Diseases of supporting tissues

The value and limits of cell-therapy cannot yet be defined for the many skeletal abnormalities and diseases. With the exception of some orthopedic reports, the pertinent literature is very sporadic so that the following data are based on the author's own recorded observations.

A concise outline of the skeletal development must be given first to arouse the understanding of the possibilities and initial points for cell-therapeutic measures and necessary additional treatments.

Development of the skeleton

The supporting tissue develops from the embryonic mesoderm and includes the following tissues (W. BARGMANN):

Unformed supporting tissues:

1. mesenchyme
2. gelatinous connective tissue
3. reticular connective tissue
4. adipose tissue
5. loose connective tissue
6. tight connective tissue

Formed supporting tissue:

1. tendinous tissue, elastic tissue
2. cartilaginous tissue
3. chorda tissue
4. bone-tissue, dentin
5. vascular system.

Whereas the unformed supporting tissues retain partly the pluripotency of the embryonic structures and represent much of the active mesenchyme (reticulo histiocytary system), the formed supporting tissues have already taken special functions.

Up to the final differentiation, the skeleton passes a mesenchymal, a cartilaginous and a bony stage. In the mesenchymal stage, the mesenchyme develops, generally via the pre-cartilage, the model of the prospective supporting tissue. Disturbances affecting the growth of the skeleton in this stage are usually aberrations from the ground-plan. Tab. 49 is a list of the most important of these aberrations. In the cartilaginous stage, the mesenchymal pre-cartilaginous rudiments are rebuilt first into cartilage. The transformation begins in the second month of embryonic life between the stages of 10 mm and 26 mm of the embryo via the chondrification centres. On the 60th day of pregnancy, the rudiments of the cartilaginous skeleton are completed up to the terminal phalanxes of the toes, and the cartilaginous skeleton is then successively replaced by bones (= substitution bones). This process sets in as from the 7th embryonic week and is accomplished at the end of the somatic growth between the 15th and 20th year of age.

Cartilage is a special form of connective tissue; its consists of cells (chondrocytes) embedded in a matrix. The matrix is composed of a fibrillary meshwork of collagenous fibrils and an amorphous ground-substance; the latter is rich in sulphates containing mucopolysaccharides (chondroitinsulphate). The gelatinous ground-substance is polyanionic, highly polymerised. Cells and ground-substance are carriers of the highly *metabolic activity* distinctive of the growth, and of the *plasticity* of the cartilage. The collagenous fibres effect the *rigidity* and *elasticity*. Cartilage has no vessels, contains only canals resembling vessels. The metabolic processes pass through the diffusion, which is rendered the more

Tab. 49: **Architectonic aberrations**

1. Craniosynostosis (= premature suture synostosis) by maldevelopment of the cranial sutures in the mesenchymal stage: Dolichocephaly, Turricephaly, Oxycephaly, Plagiocephaly, Microcephaly
2. Dysostosis craniofacialis (CROUZON)
3. Dysostosis mandibulofacialis (FRANZESCHETTI; TEACHER-COLLINS)
4. Oculo-mandibulo-facialis syndrome (FRANCOIS, HALLERMANN-STREIFF)
5. Acrocephalo-syndactily (APERT)
6. Acrocephalo-Poly-syndactily (CARPENTER)
7. mandibular hypoplasia (PIERRE-ROBIN)
8. Rubinstein-Syndrome
9. Aglossy-adactyly syndrome
10. Dysostosis cleidocranialis (cleido-pelvico-cranialis)
11. Sprengel's deformity; innate scapular elevation
12. Klippel-Feil syndrome and other vertebral segmentation disorders
13. Cranio-Rachischisis centaurica (iniencephaly)
14. Cervico-oculo-acusticus syndrome (WILDERVANCK)
15. Oculo-vertebral syndrome (WEYERS)
16. Oro-digito-facialis syndrome
17. Dysostosis spondylocostalis
18. Pectoralisaplasia-Dysdactyly syndrome
19. Osteo-Onycho-Dysostosis (Nagel-Patella syndrome, TURNER-KIESER)
20. Radiusaplasia-Thrombocytopenia syndrome
21. radioulnar synostosis
22. carpal and tarsal synostosis
23. Syndactyly-Polysyndactyly-Spoonhand
24. Ectromely
25. Polydactyly
26. Oligodactyly
27. Brachycarpie-Brachyphalangie-Brachytele-, meso-, -basophalangy
28. Dolicho-steno-carpia
29. Sirenomelia
30. Arthrogryposis multiplex (Arthromyodysplasia congenita)
31. Dystrophia mesodermalis congenita (MARFAN u. a.)

difficult the more the maturity continues (= gel condensation). With these properties, cartilage is a tissue that has lost the pluripotency of the mesenchyme but still retained many functions of the origin tissue e. g. the metabolism, the dividing activity, plasticity and elasticity. Cartilage is formed through prechondroblasts, highly synthetic chondroblasts and chondrocytes. Hydroxylapatite is embedded in the growing zones.

Disturbances in the cartilaginous stage provoke modelling abnormalities of the skeleton. The essential abnormalities are listed in Tab. 50 and 22.

Bone is a specific calcified derivative of connective tissue; its architecture depends on its function. Bone consists of cells (osteocytes) and of a lacunar meshwork. The organic ground-substance (30%–40%) consists chiefly of collagen (90–95%) and sulphate-mucopolysaccharides. The mineral salts (60–70%) constitute a homoiostatic reservoir for calcium, phosphorous and citrate ions, and are formed into hydroxyl apatite by the ossification. The ossification (osteogenesis), too, is an active cell performance of specialized cells of connective tissue, the osteoblasts, which are derivatives of the pluripotent cells of connective tissue. The initial process of ossification, the formation of crystal nuclei along the collagen fibres requires certain bioche-

mical and inorganic substances; some of them are the cells and cell derivatives, organic and inorganic substances listed in Tab. 51.

The *collagen fibres* formed by the osteoblasts are an aggregate of subunits, the so-called tropocollagen. Every molecule of tropocollagen consists of 3 peptide chains. The hydroxylation of the prolin depending on the ascorbic acid takes place when prolin unites with a nucleotide or with soluble RNA. The fibrillation is caused by a crystallization process.

Osteogenesis is either desmal or chondral, according to whether the bones are formed from the connective tissue direct or through the cartilage.

The fig. 297 a, b, outline by means of examples the relations between the derivatives of the connective tissue under physiological and pathological conditions.

Therapeutic conceptions should take into consideration these connections.

The development of the skeleton is a process regulated by cells; it undergoes

Tab. 50: **Modelling anomalies of the skeleton**

1. Achondrogenesis
2. thonatophorous nanism
3. Achondroplasia (= Chondrodystrophy)
4. Hypochondroplasia
5. Dyschondrosteosis
6. metatrophic nanism
7. diastrophic nanism
8. asphyxiating thoraxdysplasia
9. Chondrodysplasia punctata (Chondroangiopathia calcarea)
10. chondroektodermal Dysplasia (ELLIS-VAN CREVELD)
11. mesomel nanism
12. Spondylo-epiphyseal dysplasia
    a) congenita (SPRANGER)
    b) tarda
13. Spondylo-metaphysary dysplasia
14. metaphysary dysplasia
    a) Type Murk-Jansen
    b) Type Schmid
    c) Type McKusick (cartilage-hair-hypoplasia)
    d) with neutropenia and malabsorption
    e) with thymic lymphopenia
15. multiple epiphysary dysplasia (FAIRBANK)
16. Acrodysplasia epi-metaphysaria (BRAILSFORD)
17. Dysplasia epiphysealis hemimelica (FAIRBANK)
18. Enchondromatosis (OLLIER)
19. multiple cartilaginous exostosis
20. Enchondromatosis with haemangiomatosis (Maffucci syndrome)
21. fibrous dysplasia
    a) without abnormal pigment anomalies (JAFFÉ-LICHTENSTEIN)
    b) with abnormal pigment anomalies and pubertas praecox (ALBRIGHT syndrome)

Tab. 51: **Essential factors of osteogenesis**

Tissues, cells, cellular derivates	Organic substances	Inorganic substances
Mesenchyme embryonic connective tissue procartilage cartilage vessels chondroblasts chondrocytes osteoblasts osteocytes osteoclasts tropocollages collagen fibrils	Amino-acids (prolin) nucleotides soluble RNA ATP Mucopolysaccharides Vitamin D Vitamin C Vitamin A carbonic acid Phosphatase	calcium phosphorus sodium sodium citrate potassium magnesium iron fluor sulphur

many stages and is therefore exposed to a richly differentiated scale of maldevelopments. The effects of such failure depend chiefly on the time, then on the character of the malregulation. The following points must be distinguished:

1. *Aberrations of the architecture* originating up to the end of the somitic stage (28th–30th day of embryonic life); they are somitic i. e. axillary, constitute more or less gross aberrations from the architecture and form of the body. Aplasia, hypoplasia, synostosis and slots belong here (Tab. 49).
2. *Modelling abnormalities* originates after the somitic stage till the end of the somatic growth i. e. from the 5th week of embryonic life till puberty. As they include the mesenchyme and cartilaginous stages, they ought to be called dysplasia, not dysostosis (Tab. 50, 22). During this long time, the bones grow much more rapidly at the metaphysical ends than by periosteal apposition. Disturbances manifest themselves chiefly in the metaphyseal-epiphyseal zones of growth, transverse to the bone axis. Whilst the number of bone-elements is regular, the form is affected, which means that the moulding is abnormal. In question are *osteogenesis imperfecta, meta- and epiphyseal dysplasia, achondrogenesis, achondroplasia, mucopolysaccaridosis and many syndromes with skeletal dysplasia.*
3. *Structure disorders.* Changes of the bone-structure in the preformed skeleton should be summarized under the collective term «dysostosis» . In question are local or generalized dis-

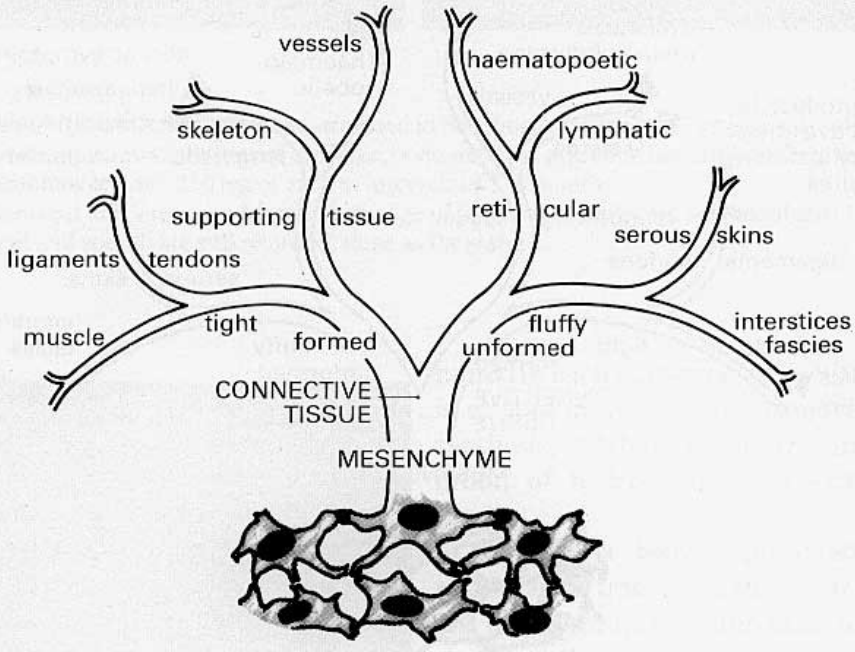


Fig. 297 a:
«Mesenchyme tree». The embryonic mesenchyme brings forth the formed and unformed connective tissues, which specialize in the nearest branching (muscles, ligaments, tendons, skeleton, vessels; haematopoetic, lymphatic system, serous skins, interstitia, fasciae). The following differentiation has been omitted for better survey (from F. SCHMID: Pädiatr. Radiologie, volume I).

turbances of the distribution between organic bone-matrix and inorganic deposits; simultaneously, the relation of elasticity: stability is changed. The spectrum ranges from the *osteomalacia* over *osteoporosis* to *osteosclerosis* and *osteopetrosis.* Disturbed metabolism, lack of vitamins, immobilization, hormonal influences are the main causes for aberrations of bone-structure. Senile osteoporosis belongs here. Of the rare cases of innate dysostosis, osteopetrosis is best known.

Therapeutic remedies

The following tissues are suited to treat skeletal dysplasia and dysostosis with cell-therapeutic measures:

Tissues of first choice: cartilage, fetal mesenchyme, connective tissue, osteoblasts, bone marrow.

Tissues of second choice: placenta, liver.

As to third quality, the use of endocrine organs ought to be considered in each particular case e.g. hypothalamus, hypophysis, adrenal gland, gonads for forms of nanism, and parathyreoidea and kidney for abnormal structures.

The *implantation therapy* can be completed by *hydrolysates* and *enzyme preparations.* Of the hydrolysates, arumalon® is the best-known. Enzyme preparations in the form of Wobe-mugos, Wobenzym® are available for oral and rectal applications. More effective parenteral or mucosal preparations are Oculucidon®, Rheumajecta® and Vaselastica®.

The biological substitution therapy should be completed by quantitative trace elements and vitamins to be deter-

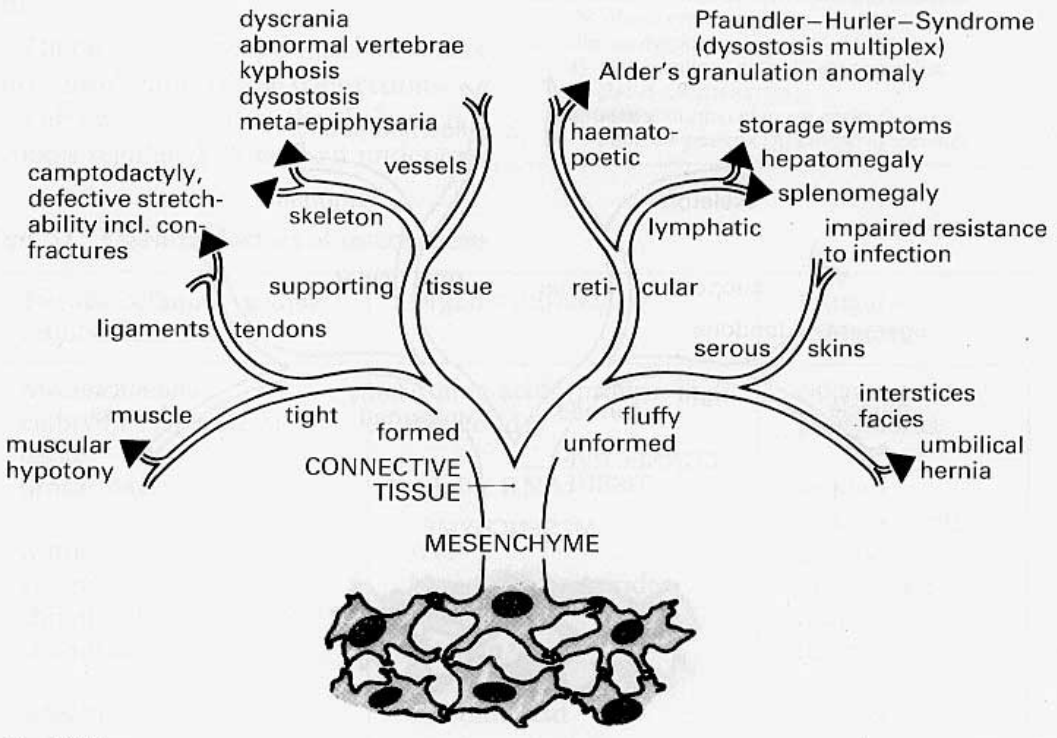


Fig. 297 b:
Development, specialization and differentiation of the mesenchyme («mesenchyme tree»); participation of the mesenchyme derivatives in Pfaundler-Hurler's disease. Besides the formed connective tissues, essential parts of the unformed connective tissues are also affected; consequently, a «mesenchymosis» in the strict sense is in question (from F. SCHMID: Pädiatr. Radiologie, volume I).

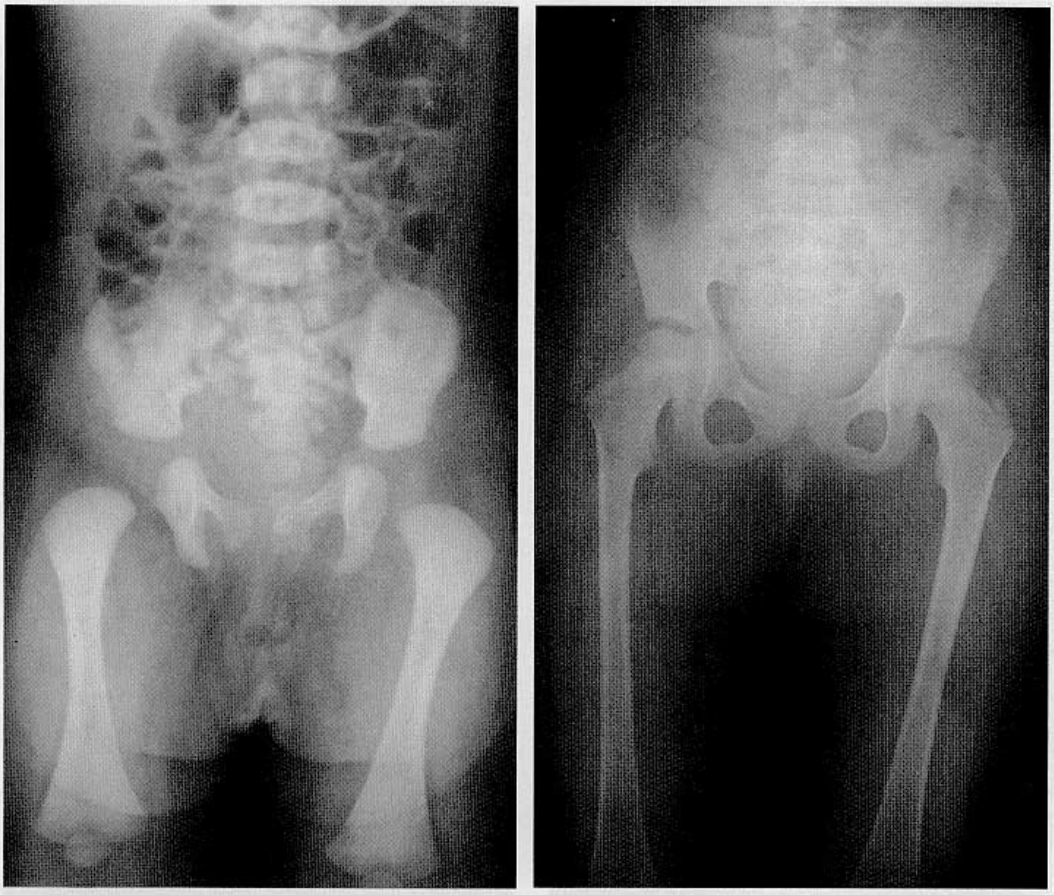


Fig. 298 a, b:
Arthro-Myo-Dysplasia
a) Shoulders, hips and knees cannot be stretched in new-born on account of articular dysplasia. Besides physiotherapy, implantations of cartilage, bone-marrow, placenta, liver and cerebral tissues are injected combined by 200–250 mg of each at intervals of 5–6 months.
b) Shoulders and hips are moved freely at the age of $9\frac{1}{2}$ years, the hips are well moulded; the static development and speech are still retarded, same as the stature.

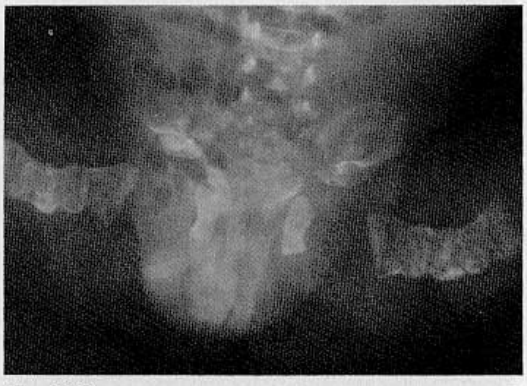


Fig. 299:
Osteogenesis imperfecta, Type Vrolik.

mined in each particular case. Vitamin C is of importance for the tropocollagen synthesis, vitamin D for the incorporation of hydroxylapatite (= calcification).

To find a proper preparation of quantitative trace elements, hair analyses may be more useful than tests on sera. In achondroplasia and osteogenesis imperfecta the calcium-content in the hair is markedly elevated, selenium lowered.

Physiotherapy, massage, gymnastics

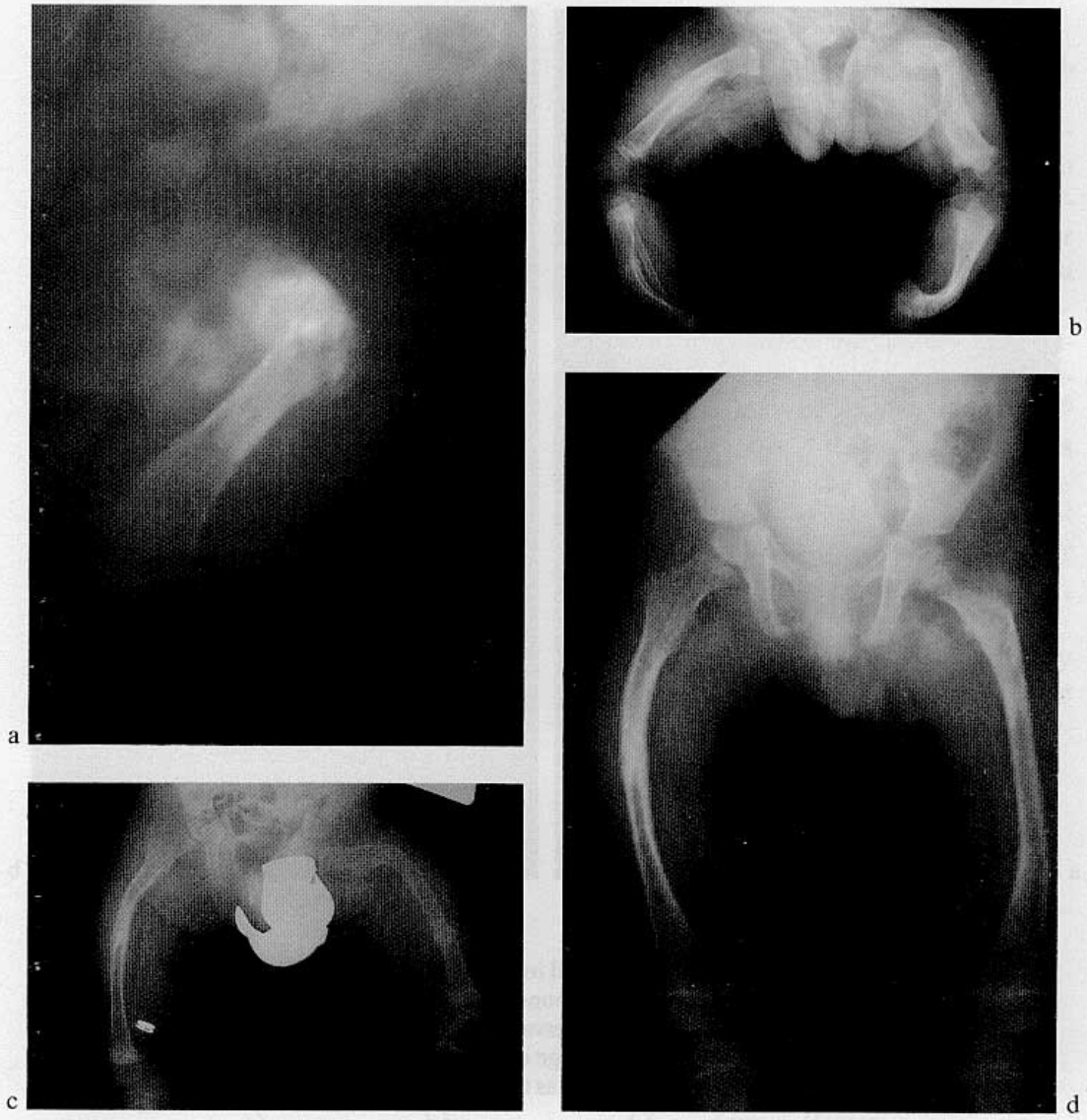
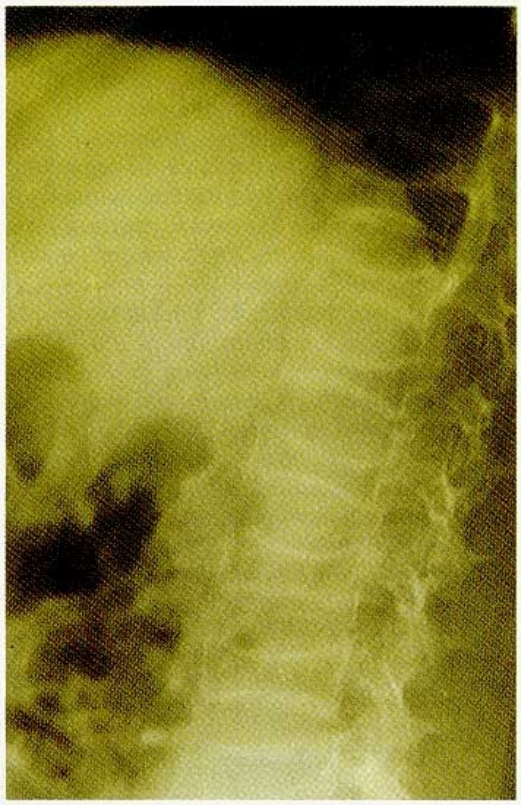


Fig. 300 a–d:
Osteogenesis imperfecta, severe Vrolik-type.
Till 5 and 6 month of age multiple bone fractures (a) and skeletal deformities. After starting the treatment less and faster healing fractures, but still deformed left femur (c) in the age of 16 month. Good reconstruction of the bones in the age of 25 month. Treated with various mesenchymal tissue-implantations.

or special physical exercises constitute an important factor to support structural processes by functional activities.

Further, a *dietetic promotion* should not be underrated. Raw vegetables and sufficient supplies of calcium by milk, salt-water fish, crabs are well suited to balance the calcium-phosphorus metabolism. Colostrum milk and raw epiphyseal cartilage added to the food have special indications. It must, however, be emphasized that all these measures relate to treatments of disorders considered as untreatable, and that the results in all must still be denoted as unsatisfactory.

As regards the skeletal abnormalities and diseases, just little can be said about the usefulness of these therapies, all the



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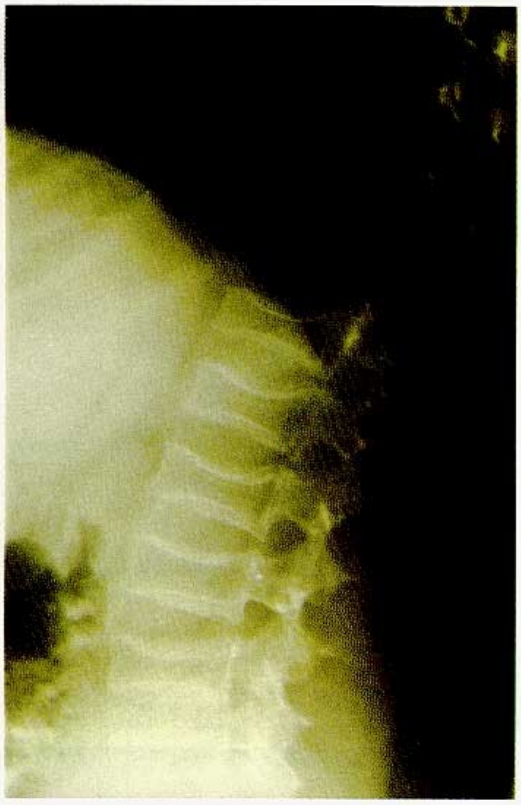

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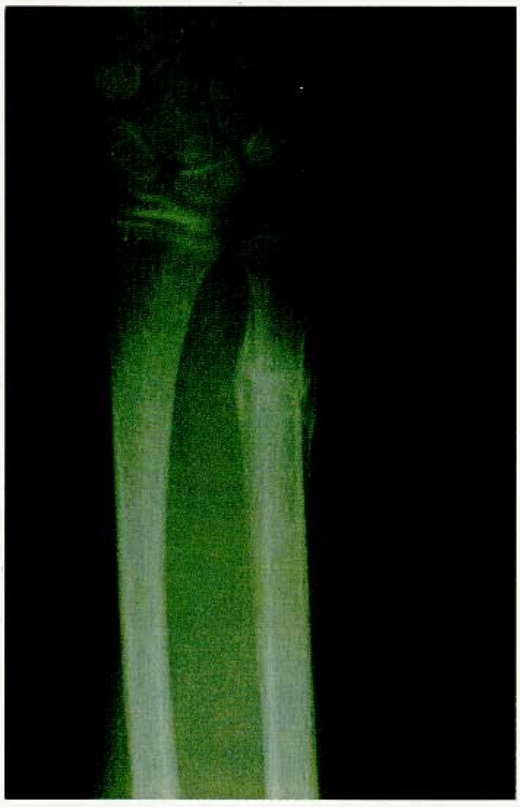
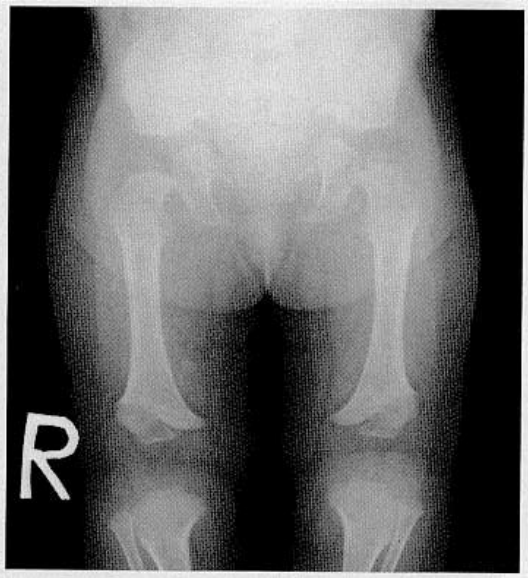


c

Fig. 301:
Osteogenesis imperfecta
The 8-year-old girl, who had suffered many fractures (so far 13 large, many small ones) was immobilized for over 2 years, unable to walk, increasingly depressed.

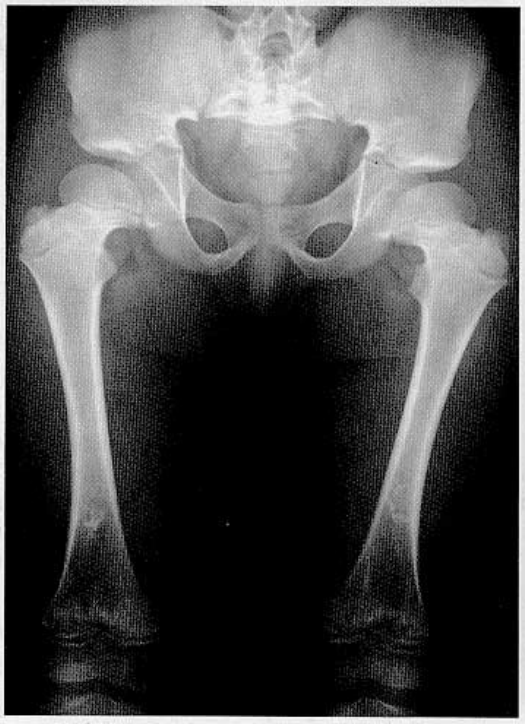
a) at 8 7/12 years, with serious dysplasia and deficiency in calcium of the entire skeleton incl. the vertebrae, she got the first implantation of 100 mg of cartilage, 75 mg of bone-marrow, 150 mg of placenta; basic treatment with 500 mg of vitamin C daily, coliacron.
b) on half-year implantations no fracture for 2 years, good mineralization, walking up to $\frac{3}{4}$ hour; only after immobilization due to Genua valga operation, new fractures occur.
c) healing ulna-fracture.



a

Fig. 302 a–d:
Achondroplasia
P. W. comes to be treated at 1 7/12 year with the classical symptoms of achondroplasia.
a) The pelvic shovels are low, roundish, the acetabula horizontal, the necks of the femora are thick, distal meta-epiphyses laterally ground off, medially drawn out like beaks, proximal tibia-metaphyses mushroom-like blown out, concave irregular calcified zones.
Gets cartilage, osteoblasts, bone-marrow, placenta and liver in combinations of 200–250 mg of lyophilisate each, at half-year intervals, at times arumalon (hydrolysate) and oculucidon (combination of enzymes).
b) At $7\frac{1}{2}$ years, short but straight femora, horizontal calcified zones on the distal femur, solidified metaphyseal structures, epiphyseal cores nearly regular.
c) At $9\frac{1}{2}$ years virtually straight hollow bones, fibula slightly curved, smooth calcified zones, regular epiphyseal cores.

d) Curve of growing stature ▶



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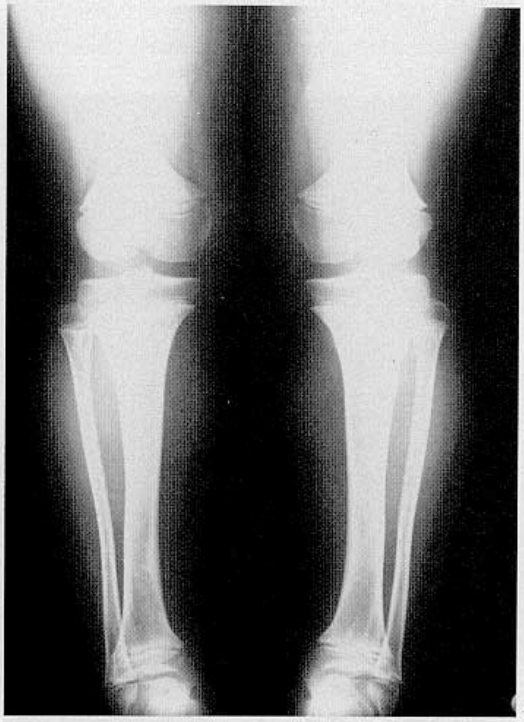
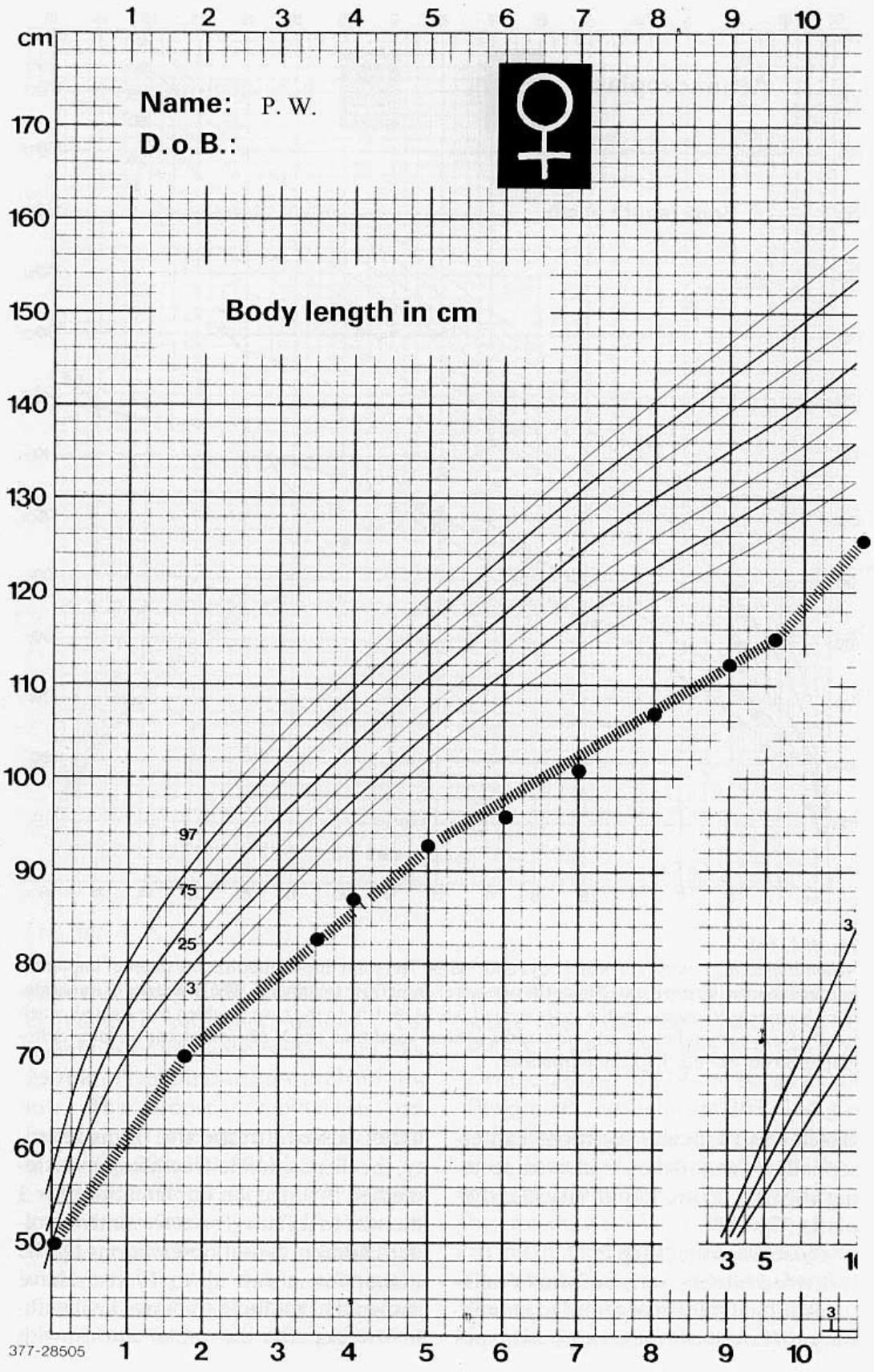


c

more since the number of the aspects under concern is often restricted.

Arthrogryposis multiplex (arthromyodysplasia)
constitutes a serious syndrome, with malformed rudiments of the joints, tendons and muscles with considerable functional restrictions as main characteristics. Four long-time observations during 6–12 years have shown that the



(Fig. 302 d)

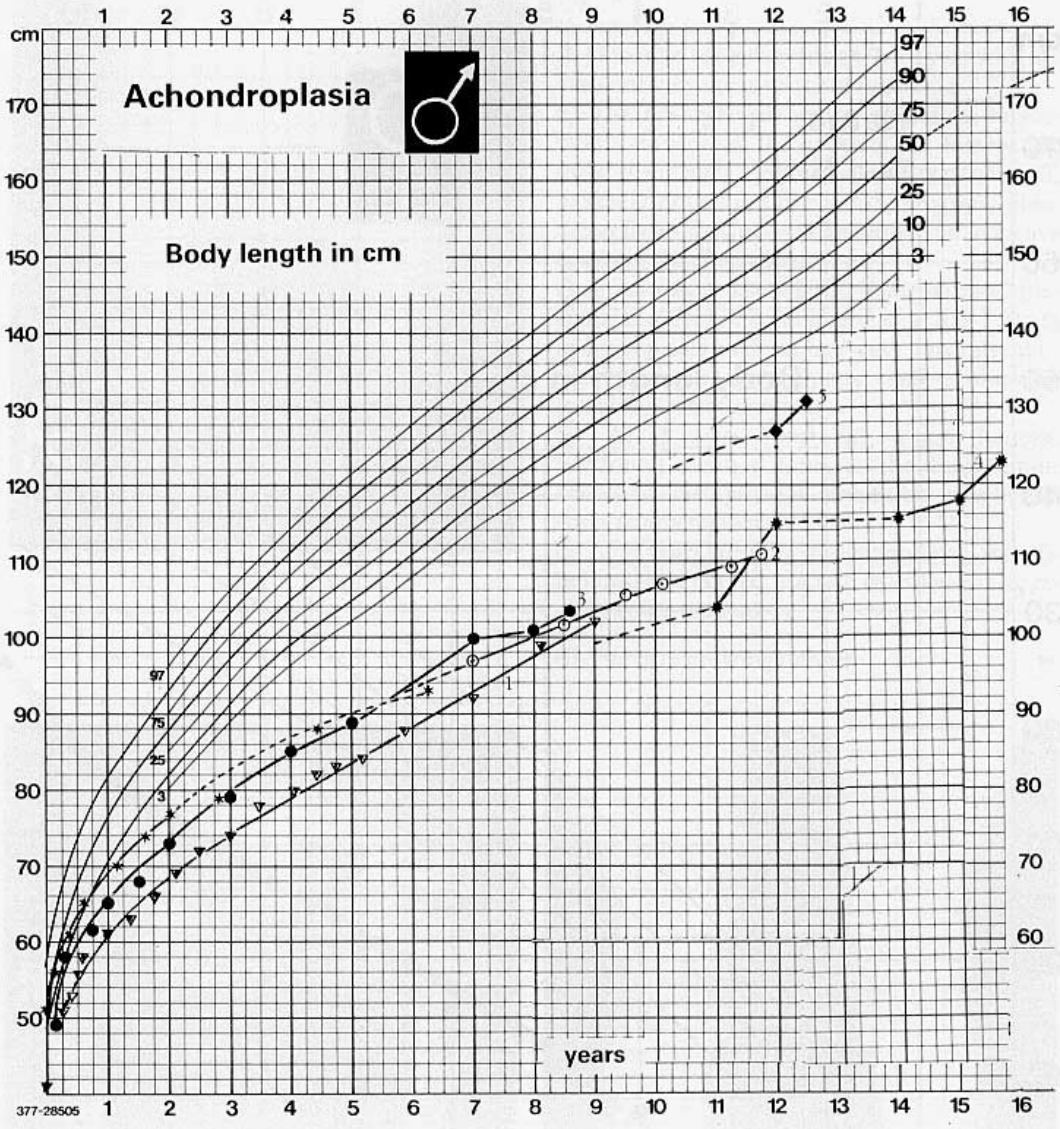
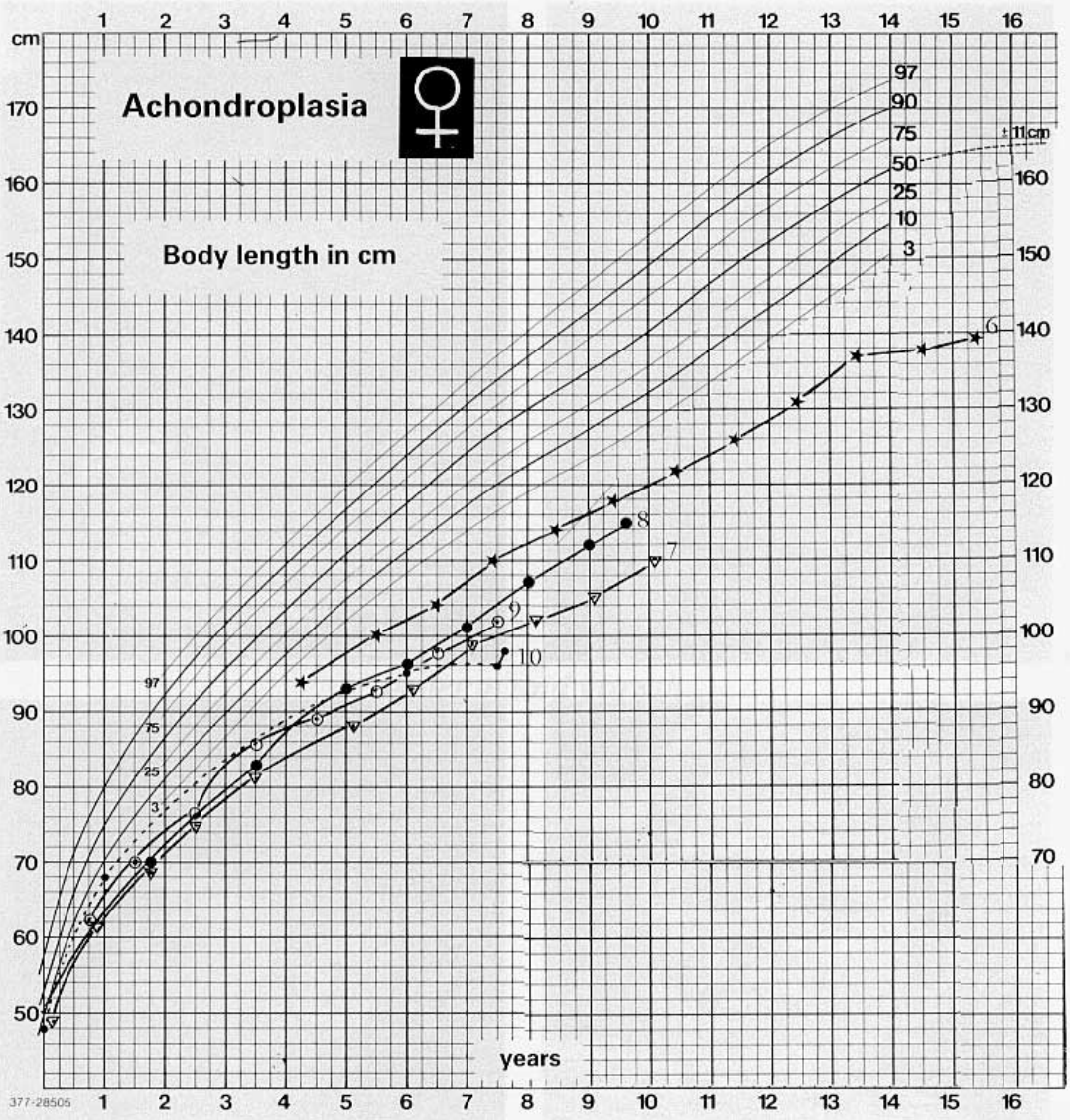


Fig. 303, 304:
Achondroplasia, growth curves of 5 boys and 5 girls. The solid lines symbolize the times of implantation treatments, the interrupted lines the periods exempt from treatments. The influence of implantations is evidenced mainly by the cases treated late (4, 5, 10). In the case 6, which was treated consistently from early infancy and evidenced a serious condition, the X-ray symptoms on later radiographs do not exclude hypochondroplasia.

skeletal and articular functions can essentially be restored even in cases seeming hopeless on account of articular dysplasia (fig. 298).

Osteogenesis imperfecta
is divided into the serious form (Vrolik-type) and mild form or retarded manifestation (Lobstein-type); other subtypes are discussed. Irrespective of the severity, the disposition to fractures can be remedied by injection implantations for 3 months in infants, for 4–6 months in older children. Seven observations by the author for in part up to 10 years have shown that multiple fractures heal within 3 weeks after the implantations, with



(Fig. 304)

pain (breathing after fractures of ribs, extremities) subsiding rapidly. The quantities of implants used so far (200–250 mg of lyophilisates) are probably too low. The proper combinations are: cartilage + placenta; liver + osteoblasts (fig. 299, 300, 301).

For *achondroplasia (chondrystrophy),* experience of many years (15 observations) is available. Though a final statement cannot yet be made, certain findings are worth mentioning. The yearly growth rate is 3–5 cm during the treatment, the final result may exceed the expected rates of untreated patients by about 10–15 cm. Untreated girls reach an average tallness of 119 cm, boys 127 cm. The growth curves in fig. 303, 304 give some individual courses in treated children. Interruptions of treatments show more clearly their positive influence on the growth of the body. It must be pointed out that treated children have no problems with the hydrocephalus, that their members are more straight in spite of their shortness, and the calcification zo-

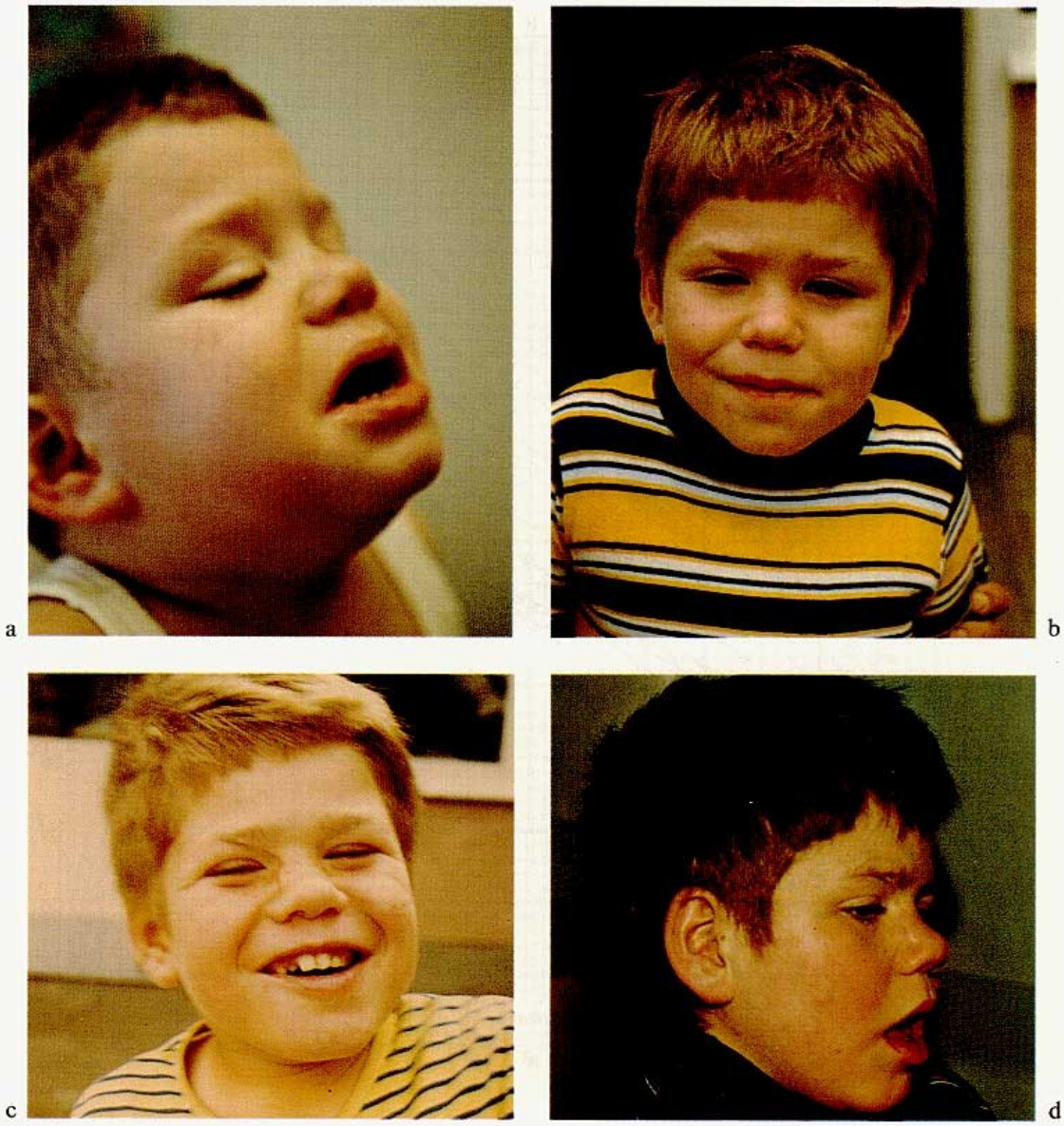


Fig. 305:
Mucopolysaccharidosis, type II

a) The boy was presented first at 3 6/12 years (670,609–701,208); diagnosis had been made elsewhere, and a short prognosis for life had been given.

b), c) In the course of regular implantations with cerebral lyophilisates, placenta, liver, not only the retrogression of the early years is stopped; the boy learns to walk, cycles on a tricycle, uses a few words, but the results won by the implantations subside again after 3–4 months.
b) 6 years, c) 8 years.

d) Beyond the 10th year, the motor functions of cleanness and the physiognomical control retrogress.

nes and metaphyses, originally uneven and often bizarrely deformed, are transferred into increasingly regular structures (fig. 302).

Mucopolysaccharidoses (see Tab. 22) proceeds with more or less serious skeletal dysplasia. The therapeutic measures have brought about so far only temporary improvements (fig. 305) and retarded the progredience. The causal principle of lacking lysosomal enzymes can be influenced with the available preparations only for a short while and insufficiently. The same restrictions apply to *spondylo-epiphysary dysplasia.*

Individual observations suggest that the healing processes in *aseptic necrosis* and *fractures* can be accelerated by cell implantations, which constitutes a prerequisite for the healing of *chronic osteomyelitis* (HERBERT; HAGMEIER; EICKSCHEN; fig. 294, 296, 306.

Most of the practical experience is available for *arthrosis* and chronic from of *arthritis* (R. ORTIZ, 1973, 1980; HERBERT, 1982). The tissular combination comprises connective tissue, cartilage, osteoblasts, placenta and liver. The clinical effect, of course, depends on the stage of the regressive changes; that is why the therapy should not be put off till the function of a joint disappears and osteophytes, calcified tendons and secondary deformations create irreversible anatomic conditions.

Skeleton and growth

The growth of the stature is the result of skeletal growth and takes place in 3 phases, namely

a) a genetic phase
b) a «hypophyseal» phase
c) a «gonadal» phase.

The first, genetically regulated phase ranges from birth till about the 3rd and 5th year and characterized by a high speed of growth. The second phase (from about the 4th–5th to the 8th–12th years) is regulated chiefly by the hypophyseal diencephalic system and stimulated by the somatotropic hormone (STH). In this phase, growth is slow-steady, with an annual increase between 4 and 6 cm. The third phase leads to another augmented growth under the influence of the adrenal-gonadal system (the so-called puberal growth outburst).

The *adrenal glands* undergo an involution after birth; after the 6th–8th years of age, the adrenal glands and gonads grow rapidly, reaching simultaneously a culmination between the 14th and 18th years. Whereas the corticosteroids show a nearly linear rise from birth, the production of gonadotropins, 17-ketosteroids and sexual hormones begins also between the 6th–8th years, but in the concentration proceeds virtually parallel to the growth of the adrenal glands and gonads (PRADER).

The growth of the stature and the development of bones are influenced usually in the same way by adrenal and sexual hormones. The physiological function of these hormones is to initiate the third growth outburst in the beginning puberty and to finish the growth by closure of the epiphyses at the end of puberty.

The earlier this group of hormones acts, the earlier the puberal growth outburst sets in, but of course is earlier finished. The final stature, therefore, is lower in girls and among certain races of southern regions than in boys, who reach puberty later, and in most members of northern races.

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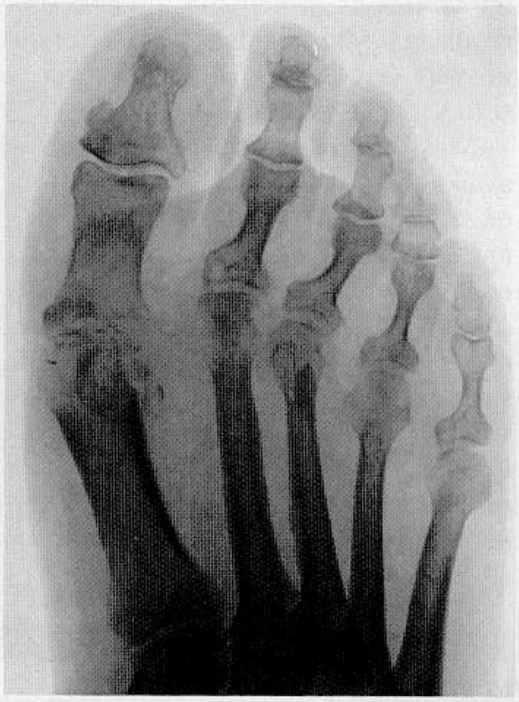

Fig. 306 a:
Focuses of *osteolysis* and destructions of all metatarsal and phalangeal joints, specially on the second ray (23. 7. 1977).

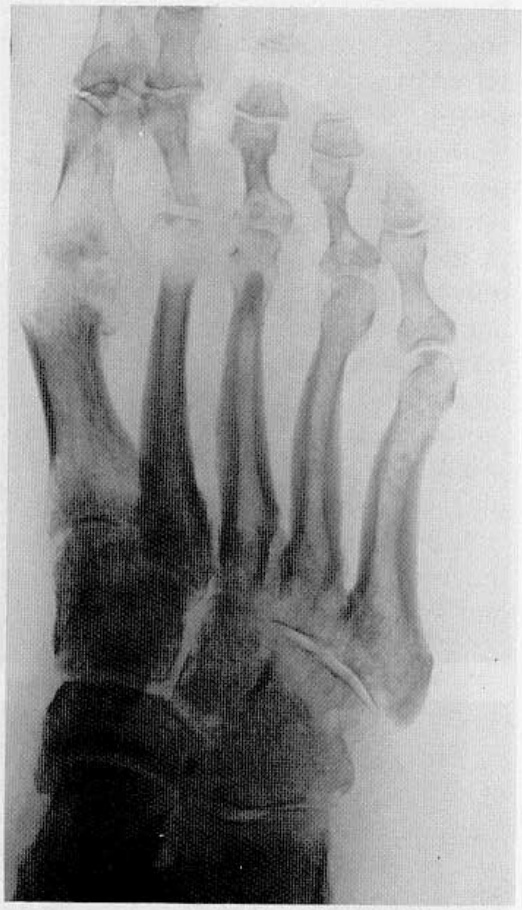

Fig. 306 b:
Advanced osteolysis of the metatarsal-phalangeal regions, spreading of osteomyelitis on the other tarsal bones (24. 10. 1977).

Chronic osteomyelitis (H. EICKSCHEN)
Anamnesis and course: E. W. born 30. 3. 1894:
27-XI-76: strong, obese man of 82 years, with Adam-Stokes' syndrome. Complete AV block. R. R. 150/90, pulse 40, disturbances of peripherous blood circulation, acrocyanosis, foot pulse right cannot be confirmed. 5. XII. 76: fractures of 4 ribs owing to downfall, admitted to Bethesda Hospital, Mönchengladbach, from there moved to Düsseldorf clinics, heart pace-maker. 15. I. 77: relative well-being, RR 150/90, pulse 72. Hallus valgus right, hammer-toe, suppurative ulcer on this toe. Blood circulation still disturbed. Operation on hammer-toe. Exostosis chiseled away. 6. V. 77: patient is presented again, suppuration on right big toe, surgical area not healed, elimination of bone-splinters, pain, walking impossible (fig. 306 a).
Admitted again after ambulatory treatment. Hospital surgeon recommended, after conservative treatment with absolute rest in bed for weeks, to amputate the right leg in the thigh. 1-VIII-77 to 13-IX-77: refusal of this suggestion, discharge from clinic, the patient was cared for in bed by his wife at home. Diagnosis: osteomyelitis in the area of right big toe (fig. 306 a, b).
Increased pain, extension of suppuration, a second fistulous opening with profuse suppuration is seen on sole at proximal phalanx of 3rd toe. Another fistula lateral on heel, with less suppuration. Increased inflammatory swelling of the foot, sharp pain. Placing on splints, daily dressings with diverse ointments, baths, highly dosed antibiotics, ampicillin, eusaprim, tetracyclin, and after tapping

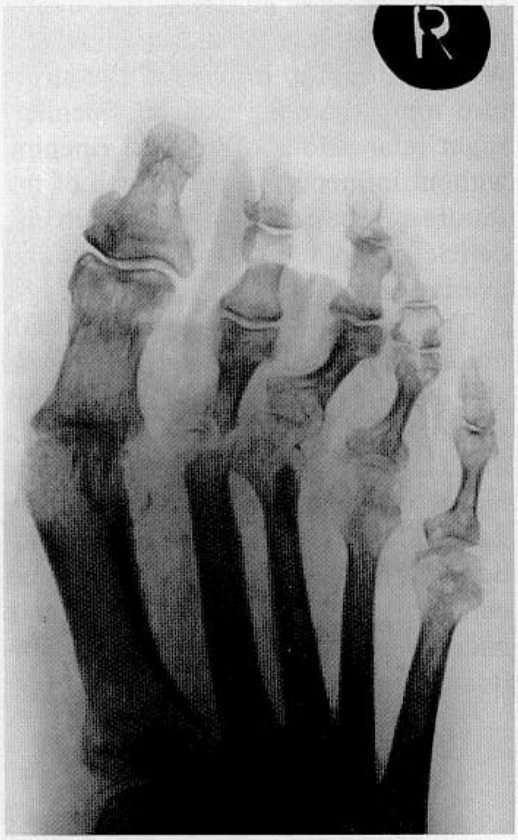

Fig. 306 c:
Beginning restructuring of the osteolysis areas, especially clear in metatarsal I; on the other metatarsals still many focuses of osteomyelitis (14.4.1978).

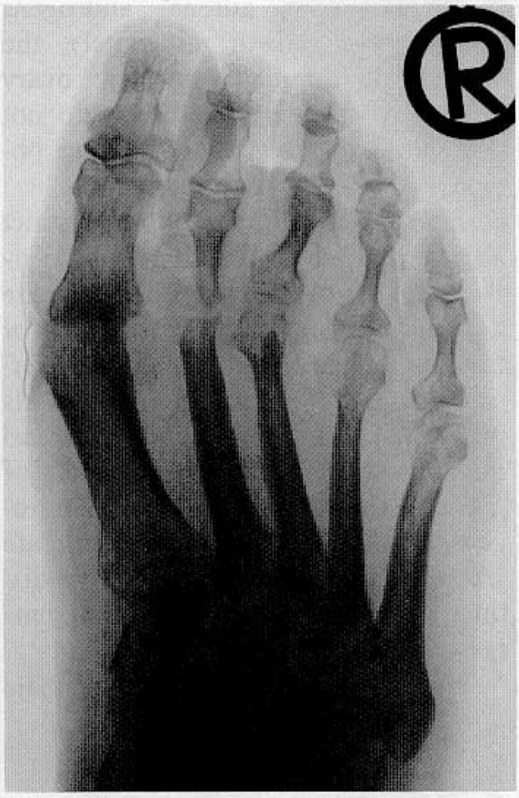

Fig. 306 d:
Restored bone-structure on the metatarsal I distal defective substance of the proximal phalanx II, extensive healing of the osteomyelitic focuses of osteolysis (4.8.1978).

the pus and test for sensitivity, adequate further treatment. No improvement, on the contrary, slow continued increase of findings. 27-X-77: roentgenographic examination (fig. 306 b). 23-XI-77: no change of findings, further daily changes of dressing, profuse suppuration, sharp pain.
Resistocell® fet. mesenchyme
First dose of 1 ampoule (100 mg of lyophilisate). Simultaneous cessation of all antibiotics, further changes of dressings, placing on splints, rest in bed, injection tolerated without local reaction.
21-XII-77: suppuration subsided considerably. Pain clearly diminished. The foot-relief seems to be restored. Edema and inflammatory secondary reactions subside.
23-I-78: Foot bears weight for the first time after a year. Patient ist out of bed. Suppuration stopped completely! Slight pain. 25-II-78: Resistocell® 2nd dose of 1 ampoule (100 mg of lyophilisate).
22-III-78: lasting improvement. Patient can walk, climb stairs, foot bears full weight. Suppuration dries up.
14-IV-78: roentgenological examination of right foot (fig. 306c): restructuring of osteolysis.
4-VIII-78: roentgenological control (fig. 306 d): extensive healing of osteomyelitic focuses.
Ater injected implantation of 100 mg of fet. mesenchyme (Resistocell®) decisive change of illness – after 1 year chronicity with progression. During the following months steady clinical improvement with reconstruction of skeletal lesions (fig. 306 d).

Physiologically, adrenal androgens promote the growth moderately, the skeletal development strongly; ovary oestrogens during adolescence do not promote the growth but favour obviously the skeletal development.

Hyperfunctions have more distinct aberrations: adrenal androgens accelerate much and usually finish earlier the growth and ossification when used for the adreno-genital syndrome; an overproduction of adrenal glucocorticoids inhibits growth, skeletal maturation and mineralization in the combination of Cushing's syndrome. Testicular androgens (e. g. Leydig cell tumour) accelerate growth and skeletal ripening more distinctly than increased ovary-oestrogens (granulosa cell tumour).

Hypofunctions of the adrenal-gonadic system work less intensely than hyperfunctions. Lack of adrenal steroids *(e. g. Morbus Addison)* influences the structure more than the skeletal ripening; slight retardations of skeletal ripening without influence on the growth of the stature may be caused during puberty by deficiencies of testicular androgens and ovarian oestrogens *(hypogonadism)*.

The gonads not only correlate with the adrenal glands but are influenced also by the hypothalamus-hypophysis system, its hormones and releasing factors. Gonadotropins, follicle-stimulating hormones and luteinising hormones are decisive. Before deciding on a therapeutic plan for special aspects, one should consider the interactions within the endocrine system as shown in the synoptic survey of fig. 282.

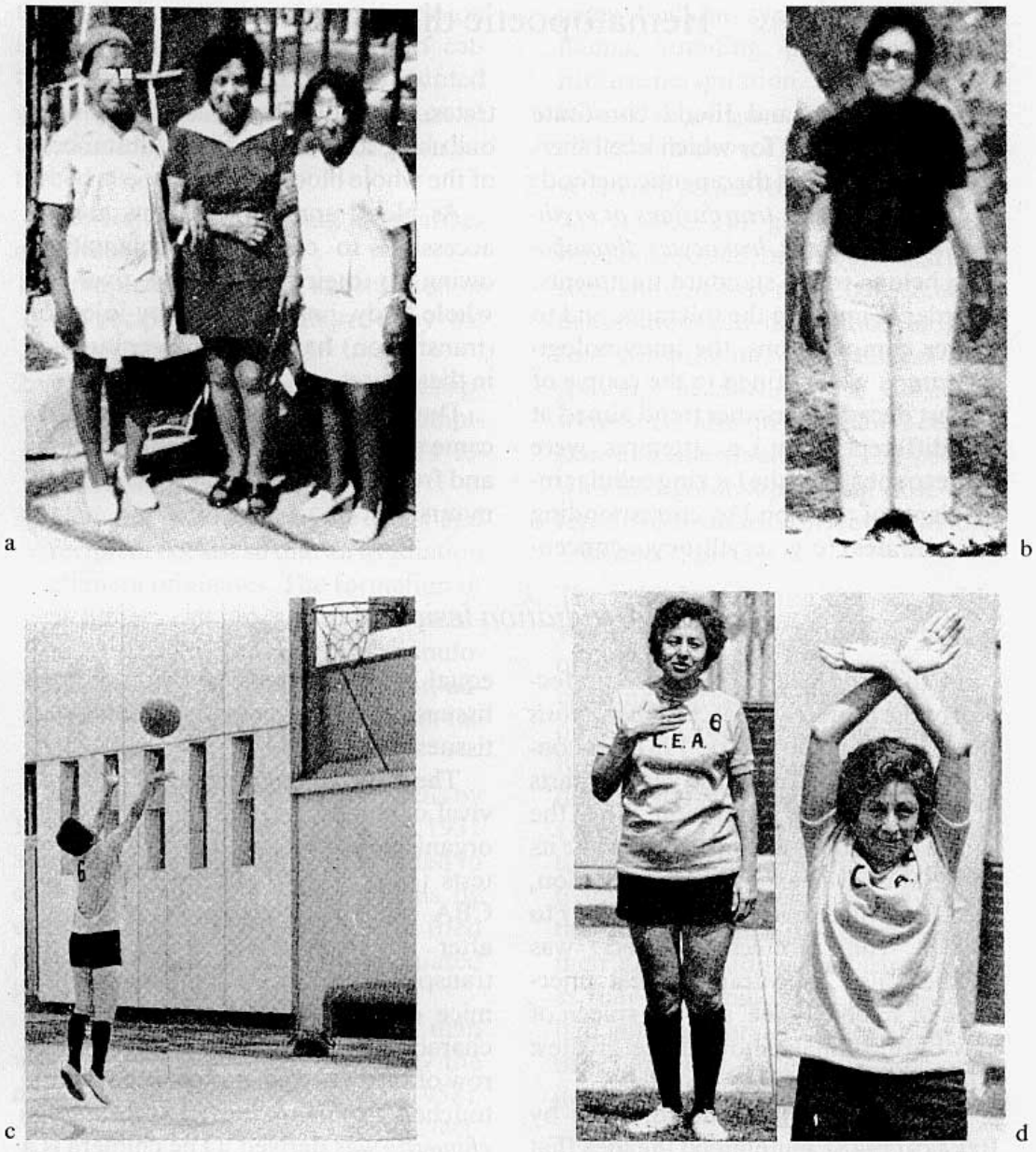

Fig. 307:
Chronic polyarthritis in a case of Lupus erythemadotes visc. (case F. Ramos ORTIZ, 1973).
The woman of 40 years falls ill of generalised articular swellings, fever, loss in weight (24 kg), can move only if supported by two persons (a). Hypercorticism after cortison treatment (b). The first cell-therapy is conducted after $1\frac{1}{2}$ year, causes an exacerbation of pain in the joints and fever, the second implantation follows half a year later and initiates a slow improvement and remobilization (c, d), which persists during a subsequent observation of 6 years.