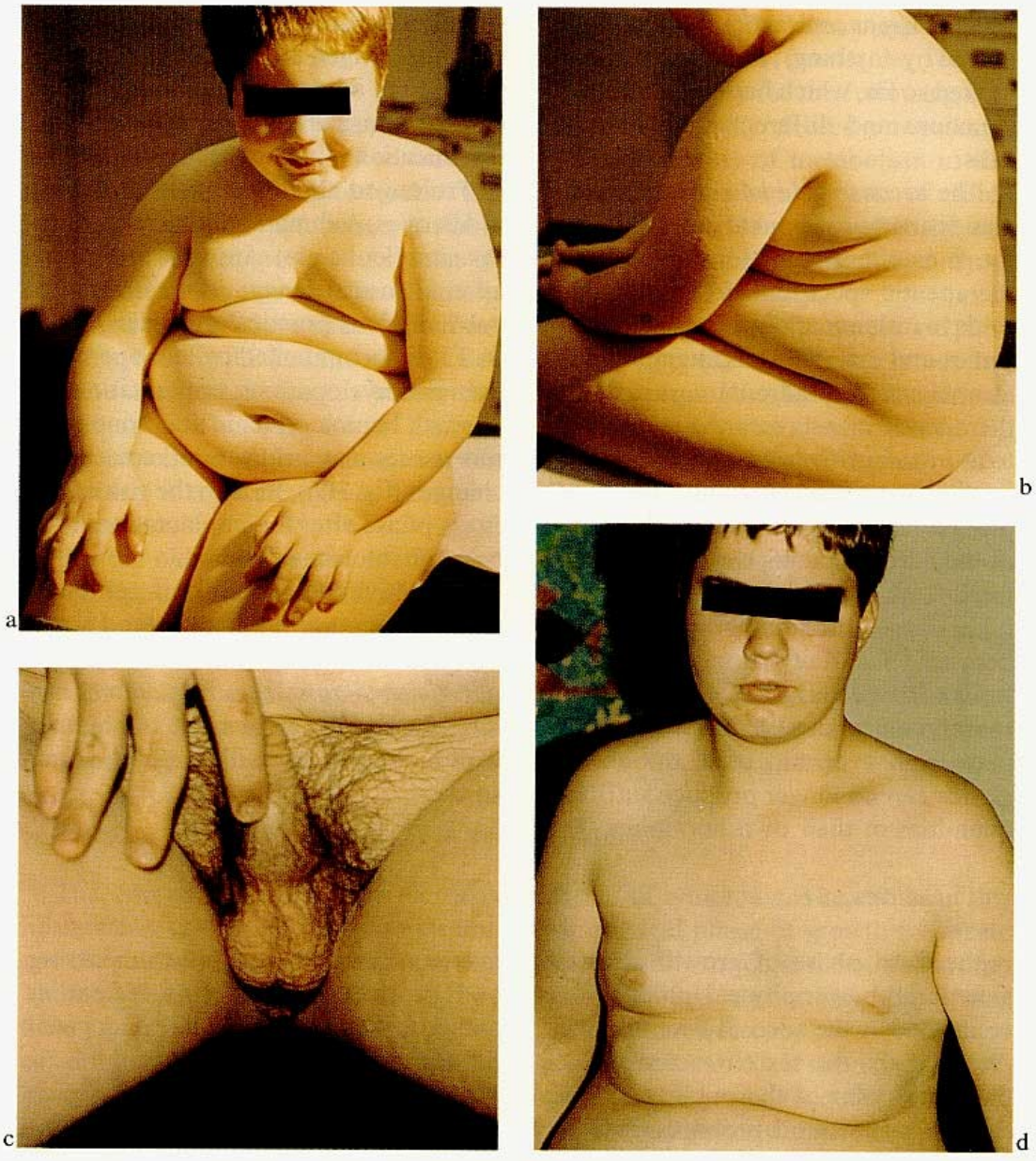

Fig. 283:
Prader-Willi's syndrome
The boy is presented for the first time at $6\frac{1}{2}$ years. 127 cm (+ 7 cm), 53.1 kg (+ 27.5 kg = about 110% overweight), apron obesity (a, b), genital hypoplasia, flat scrotum, testes only palpable as a fluffy texture.
The parents are chiefly worried about the lack of impulse, absence of striving for performance and abnormally deep sleep; he cannot be sent to school.
From $6\frac{1}{2}$ to 12 10/12 years, at half-year intervals, implantations of hypophysis, hypothalamus diencephalon temporal brain, frontal brain, male adrenal gland and testes, by double combinations of 200 mg of lyophilisate.
At this time 170 cm, 82.8 kg (the weight had been up to 100 kg), attends the 6th class of elementary school, mean performance, testes palpable and adequate to age, the genital hypoplasia has been remedied, pubes (c, d).

that age do not know what to do with their extremities. The harmonious-natural movements become more clumsy, more abrupt, reluctant to anxious, before in the second half of puberty the harmonious coordination of movements is restored.

According to the sex, the body gives the adolescents different problems:

Girls are more often afraid of growing too big rather than of remaining too small. The form of the body, needed with new movements, is paid more attention. Girls do not like to be too fat, are afraid that their breasts might remain too small. The frequently assymmetric budding of the breasts makes mothers and daughters suspect that some disorder might be the cause. The hairs on the body are the subject of apprehensive observation. Girls do not like to wear glasses.

Boys would like to be taller, to have more muscles and broader shoulders, use more consciously their newly acquired physical capacities (sport). At the beginning of puberty, the question of small genital organs arises frequently, later the impurity of the skin (acne) will prevail. The stronger and more specific effluvium proceeding with the hormonal change may provoke uncertainty in both sexes when getting into touch with the environment.

With the speed of growth and the hormonal change, circulatory problems and inconstancy of temper caused by hormones proceed. Among them are:

lability,
easy fatigability,
lack of concentration,
unsettlement,
wayward reactions,
nervousness.

Phases of dislike alternating with phases of showing off. Physiologically, in part, a «change of shift» results in the secondary schools. Whereas boys have difficulties mostly between 11 and 15 years of age, and the girls are usually better, well-behaved and less problematic, the girls slow down in their work during the second phase of puberty or find it hard to maintain their reputation of being «good pupils». For boys, however, their achievements at school stabilizes between the 15th and 19th years of life unless the physiological break as secondary schools stops them.

Pathology of puberty

With sexual-specific clinical aspects, the following principles of pathological variants of puberty result:

1. premature puberty;
2. retarded puberty;
3. missing puberty.

The premature appearance of the characteristics of puberty makes up

1 a) a *constitutional-geographical variant.* In warm countries and regions nearer to the equator, puberty occurs usually earlier than under northern latitudes and in humans with light pigments.

1 b) The *premature appearance of single secondary sex characteristics* as alpha-premature, mostly transitory budding of the breasts, beta-premature puberty (before the 7th year of age).

1 c) *Pubertas praecox vera* with appearance of the secondary sex characteristics before the 8th year, and of the menarche before the 10th year of age. The causes are usually not traceable, sometimes a hamartome of Tuber cinereum or a Weil-McCune-Albright syndrome (Pubertas praecox + fibrous, polystotic or monostotic skeleton dysplasia + Café au Lait spots on the skin) is found.

1 d) *Pseudopubertas praecox* with appearance of secondary sex characteristics in cases of adrenal or ovarian tumours.

Retarded puberty is seen:

2 a) in constitutional maldevelopment,
2 b) in malnutrition and unfavourable environmental conditions,
2 c) in hypoganadism (most serious primary form: Ulrich-Turner's syndrome, 45XO-chromosome aberration),
2 d) missing hypophyseal gonadotropins with secondary hypoganadism (in panhypopitutarism, hypophyseal nanism, serious hypothyreosis).

Missing puberty is a rare event in

3 a) Dystrophia adiposo-genitalis;
3 b) Prader-Willi syndrome (fig. 284);
3 c) other forms of intersex.

Special somatic problems result as hypertrichosis in girls and in hirsutism. Hypertrichosis is usually familial, occurs often in cerebral dysplasia, sometimes owing to medicaments (cortison, antiepileptics).

Infertility

Disorders of fertility in males are due to various causes (Tab. 42); their effects are listed in the spermiogram. Accordingly, the forms as per Tab. 43 are distinguished. The diagnostic measures must take into consideration the roughly anatomic analyses and hormone analyses. Attention must be paid to cryptorchisms, undescended testicles, varioceles or hydroceles, size of the testicles and (diminished) consistency of the testicles. Testicle biopsy, analyses of hormones (gonadotropins, androgenes), analysis of chromosomes and possible test for the patency of the spermatic ducts; vesiculography and epididymography complete the number of diagnostic possibilities. The assessment of the spermiograms is not based on the number alone; motility of the sperms, pathological forms and the content of fructose are further criteria.

The practical experience in this field exceeds by far the literary records, which are restricted to few authors: W. CAMER-

Tab. 42: **Causes of male infertility** (to be ascertained anamnestically)

mumps-orchitis
orchidopexy
testicular trauma
herniotomy
gonorrhoea
urogenital Tbc
chronic prostatitis
urethritis
varicocele or hydrocele operation
strong smoker
alcoholism

Tab. 43: **Cell therapy indicated:**

if spermiogram normal – or oligospermia I – or oligospermia II in case for azoospermia
if testicular biopsy normal – or diffuse tubular testicle atrophy – or focal tubular testicle atrophy but reproductive epithelium still exists.

If the spermiogram shows aspermia or the histological findings reveal total fibrosis, cell therapy is not indicated.

ER (1958, 1978, 1982); NIKOLOWSKI (1956), JANSON (1952, 1953, 1957); A. C. GIANOLI (1971). At the congress of therapeutists held in Karlsruhe (1957), W. HEUBNER dealt with the subject («Cell therapy and endocrinology»). H. RONNEBERGER (1961) and TUCHLINSKI confirmed the therapeutic effects seen in man with the results of cell therapy obtained in infertile bulls and results established in stallions by AEHNELT (1960).

W. CAMERER conducted a subtile double-blind study on 10 men suffering from fertility disorders (with 2 simultaneously infertile women) and an infertile woman. The case histories (W. CAMERER, 1978) are worth reading for the multi-dimensional diagnostic and therapeutic measures, moreover for the long times of subsequent observation. Conception occurred in 8 cases of 11, including 2 patients with serious, bioptically proved changes of the testicles. Used for each series of injections were lyophilisates of testes (ovary in hypofunction of the ovaries), placenta of male and female feti, hypothalamus.

The cells of the testicular tubuli are very regenerative and favour the metabolism. According to A. C. GIANOLI, striking improvements of spermiogenesis may be anticipated in oligospermia, tests should be conducted in asthenospermia. No results are likely to appear on the spermiogram in aspermia nor can be expected in total fibrosis.

Ovarian insufficiency

G. LEWANDER (1941, 1957) and J. BERNHARD (1958, 1963) demonstrated the induction of implanted endometrial tissue on the uterus of castrated rabbits. The specificity of the effect was inferred per exclusionem because implantations of fetal liver, spleen, lung, heart and placenta caused no endometrial new formations. In 4 test series, castrated rabbits got injections of lyophilisates of endometrium from a pregnant rabbit; in all series, a regeneration of mucosa with a distinct formation of glands in the recipient was observed. Fresh tissue and lyophilisates had the same effect; oestrogens were not traced in the tissues.

Papers by W. CAMERER (1957, 1978, 1982), GOOS and MAISCHEIN (1957), VORSTER (1958), HOLMER (1958), J. BERNHARD and W. KRAMPITZ(1963, 1967), RÜMELIN (1970) deal with partly experimental, partly clinical problems of the female menopause and amenorrhea.

Therapeutically, it is expedient to distringuish *amenorrhea* and *oligomenorrhea*, as expressions of functional insufficiencies in the mature age of the woman, from the physiological concomitant symptoms of the subsiding ovarian function in the menopause.

For the chromosomal *ovardysgenesis* as part of *Turner's syndrome* (fig. 246), questions of the growing stature and of the properties of the body are more important than the fertility. During the maturation of the woman, however, the problem of fertility prevails. Non-biological habits (contraceptive pill) and ideals of beauty (Twiggy-types) have augmented this field of gonadal dysfunctions during recent years. The cell therapy does surely more for the *menopausal involutionary symptoms* and has better physiological and more lasting effects than a hormone-substitution therapy.

Central tissues for cell therapy to treat *gonadal-ovarian insufficiency* are the ovaries and adrenal glands. Considering the general medical aspects of the outfall

symptoms, the selection of organs should have an adequate scope. Hypothalamus, placenta, liver, connective tissue ought to be use in certain cases, too, according to the clinical symptoms.