Pohybové ústrojí

Pokroky ve výzkumu, diagnostice a terapii

Vydává
Společnost pro pojivové tkáně ČLS J. E. Purkyně z.s.
Odborná společnost ortopedicko-protetická ČLS J. E. Purkyně z.s.
Ambulantní centrum pro vady pohybového aparátu, s.r.o.

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POHYBOVÉ ÚSTROJÍ

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Při příležitosti sympozií je dvakrát ročně vydáváno supplementum.

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LOCOMOTOR SYSTEM

Advances in Research, Diagnostics and Therapy

Published by The Society for Connective Tissues, Czech Medical Association of J. E. Purkyně, Prague, Society for Prosthetics and Orthotics, Czech Medical Association of J. E. Purkyně, Prague, Czech Republic and Ambulant Centre for Defects of Locomotor Apparatus Prague, Czech Republic

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Submitted papers: Locomotor System will review for publication manuscripts engaged in diagnostics and interdisciplinary treatment of genetic and metabolic skeletal disorders, limb anomalies, secondary osteoporosis, osteo/spondyloarthritis and another disorders that negatively influence development and quality of locomotor apparatus during human life. Both papers on progress in research of connective tissue diagnostics, medical and surgical therapy of multiple congenital abnormalities of skeleton mainly in the fields of paediatric orthopaedic surgery and plastic surgery, orthotics and prosthetics treatment, and papers dealing with biomechanics, clinical anthropology and paleopathology are appreciated.

The journal has an interdisciplinary character which gives possibilities for complex approach to the problems of locomotor system. The journal belongs to clinical, preclinical and theoretical medical branches which connect various up-to-date results and discoveries concerned with locomotor system. You can find the volumes of Locomotor System journal at http://www.pojivo.cz/cz/pohybove-ustroji/ since 1997 (free of charge). Since 2013 only electronic edition of the journal is available. That is why we recommend to all subscribers and those interested apply at http://www.pojivo.cz/en/newsletter, enter personal data, titles and e-mail address where the journal will be mailed.

Abstracts of presented papers are excerpted in EMBASE/Excerpta Medica (from the year 1994) and in the Bibliographia medica Čechoslovaca (from the year 2010). We prefer the manuscripts to be prepared according to Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Vancouver Declaration, Brit med J 1988; 296, p. 401–405).

25. ročník časopisu Pohybové ústrojí připomínající odkaz
doc. MUDr. Milana Rotha, DrSc. vědě a medicíně,
je věnován jubilantům členům redakční rady

prof. MUDr. Ctiborovi Povýšilovi, DrSc. (75 let)
doc. RNDr. Pavlovi Bláhovi, CSc. (75 let)
prof. MUDr. Josefovi Hyánkovi, DrSc. (85 let)
a
doc. Dr. Med. Kazimierzovi S. Kozlowskému (90 let)

The 25th volume of Locomotor System journal commemorating a legacy
of Associate Professor Milan Roth, DSc. to science and medicine
is dedicated to the anniversary of

Professor Ctibor Povýšil, DSc. (75 yrs.)
Associate Professor RNDr. Pavel Bláha, PhD. (75 yrs.)
Professor Josef Hyánek, DSc. (85 yrs.)
and
Associate Professor Dr. Med. Kazimierz S. Kozlowski, M.R.A.C.R. (90 yrs.)

POHYBOVÉ ÚSTROJÍ, 25, 2018, č. 1

Pokroky ve výzkumu, diagnostice a terapii

OBSAH

LOCOMOTOR SYSTEM, 25, 2018, No. 1

Advances in Research, Diagnostics and Therapy

CONTENT

SLOVO ČTENÁŘŮM PÚ 2018, ROČNÍK 25, ČÍSLO 1
A WORD TO READERS LS 2018, VOLUME 25, NO. 1

Vážení čtenáři, autoři a inzerenti!

Děkujeme za Vaši pomoc při tvorbě mezioborového odborného recenzovaného časopisu *„Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii (dále PÚ)".*

Od roku 2013 je časopis PÚ vydáván pouze v elektronické formě (v roce 2014 bylo přiděleno nové ISSN 2336-4777). Časopis PÚ byl v roce 2008 zařazen Radou pro výzkum, vývoj a inovace vlády ČR na Seznam recenzovaných neimpaktovaných periodik vydávaných v České republice. V souvislosti se změnou v elektronickou formu vydávání v roce 2013 časopis nedopatřením vypadl z tohoto Seznamu. Od roku 2015 je elektronická forma Pohybového ústrojí opět na Seznamu recenzovaných neimpaktovaných periodik.

Všechna čísla a dvojčísla časopisu (včetně Suplement) vydaná od roku 1997 naleznete ve formátu PDF na webové doméně Společnosti pro pojivové tkáně ČLS JEP z.s. http://www.pojivo.cz/cz/pohybove-ustroji/ (bezplatný přístup).

Od roku 2016 vydáváme po recenzi příspěvky v chronologickém pořadí jako číslo 1 a 2, dále dvě samostatná Suplementa s příspěvky ze symposií Kubátovy dny a Prague-Lublin-Sydney-St. Petersburg Symposium. Nedostatek příspěvků je příčinou zpoždění vydávání. Začátkem roku 2020 byla vydána plánovaná 2 čísla časopisu PÚ, 2019, ročník 26.

Nyní se Vám dostává k přečtení opožděně vydané číslo 1 časopisu PÚ, 2018, ročník 25, který je věnovaný vzpomínce na pana doc. MUDr. Milana Rotha, DrSc., jehož celoživotní vědecká práce nebyla ve své době doceněna.

V roce 2018 životní jubileum oslavili naši vážení kolegové prof. MUDr. Ctibor Povýšil, DrSc. (75 let), kterému byla udělena Zlatá pamětní medaile České lékařské společnosti J.E. Purkyně (ČLS JEP) z.s., doc. RNDr. Pavel Bláha, CSc. (75 let), který byl oceněn Čestnou medaili ČLS JEP z.s., prof. MUDr. Josef Hyánek, DrSc. (85 let) a doc. Dr. Med. Kazimierz S. Kozlowski (90 let). Ocenění byla udělena 16. 3. 2018 při zahájení 23. Kubátových dnů.

Při příležitosti konání 20th Prague-Lublin-Sydney-St. Petersburg Symposia 13. 9. 2018 bylo uděleno čestné členství ve Společnosti pro pojivo tkáně ČLS J.E. Purkyně z.s. panu prof. MUDr. Milanovi Bayerovi, CSc. Čestnou medailí ČLS J.E. Purkyně z.s. byl oceněn Associate Professor Michael Bellemore, MD, F.R.A.C.S ze Sydney. Odborná CV všech jubilantů a oceněných jsou uvedena v Suplementu 1 resp. Suplementu 2 časopisu Pohybové ústrojí, 2018, ročník 25.

Koncem roku 2018 jsme se rozloučili se dvěma významnými členy redakční rady časopisu Pohybové ústrojí a čestnými členy SPT ČLS JEP a Ortopedicko-protetické společnosti ČLS JEP panem doc. MUDr. Ivanem Hadrabou, CSc. a panem profesorem MUDr. Jaroslavem Blahošem, DrSc.

Vzpomínky na tyto naše 2 kolegy, kterých jsme si vysoce vážili, byly publikovány v Suplementu 1 časopisu PÚ 2019, ročník 26.

Jako v letech minulých je posláním časopisu PÚ uveřejňovat vědecké práce zabývající se diagnostikou a symptomatickým mezioborovým léčením genetických kostních chorob, vrozených defektů končetin, sekundární osteoporózy, osteo/spondyloartrózy, ale i jiných chorob, které ve svých důsledcích negativně ovlivňují vývoj a kvalitu pohybové ústrojí v průběhu lidského života. Dále práce vycházející z výzkumu pojivových tkání na všech úrovních poznání, práce orientované na biochemickou, morfologickou, genetickou a molekulární diagnostiku chorob pohybového ústrojí. Zvláštní pozornost je přikládána pracím z oblasti ortopedické a antropologické biomechaniky, neuroadaptačním změnám skeletu v období růstu, řízené remodelaci pojivových tkání, studiím muskuloskeletálních a neuronálních interakcí v závislosti na léčebných metodách (kalciotropní léky, rehabilitace, ortoticko-protetické a operační léčení) a v neposlední řadě sdělením antropologickým a paleopatologickým. Oceňujeme především interdisciplinárně zaměřené práce. V anglickém jazyce jsou publikována sdělení zahraničních i našich autorů. Žádaným doplněním obsahu časopisu jsou zprávy ze sjezdů a konferencí. V rubrice zprávy zveřejňujeme oznámení o životním výročí členů RR časopisu, SPT ČLS JEP z.s., Ortopedicko-protetické společnosti (OPS) ČLS JEP z.s. a významných osobností, sdělení o prioritních pozorováních, ze studijních a poznávacích cest aj.

V každém ročníku naleznete směrnice pro autory příspěvků, kterým věnujte prosím pozornost při tvorbě Vašich vědeckých sdělení.

Souhrny prací publikovaných v časopisu jsou excerpovány v EMBASE / Excerpta Medica (od r. 1994) a v Bibliographia medica Čechoslovaca (od r. 2010).

K prosazení časopisu Pohybové ústrojí mezinárodně je velmi významné citovat práce v našem časopisu uveřejněné v příspěvcích posílaných do zahraničních časopisů s impakt faktorem. Pro zvýšení úrovně časopisu PÚ je nezbytné získávat původní kvalitní práce a kazuistiky, které doporučujeme publikovat v angličtině, s cílem zvýšit zájem o náš časopis v odborném světě. Souhrny původních prací doporučujeme psát co nejvýstižněji, strukturovaně, česky a anglicky (objectives, methods, results and discussion), s klíčovými slovy.

Těšíme se na Vaši spolupráci a tvůrčí připomínky.

Redakční rada

OBRÁZEK NA TITULNÍ STRANĚ ČASOPISU A POPIS NEUROADAPTIVNÍ DEFORMITY KOSTÍ

Vlevo. neuroadaptivně-dysplastické změny kostry zadních končetin pulce (Rosničky kubánské) chovaného v 0,5 % roztoku alkoholu (nervový teratogen), který vedle známého centrálně-nervového působení zřejmě též narušuje neurální extenzivní růst. Energeticky náročný růst nervového skeletu a příslušných nervových kmenů je působením teratogenů insuficientní. To se projevuje makromorfologicky přímějším průběhem kratšího sedacího nervu vzhledem k ohnutému, tj. delšímu femoru. Rostoucí kosti se musely přizpůsobit příliš krátkým přímo probíhajícím nervům. Nervy jsou výrazně kratší než zakřivené kosti, i když jsou uvolněné v neutrálním postavení (**1, 3**).

Uprostřed. Dislokace v kolenních a hlezenních kloubech u zadních končetin osteolathyrického žabího pulce. Vzorky zadních končetin pulce, zvětšení 6–8x, projasnění speciální technikou (**4, 5**). Osteolathyrismus vzniká u rostoucích živočichů krmením hrachorem vonným (Lathyrus odoratus, sladký hrách) nebo chemickými osteolathyrogeny, které narušují maturaci kolagenu. Osteolathyrogeny narušují neurální růst a působí stejným nepřímým osteoneurálním mechanismem na rostoucí skelet jako klasické kostní teratogeny. To znamená, že způsobují primární porušení růstu míchy, komplexu nervových kořenů a periferních nervových kmenů.

Vpravo. Schéma idiopatické skoliózy jako důsledek "neuroadaptivní" odpovědi obratlového (páteřního) obalu na přehnané zpomalení spinálního nervového růstu (míchy a jejích kořenů). Pozoruhodná

tendence idiopatické skoliózy ovlivnit dolní hrudní páteř může být snadno spojena s faktem, že míšní segmenty Th5–10 jsou nesporně nejdelší, takže jejich růst je více energeticky náročný a více zranitelný než jiné segmenty míchy. Mícha v dolní hrudní krajině je tudíž náchylná k přehnanému zpomalení růstu, což se manifestuje neuroadaptivní deformitou rostoucího obratlového obalu (**2**).

TITLE PICTURE AND DESCRIPTION
NEUROADAPTIVE BONE DEFORMITIES

Left. Neuroadaptive-dysplastic experimental-teratogenic deformities of the hindlimbs in a frog tadpole that was kept in water with alcohol (0.5 per cent alcohol solution). Alcohol is well-known neural teratogen which has not only effect on the central nervous system but also disturb the neural-extensive growth. Growing bones had to adapt to too short, straight coursing sciatic nerves. Even when slackened in neutral posture the nerves are distinctly shorter than the bowed bones (**1, 3**).

Middle. Dislocation at the knee and at the cruro-tarsal joints in an osteolathyric frog tadpole. A tadpole specimen of the hind limbs, magnification about 6–8x, staining amphibian peripheral nerves with Sudan black (**4, 5**). Osteolathyrism is produced in growing animals by ingestion of peas of Lathyrus odoratus or by chemical osteolathyrogens which cause disturbance of collagen maturation. Osteolathyrogens interact with the neural growth and work by the same indirect osteoneural mechanism upon the growing skeleton as the classic skeletal teratogens. It means that cause a primary growth impairment of the spinal cord – nerve roots complex and of the peripheral nervous trunks.

Right. The scheme of idiopathic scoliosis as a consequence of "neuroadaptive" response of vertebral envelope to exaggerated slowness of spinal neural growth. The striking tendency of idiopathic scoliosis to involve the lower thoracic spine may be readily related to the fact that Th5–10 spinal cord segments are by far the longest so that their growth is more energy-consuming and more vulnerable than that of the other segments. The lower thoracic spinal cord is thus prone to undue growth slowness which becomes manifest in neuroadaptive deformity of the growing vertebral envelope (**2**).

REFERENCES

1. ROTH M. Role of neural growth in the pathomechanism of skeletal dysplasias: an experimental study. Locomotor System, 2, 1995, No. 3, pp. 85–111
2. ROTH M. Macroneurotrophic features of growth hormone effects upon the spine and hip. Locomotor System, 3, 1996, No. 2, pp. 72–108.
3. ROTH M. Neuroadaptive Pathomechanism of Bone Dysplasias (in Czech). Locomotor System, 5, 1998, No. 3–4, pp. 127–132.
4. FREIHOFER W.C, COMPAGNO LJV. Additional notes on the use of Sihler technique of staining nerves of small whole specimens of fishes and other vertebrates. Copeia, 1977/3 p. 587–588.
5. NISHIKAWA KC. Staining amphibian peripheral nerves with Sudan black B: Progressive vs. regressive methods. Copeia, 1987/2, p. 489–491.

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MEMORY OF ASSOCIATE PROFESSOR MILAN ROTH, MD, DSC. (1923–2006)

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During The 20th Prague-Lublin-Sydney-St. Petersburg symposium, the topic Interdisciplinary approach to growing skeleton 2, that was held in Kroměříž, September 12–16, 2018, a very special session was dedicated in memory of the Czech outstanding scientist Milan Roth in occasion of 95 years since his birth. Milan Roth discovered the anatomical dis-congruency of growth between the neural tissue and the enveloping skeleton, and experimentally proved neurospinal relation between the spinal cord with the nerve roots and its spinal envelope and the other neuro skeletal relations. His scientific works were ahead of his time.

In the session III of the anniversary The 20th Prague-Lublin-Sydney-St. Petersburg symposium that was dedicated in memory of Milan Roth, we tried to draw attention to his experimental work which explains "macro-neuro-trophic" origin of some systemic and congenital extremities defects of locomotor system. Abstracts of presented lectures dedicated in memory of Milan Roth were published in Supplement 2 of the journal Locomotor System – Advances in Research, Diagnostics and Therapy, 2018, vol. 25.

Associate Professor Milan Roth, MD, DSc. was born in October 6, 1923 in the village Lelekovice. He graduated at grammar school in Brno. From 1942 he attended the Institute of Languages and studied English and German language. Because of the Second World War he was totally put (he had to work) in the factory Klöckner in Kuřim from July 1943 since the end of the War. He started to study medicine at Masaryk Medical Faculty in Brno in 1945. After graduation he worked at the surgery department in Bruntal for a short time before he had to initiate the military basic service. He was sent to radiological department of Military Hospital in Pilsen. His whole life love to radiology he started just there. After termination of military service obligation, he started to work at Radiological Institute in Olomouc. He was admitted to Radiological Department at The Faculty Hospital of Saint Anna in Brno in two years. He defended his PhD dissertation successfully in 1964. Nevertheless, his habilitation procedure was stopped from the political reasons. The title Associated Professor he reached after the Velvet Revolution in 1989 and the doctorate disertation he defended in 1991. When he was retired, he changed his work place to the Radiological Clinic of Medical Faculty of Masaryk University in Brno - Bohunice. He definitively ended employment in 1995.

Roth´s research interests had two directions – neuro-radiological (he was one of founders of European Neuroradiological Society) and orthopaedic – radiological. This unique professional combination with the interest of zoology and phylogenetics led him to the macro-projection of development and it´s macro-relation of neuronal and bone tissue, which are commonly treated, investigated and examined completely separately.

The term "osteo-neural macro-synthesis" explains generalization of cerebral-cranial development relation to „axial organ" – spinal cord and vertebral column and extremities – peripheral nerves and long bones of extremities. This approach shows substantiated and experimentally based interpretation still mysterious, above all, "dysplastic" disease states of the skeleton.

Roth´s experiences were collected in many papers with various reactions. Most of publications were in English. The overview of his publications was presented in the Locomotor System Journal (Pohybové ústrojí, 5, 1998, č. 1–2, s. 93–95) on the occasion of professor´s 75th anniversary. His fundamental cognition was published in monography: "Neurovertebral and Osteoneural Growth Relations" (Brno, J.E.Purkynje University Press, 1985, 201 pp.) – **figure 1**.

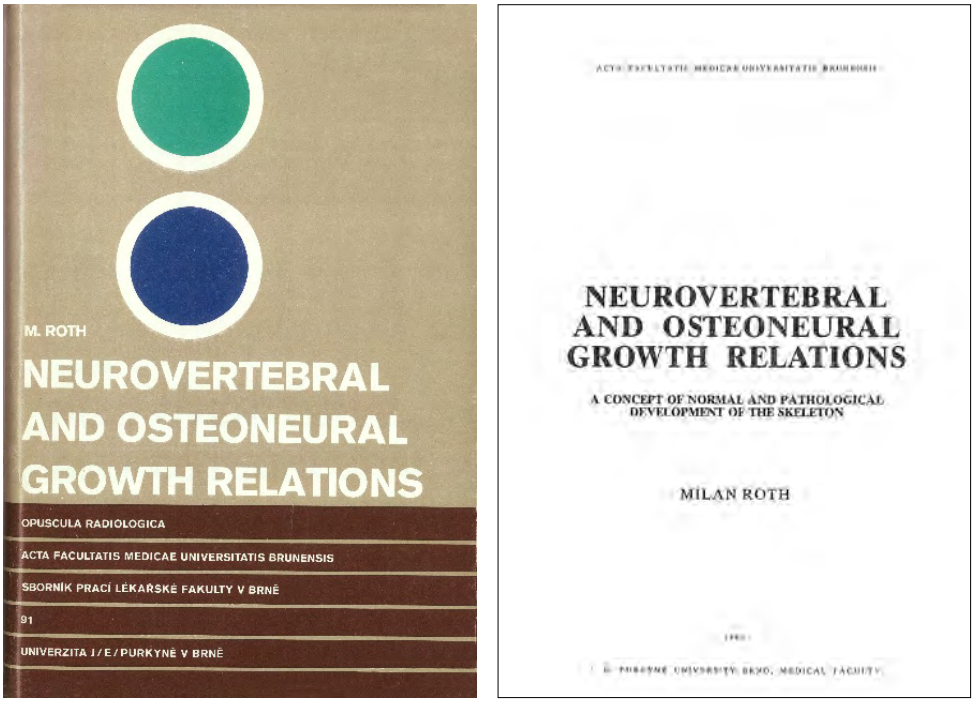

Fig. 1. Cover and first page of monography "Neurovertebral and Osteoneural Growth Relations"

There is a list of some his latest publications:

- ROTH M. Skeletal teratogenesis. Intermezzo Riv Neuroradiol 10, 1997, pp. 59–62. – ROTH M. Cancerogenesis. Intermezzo Riv Neuroradiol 10, 1997, pp. 337–40. – ROTH M. Morphology and development of the spine: Plea for a doubt. Intermezzo Riv Neuroradiol 11, 1998, pp. 313–20.

He was a member of the Editorial board of the journal Locomotor System from 1995. He published in this journal four very interesting experimental papers:

- ROTH M. Role of neural growth in the pathomechanism of skeletal dysplasias: an experimental study. Locomotor System, 2, 1995, No. 3, pp. 85–111.
- ROTH M. Macroneurotrophic features of growth hormone effects upon the spine and hip. Locomotor System, 3, 1996, No. 2, pp. 72–108.
- ROTH M. Rheumatoid Deformities of the Skeleton: Animal Models and Neuroadaptive Pathomechanism. Locomotor System, 5, 1998, No. 1–2, pp. 40–49.
- ROTH M. Neuroadaptive Pathomechanism of Bone Dysplasias (in Czech). Locomotor System, 5, 1998, No. 3–4, pp. 127–132.

The supporters of „macro-neuro-trophic" origin of systemic and extremities defects of locomotor system argue for the theory with the fact that bone tissue has got no nerves inside. They confess the disorders of growth of bones or genesis of osteoporosis as an impact of damaged "neuro-trophics" (for example shortening of one lower extremity after the injury - interruption of sciatic nerves during the growing period or children with cerebral palsy (hemiparetic forms) and/or Sudeck algoneurodystrophy syndrome after the fracture or prolongation of the shank).

If we consider Donaldson's "nervous skeleton" (1937) to be plausible, that is to say a felt, ubiquitous net of the peripheral nerves that diffuses through the body and which is subperiostally and endostally, then it is obvious that the limb skeleton is in the most intimate relation to the nerves, more intimate than it is between the brain and its neurocranial envelope. The skeleton is literally "embedded" into the nerve skeleton and is actually a "cast" of the cavity located in the nerve tissue.

It is evident that in particular longitudinal bone growth is not possible without an adequate increase of the said surrounding skeleton and nervous stems. Thus, if the nervous skeleton is unable to grow, then the bone "cast" can´t grow.

It should be borne in mind that the neural skeleton and the peripheral nervous system grow with a long or extensive type of growth that is energy-metabolically more demanding and therefore also more vulnerable to general teratogenic environmental factors than the commonly known cell type of growth.

Roth still maintained his enthusiastic workflow and interest in the discipline even in a gradually deteriorating state of health. He has not published any professional publications, although he has always been firmly convinced of the correctness of his opinions, hypotheses, and experimental evidence. Unfortunately, he did not finish the monographic work he had arranged in Italy.

At the end of his life, the Dutch orthopedist – doctor Piet van Loon, an admirer of his work, hoped to meet together, but the health of Roth did not allow it anymore. He died on 2nd April 2006 (in his 83 years).

In 2006, in memory on Milan Roth Professor Miroslav Kolář, MD, DSc. and Assoc. Professor Ivo Marik, MD, PhD wrote: Advances in molecular genetics, recognition of the significance of other hox genes, hedgehog protein in embryo, development and its disorders, resulting in developmental abnormalities and malformations, the study of new cell adhesion molecules and receptors will certainly contribute to a more precise explanation of the etiopathogenesis of genetic skeletal disorders (bone dysplasias, congenital limb and combined defects) that we see as experiments of the Nature.

We are convinced that the life work of Roth will carry out further studies to test his entirely original experiments and hypotheses into clinical practice.

CONCLUSION

Today, scientific works of a few clinical experts proved at clinical cases that the results of experimental work of Milan Roth explains pathogenesis of some skeletal deformities such as idiopathic scoliosis, deformities of long bones, syndactyly, macrodactyly and local hyperplasia (gigantism), pseudoarthrosis in neurofibromatosis, etc and etc. Last but not least there is a space for next explanation of functional adaptation of bones and investigation of bone physiology and pathophysiology. Unfortunately, Milan Roth was not understood in the ninetieth years of the 20th century.

The legacy of Milan Roth to medicine fully accepted colleagues from the Children's Rehabilitation Centre of Orthopaedics and Traumatology "Ogonyok" in St. Petersburg, Russia headed by director **Professor Mikhail Dudin, MD, DSc.** They developed practical methods of real prevention and comprehensive treatment of the most frequent pathology of the musculoskeletal system – deformations of the spinal column, in the first place adolescent idiopathic scoliosis. The experimental work of Milan Roth had become an invaluable basis for their scientific and clinical praxis from the end of 20th century.

The next who was fully influenced and highly appreciate Milan Roth scientific work are some colleagues from Netherland, first of all the Dutch orthopaedist – **doctor Piet van Loon** who is the main author of the next outstanding review paper *"Legacy of Milan Roth: Osteoneural growth relations, the biomechanic and neurodynamic processes of physical body growth in vertebrates with tension as its tool to overcome gravity. Clinical implications of discongruent osteoneural growth"*.

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THE 21TH PRAGUE-LUBLIN-SYDNEY-ST. PETERSBURG SYMPOSIUM – ORTHOPAEDIC ANTHROPOLOGY 2

3rd–5th September 2019 | Humpolec | Czech Republic

Hotel „Octárna“

Professor Ivo Mařík (orthopaedic surgeon, paediatrician, osteologist, Prague, CZ) – is opening the **Session III – Spine disorders: pathogenesis, diagnosis and treatment. Lectures dedicated in memory of Milan Roth**
Co-Chairmen: on the left Professor Tomasz Karski, MD, PhD (Lublin), on the right Professor Mikhail Dudin, MD, DSc (St. Petersburg, Russia)

Participants of The 20th Prague- Lublin-Sydney-St. Petersburg Symposium, Kroměříž, September 12–16, 2018

Olga Hudáková, MD, PhD introduced shortly scientific curriculum vitae of Associate Professore Milan Roth, DSc. (Czech scientist from Brno, Moravia) and mentioned his experimental work that was not adequately appreciated during his lifetime.

Piet von Loon, MD (orthopaedic surgeon, Deventer, Netherlands) presented very interesting lecture „A short cord can cause scoliosis": Osteo-neural growth relations by Milan Roth (1923–2006) – a concise concept in morphogenesis and a useful scientific base for Orthopaedics and Neuroscience. An overview of his legacy in biomedical science". Discussion between Professor Mařík and Piet.

Other discussants:

Professor Václav Smrčka, MD, PhD (paleopathologist and plastic surgeon, Prague) see bellow right

and **Associate Professor Michael Bellemore, MD, FRACS** (paediatric orthopaedic surgeon, Sydney, Australia) – see bellow left

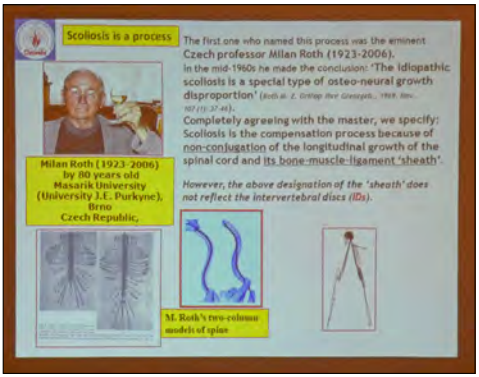
Associate Professor Michael Bellemore, MD, FRACS

Professor Václav Smrčka, MD, PhD (paleopathologist and plastic surgeon, Prague)

Professor Tomasz Karski (paediatric orthopaedic surgeon, Lublin, Poland) gave a lecture „Biomechanical etiology of the so-called idiopathic scoliosis. New classification. New therapy. Clinical material based on observation from 34 years (1984–2018) and presentation from 1995 (23 years)"

Professor Mikhail Dudin (paediatric orthopaedic surgeon, director of „Ogonek",)
St. Petersburg, Russia) gave a talk „Reflections about the perspectives of scoliosology" and other lecture "Idiopathic scoliosis treatment or how to 'loose spring". He mentioned the results of theoretic and experimental works of Milan Roth from 60ties years of 20th century when Roth explained the ascent of spinal cord as a result of physiologic growth disproportion between the rapidly elongating vertebral column and the slower growing spinal cord , and also the pathogenesis of idiopathic scoliosis based on the disturbance of the relative vertebro-neural growth. He showed original Roth´s pictures of models of vertebro-neural relations, too – see bottom right

Associate Professor Martin Repko, MD, PhD (spondylo--surgeon, Brno, Czech Republic) dealt with his experience in a lecture "Growing scoliotic spine – limits of conservative treatment and indication of surgery.



Original Roth´s pictures of models of vertebro-neural relations

Assistant Professor Milan Filipovic (spondylo-surgeon, Brno, Czech Republic) and co-workers presented a paper The role of growth guidance systems in surgical treatment of early onset scoliosis.

From left: Professor Ivo Mařík, MD, PhD (Prague, CZ), Professor Tomasz Karski, MD, PhD (Lublin), Olga Hudáková, MD, PhD (Prague), Professor Milan Bayer, MD, PhD (Prague) and RNDr. Daniela Zemková, PhD (Prague)

Next participants of the Session III – Spine disorders: pathogenesis, diagnosis and treatment.

Radek Vondráček, MSc, Chairman of the Chamber of Deputies of the Parliament of the Czech Republic with his wife

From left Radek Vondráček, MSc, Olga Hudáková, MD, PhD, Professor Tomasz Karski, MD (Lublin, Poland), PhD

From left Alexandra Nikitina, MD (St. Petersburg, Russia), Semen Petrov, MD (St. Petersburg, Russia), Galina Pankratova, MD (Ryazan, Russia), Tatjana Dudinova, MD, (St. Petersburg, Russia)

Professor George Lyritis (Athens, Greece) with his wife and young Greek colleagues. On the right side RNDr. Martin Braun, PhD (Prague, CZ)

Professor Michael Bellemore, MD, FRACS (Sydney, Australia) with his wife Jennifer

LEGACY OF MILAN ROTH: OSTEONEURAL GROWTH RELATIONS, THE BIOMECHANIC AND NEURODYNAMIC PROCESSES OF PHYSICAL BODY GROWTH IN VERTEBRATES WITH TENSION AS ITS TOOL TO OVERCOME GRAVITY. CLINICAL IMPLICATIONS OF DISCONGRUENT OSTEONEURAL GROWTH.

Contemporary biomedical science and neuroscience do lack knowledge on how the intrinsic characteristics of growth in morphogenesis and pathogenesis are governed by the Central Nervous System (Neurotrophism). Skeletal deformation and carcinogenesis in a un unexpected new etiologic framework.

The concise concepts on morphogenesis and the growth by stretch of the "Nervous Skeleton" by Associate Professor Milan Roth of Brno (1926–2006) and all its consequences for etiology, pathogenesis, prevention and diagnostics in, at first, orthopaedic and neurologic disorders are disclosed. His scientific journey is revisited: from his early observations in scoliosis by pneumomyelography to understandable explanation why the human body is at risk for many exclusive human disorders in form and function in case of discongruent osteo-neural growth under influence of well knowned intrinsic and external factors.

P. J. M. van Loon[1] and J. A. Grotenhuis[2]

[1] Orthopedic surgeon, formerly Care to Move Orthopedic Centre, Deventer, The Netherlands

[2] Emeritus Professor of neurosurgery of Radboud University Medical Centre Nijmegen, The Netherlands

1. INTRODUCTION

In orthopaedic literature an understandable biomechanical etiology of scoliosis and many other spine- and not spine related musculoskeletal conditions, thus the set of causative factors needed for that, is still lacking. But looking into recent literature on musculoskeletal conditions without direct trauma, genetic defects or infection, there are only few without the proverb "Idiopathic" in its name or description. Where for more than two centuries in European Orthopaedics the spinal deformities in healthy children were explained exclusively as load dependant deformities as an effect of sitting of children during long periods (school, embroidery, sitting child labour, or heavy labour on farms or in construction before the skeleton was matured, from the seventies in the last century "idiopathic" is popping up round many musculoskeletal conditions out of Anglo-American medical societies. Knowledge under what kind of circumstances bone, cartilage and spinal discs will be formed properly or can be deformed was however already sought out in the field of biomechanics

and addressed in classic Orthopedics, including the preventive power of body exercises in "(school) gymnastics", all around the basic biomechanic knowledge on posture (Haltung, Leibeshaltung or Alignement in German). Wolff's Law on remodelling of bone in response to loading achieved via mechanotransduction, is an undisputed base in science on a growing skeleton. But how deformation of the total spinal structure, centre part of our body posture, is actually achieved is nowadays said unknown and called "idiopathic" in Anglo-American literature. The main black box on "how Nature works" in a growing individual to reach optimal end results had to lead at a given moment to the important role the nervous system plays, by its own growth, and on its role in morphogenesis and in patho-anatomy of all other organ-systems(Neurotropism), fist of all the locomotor system. Just because endo-, ecto-and mesodermal tissues during growth become all firmly attached on cellular level with those billions of nervous cells, gives us a clue about the importance of nervous cells in creating and maintaining "health". The formation of billions of synaptic connections during the growth, all new somatic cells had to be connected with one of more nervous cell or dendrites attached to their stem cells, means an intriguing piece of neuroscience. The well-known fact, that all those billion nerve cells in the world of vertebrates are already formed about three months after gestation is a major fundament on the concepts here to be discussed. That neurogenic part of morphogenesis was never researched in depth till Milan Roth started this after his unexpected observations on central cord and roots in pneumomyelography in scoliotic patients.

In a process of reversed engineering by the first author on getting scientific evidence behind the effectiveness of a new found brace technique in spinal deformities as scoliosis and kyphosis (TLI: Thoracolumbar Lordotic Intervention) the vast research of the neuroscientist Associate Professor Milan Roth, neuroradiologist in Brno, in (then) Czechoslovakia was revealed in extenso. The original search was headed for explanations in the found relationship between abnormal form and abnormal function (bad posture and decreased sagittal flexibility) in thorough clinical examination of the locomotor apparatus in adolescents. A relation between spinal deformities, including "bad postures" and increased tension (thightness) in the neuromuscular structures (highly innervated myofascial structures as now commonly seen in "tight hamstrings") in the legs of adolescents was consequently found in practice (PvL).

Roth found, researched and delivered the first concept ever on basic natural principles to explain how a growing organism can come to its final form under guidance and control of the Central Nervous System. He found answers why only the human spine can easily deform into scoliosis as a result of asymmetric tension in the CNS, that has a hard job to balance a heavy weight of our skull on a flexible, but because of our bipedality and human specific motion intriguing spine. As a consequence of obeying all Natural Laws of a growing organism a further proof of "Form follows Function", as a nondisputed axiom in Biology, become supported by his work.

His most intriguing step in biology and Medicine is that in which he brings us towards understanding the most malignant and life-threatening condition in modern man, cancer, is his concept on the loss of neural control of those somatic cells, that lost or never had synaptic contact with the neighbouring neural cells in case of too fast activity, as can be expected in children with high velocity growth spurt.

There is no better introduction to his legacy than to copy the first part of Milan Roth's own introduction in his book "Neurovertebral and Osteoneural Growth Relations" out of 1985:

"The progress of modern biology and medicine is associated with the unfavourable phenomenon known as the interdisciplinary barrier. By the steady increase of the latter the constructive communication between the representatives of individual branches of science is rendered ever more difficult. This communication is however, vitally desirable for synthesis and exploitation of knowledge accumulated in in vast and frequently very remote fields of research. With this object in mind the present author has undertaken an attempt to correlate, on the basis of own specific approach and of knowledge acquired by study of extensive literature, some facts concerning fields as remote as developmental anatomy and physiology, experimental embryology and teratology on the one hand with those of clinical disciplines as roentgen morphology and pathology of the skeleton as well as oncology at the other hand. Such a project may appear far too ambitious to be realizable but the author is confident of being able to disclose for the reader a principle common to all the above-mentioned branches of biological science."

2. BIOGRAPHY

Associate Professor Milan Roth died on April 4 2006, due to complications of a second CVA, on the same day his concepts were presented extensively for the first time on an international symposium on scoliosis in Oxford.[4] He was an Associate Professor of neuro-radiology of the J.Ev.Purkyně University (now: Masaryk-University) in Brno, capital of Moravia in Czechoslovakia, now the Czech Republic, but dedicated his scientific career to explore the "black box" in biomedical knowledge.

Milan Roth was born on October 6, 1923 in Lelekovice, a small village north of Brno, in a local schoolmaster's family. After completing his grammar school studies in Brno in 1942, he spent a year improving his language skills because the Czech universities were closed at the wartime. Since 1943 till the end of World War II, he was forced to work for the German occupiers in an armament factory in Kurim near Brno as part of the "Totaleinsatz" in warfare of the Nazi's. After the war, he studied at the Medical Faculty of (now) Masaryk University in Brno, completing his studies on September 29,1949. First, he was assigned to the department of surgery at the local hospital in Brunntal in northern Moravia (till January 31, 1950). During 1950-1952 he served in the army, most of the time at the Department of Radiology of the Military Hospital in Plzen (Pilsen). After completing his military service, he spent a short time at the pulmonary department of the local hospital in Prerov, and then at the Central Department of Radiology of the Medical Faculty in Olomouc (now Palacky University). Since November 1, 1954, he has been with the Central Department of Radiology of the Medical Faculty in Brno (now Masaryk University) that became Department of Radiology and Nuclear Medicine in 1960, and this was his workplace till his retirement in August 1989. Only in his early career he worked as a fellow, not accompanied by his young family as that was forbidden under the communistic regime, at the Karolinska Institute of the University of Stockholm, Sweden.

After this scientific fellowship abroad, he got an appointment in Brno in basic research too, in the field of anatomy. In that research trail on finding the biomedical explanation on the role of the CNS

Fig. 1. Milan Roth at the age of 80

in spinal deformities, he could extend his findings to a much more important level: the explanation of growth of natural bodies to overcome gravity and come to species specific morphogenesis and deformities, like scoliosis in men. His first observations with pneumomyelography started his endless interest in what is going on during morphogenesis and how you could understand the role of the nervous tissue in macroscopic features, which in his concepts brought us the explanation on cellular level, always on a Socratic way asking himself the question if the steps he made in building his theory could be denied by others.

By all sorts of restrictions and censorship under the communistic repressive rules, he could not get access to meetings and societies in the free world. He wrote a lot of articles in Czech, German and English language, all with Russian summaries, and almost all inaccessible for the "Western" mainstream medical science, before he wrote down his legacy in his Opus magnum, a book (in English): Neurovertebral and Osteoneural Growth relations, published by the University of Brno in 1985. After the Velvet Revolution he managed to publish abroad on his extended thoughts on etiology of all growth dependant musculoskeletal and spinal cord conditions even into more common lifestyle related conditions, that can now be seen as one of the biggest socio-economic burden of diseases:

herniated discs, disc degeneration and spinal stenosis. His concepted etiology of cancer can be the game changing theory in oncology, because of its simplicity, that will not so much bring curing therapies, but certainly can bring back the huge power of preventive Medicine, as cancer is worldwide seen as a consequence of our way of life (Zivilizationskrankheiten).

After his retirement on the University he stayed a part-time radiologist of the Radiodiagnostic Clinic of the hospital in Brno - Bohunice. He suffered a brain stroke early in 1999, became seriously aphasic. Just before the planned visit of the first author, his medical condition detoriated quickly because of a second CVA. Milan Roth passed away peacefully amidst his family on April 4 2006.

His work remained largely unnoticed in the mainstream of the international world of neuroscience, orthopaedics, neurology or neurosurgery and had only some influence in Anatomy and Embryology. But in his own country he was recognised and honoured by the Society for Connective Tissues, CMA J.E. Purkyně. He also was for a long time in the redaction of journal Pohybové ústrojí (Locomotor system). It is a true honour to give this support to give him posthumous the chance to be recognised forever as a scientific leader in Medicine.

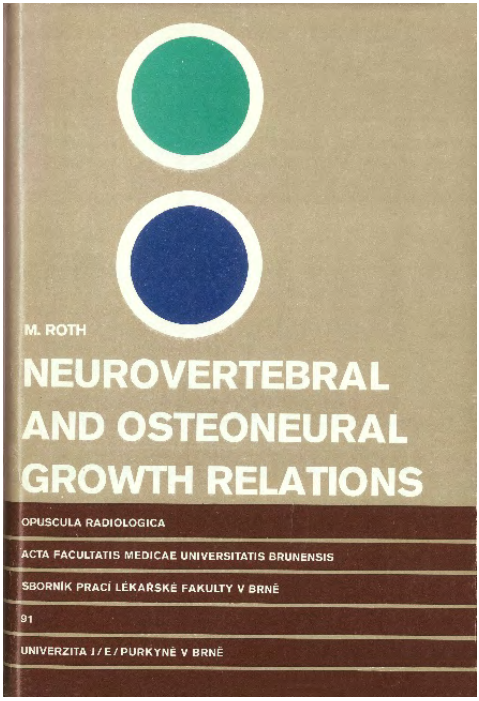


Fig. 2. Picture of the title and the front of his book (1985)

At the end of this contribution a bibliography of selected articles and a summary of his book is added with the main purpose to disclose them to a wider audience.

His main concept is the concept on skeletal morphogenesis and the way the billions of not connected nerve cells are capable of developing an extremely interconnected "Nervous Skeleton" and create and maintain contact with all the many billion new somatic cells that grow by mitosis in a centrifugal wave from the axial spine-cord complex. The overall concept he developed is based on the existence of 2 different types of growth of the spinal column, viz., the cellular-divisional (mitotic) growth of bone and soft tissues and the extensive (stretch) growth of the nervous structures. The neural extensive growth proceeds at a slower rate than the bone growth. Which is manifested most conspicuously in the ascent of the spinal cord. In his concept a number of normal as well as pathological features of the skeletal morphogenesis- above all the gross deformities of the

body-parts which grow rapidly in length such as the spine, the extremities or the facial skeleton – are explained by the disturbed relation of the two growth types caused by an insufficiency of the vulnerable neural extensive growth.

3. OVERVIEW OF THE RESEARCH WORK OF MILAN ROTH

His biomedical scientific legacy is of such a wide scope that it is difficult to specify, discuss or review all his work in this contribution. It can however be divided it in four main chapters:

1. Analytical work, undertaken mainly during the decade 1960-1970, in which he laid the fundaments of the research into the suspected interdependency in growth of the skeleton and the CNS. It was supported by examining and integrating his interpretation of older work in the fields of biology, embryology, anatomy and physiology.
2. Creation of mechanical models of the spine and the central cord roots complex, to mimic the processes of spinal growth and the pathway of deformations. Creation of intelligent "infographics" in drawings of the macroscopic growth as an extrapolation of the suspected processes on cellular level. With this drawings he could explain and visualise the processes of interrelated types of growth in the growing body in regard of the time relapsed and the existing tensile forces, that are needed to "mould" the volume increase by mitosis of somatic cells into species and families related adult anatomy .The moulding is done by muscular actions which also depicts in midterm embryological stage the places where joints will be formed.
3. Proposing the integrated concept of neuro-osseous growth relations and the causes of possible discongruency between the two types and its role in explaining the normal development of tissues creating the organs and organic systems, viewing the thoracolumbar spine as a crucial primary part in formation and functionality of the skeleton and nervous tissue.
4. Publishing articles from 1970 till 1998 in which he consequently built upon his earlier integrated concepts. This included papers on topics such as scoliosis, Scheuermann's disease, the Arnold Chiari malformation and Syringomyelia, the role and development of the neural foramen in order to get better understanding of the pathoanatomy of stenosis.

Unhappily, there is no clue in reading his work, or any mentioning in discussions by himself, that he was aware of the research done on the clinical part of growth in healthy schoolchildren. This was sought out in the German speaking world of orthopaedics in the 19th century, that reached its zenith of knowledge on healthy growth around 1914. At that time there was much emphasis on the relationship between (bad) sitting positions in early childhood at home and on schools with the occurrence of scoliosis and hyperkyphosis.

As we see nowadays in most countries, the sedentary lifestyle of children must be responsible for the huge increase in musculoskeletal conditions in absence of any preventive or hygienic knowledge on the importance of a healthy natural posture (alignment) of the growing body. Two World Wars took care of permanent distraction of focus of mainstream medicine on this part of health as part of classic orthopaedics. There is ample evidence that from 1914 on the complete Anglo-

American scientific and medical world cut all influence out of the German speaking world, leading to a huge loss of knowledge on prevention that could be provided to the growing child. The passive deformation of discs cartilage and bone by external and lifestyle dependant pathologic loading patterns caused by sitting is a fast-increasing feature in modern youth with its sedentary lifestyle from the start. The authors stress, that the classic orthopaedic knowledge on healthy growth and the found disturbing factors are completely explained in its deepest biomedical background of Natures capabilities how growth (morphogenesis and physiogenesis) could be optimised, by the research of Roth. If there is a lack of mobility and exercise by which the nervous tissue will be stretched (grows) the skeleton and its easily deformable parts (discs and cartilage) will show deformations. It is important to emphasise, that in his days the physical education of the mean growing child in his country and the knowledge on prevention in the proper care for good postures out of the European Orthopedics and schools of gymnastics still existed and was provided. Obviously, he therefore focussed on the pathologic cases he encountered in his work as neuroradiologist.

3.1 Analytical work

Roth's knowledge of the superb work of European scientists on the deformed spine, gross morphology-anatomists, embryologists, biologists and orthopaedics which he often quoted, was prodigious, being aware about the grounds of their disputes on certain earlier concepts, mainly on scoliosis. An increasing number of anatomists and orthopaedics were investigating skeletal problems in Europe in the late nineteenth century, which included spinal deformations with its topic scoliosis, with names such as Lorenz, Nicolodani, Albert and Schulthess noted. Wolff's Law on Bone formation and the principle named after Hueter and Volkmann are leading until today. But both lack any clue on the role of the nervous system during growth. They conducted anatomical studies, mainly on cadaver spines and details in vertebrae and discs. Roth was the first to step into the black box between visible changes in posture and the intriguing role of the nervous tissue in its bony housing by his own discoveries and observations resulting from his expertise in pneumencephalo- and myelography. As one of the first with expertise in creating contrast X-rays of the spinal canal by inflating air in the intradural space he made new observations on unknown pathologic features of the position, calibre, asymmetries leading to a suspected presence of tension in the central cord and vertebral roots in especially scoliotic spines. He stated: *"The traction effect of the spinal nerves is of decisive influence upon the position of the spinal cord within the spinal canal as well as upon the shaping of the vertebral foraminae, a conclusion we reached in our own radiographic studies, published in 1965 and 1966"*.

Phylogenetic work

The hypothesis that the tensionless position of the central nervous system matures into the adult skull and spine was demonstrated in worms and other, higher developed animals as well as in radiological and cadaver human studies. He stresses the phylogenetical criteria incorporated in Holzer's Neuroprotective mechanism, in which all vertebrates should grow in such a way, that the central cord, the brain and the nerve roots dwell in rest completely free of contact, are equally surrounded by liquor cerebrospinalis and can move freely in the bony "house" that protect them by

1. The growth in length of the vertebrate body including man proceeds, together with differentiation, in the *craniocaudal direction* (Fig. 2). This biological law has not been adequately appreciated in human biology and medicine. In the anatomical, anthropological, paediatric or orthopaedic monographs the growth in length of the human body is consistently designed as though it proceeded from the feet to the head, i.e. with the feet at the same level in the schematic drawings.

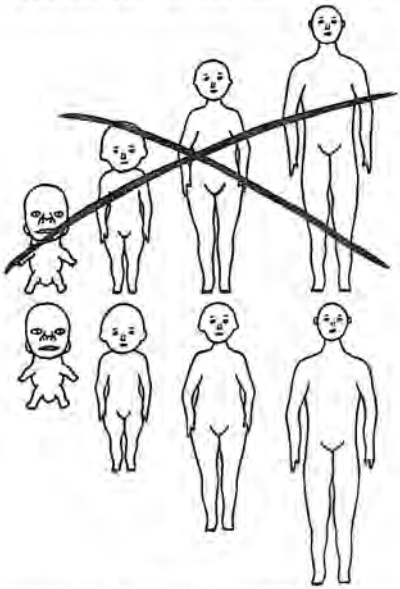


Fig. 2. The correct *(below)* and incorrect *(above)* conception of the growth in length of the vertebrate body.

Fig. 3. Drawing and explanation of a more neuroscientific view on growth in vertebrates, based on the principles by Kingsbury of cephalo-caudad growth (Book, 1985, page 12)

enough circumferential space for the liquor cerebrospinalis. This must be even be true in maximal range of motions of the spine and big joints. By applying study to the normal state and growth he allowed us to develop understanding of the requirements of the central nervous tissues during growth into adult anatomy.

Experimental teratogenic work on the role of the nervous system and disconnected Osteoneural Growth Relations in Carcinogenesis.

The concepts of Roth on the possibility to get cancer in many humans' organs is of a never seen intelligence and imagination to understand what cells, or islands of cells can do in the case of escaping the constant control in function by nervous cells. This escape by insufficient quantitative

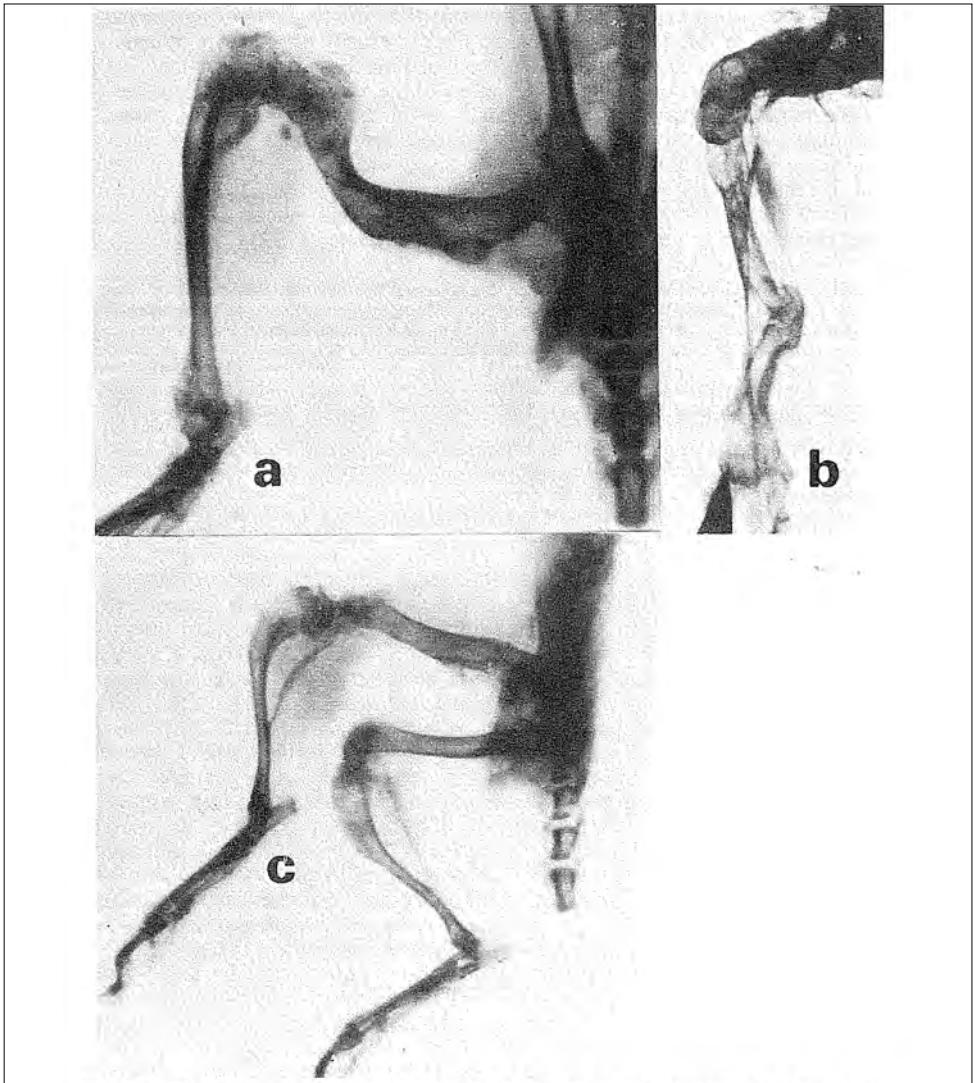


Fig. 62a–c. Roentgenograms of the hind limbs of adult osteolathyric rats (a, c), hind limb of an osteolathyric frog tadpole (cleared with the Williams' technique and photographed in full extension) in (b). Femoro-tibial "sticking out" with excessive varus deformity of the tibia in (a) is related to the same cause like the cruro-tarsal deformity in the tadpole (b), viz., to the excessive growth insufficiency of the sciatic nerve. Sciatic nerve section performed at the beginning of the experiment (*lower* placed limb) has an important preventive effect upon the osteolathyric bone changes (c).

Fig. 4. Some examples of animal extremities (a. rat; b. tadpole) in which the effect of lathyrus injected in the amnion shows postnatal bowstring effect of the N. Ischiadicus) and bowing and varus of bones.

synapse-formation between nerve cells and their attached somatic cells in a period of growth that shows discongruency, can lead to undifferentiated cell division and autonomous, but malignant behaviour. He postulated firmly, that if groups of cells miss any control by the nervous cells, they will grow in all directions as a "tumour" in many forms can spread as metastases and behave on malign way quit easily. In order to understand the role biochemistry plays (and still plays) in the development of a range of deformities of the spine, extremities and jaw, Roth conducted experimental studies on teratogenesis to clarify the role of the up to then neglected osteo-neural growth patterns, an area in which the growth by stretch of the nervous system interacts with other tissues. Roth was able to impair the stretching properties of the nervous system by exposing it (intra-uterine) to either teratogenic substances or by lowering the level of oxygen (as in Cerebral Palsy) within it. In these experiments, he was able to create spinal deformities as scoliosis in animals like chicken, ducks, tadpole and rats.

His experiments demonstrated that the so-called passive role of neurogenic tissue, especially in the central cord, was transformed into a major, active role during the development and growth of the spine and the extremities. This ability of nervous tissue to grow by extension is phylogenetically determinate. Growth and errors of growth of the vertebrate spinal skeleton was depicted by his concepts, allowing the "intimate relation existing from the very beginning of development between the nervous and the bony tissue to continue working incessantly during the whole growth period of life".

3.2 Mechanical models of the spine, spinal growth and deformations

After concluding that in scoliosis (as the first deformity he investigated) there is a mismatch or discongruency in growth of length between the skeleton and the nerve cells, Roth developed and made his own mechanical models for different issues in a quest for an better understanding of the development of the normal, as well as the distorted or deformed spine (and skeleton). He was fully aware that forces in nature are often invisible, such as the forces of growth and tensions within the body. He realised that only the consequences of these forces on a body can be seen and thus a conceptual clarification of the universally adopted relationship between form and function (i.e. acting forces) is essential in order to understand these important processes in nature.

In a paper on the models of neuro-vertebral relations, Roth described an elastic model which could dynamically reproduce the physiological relationships of the growth of osseous structures with that of nervous tissue. Using Plexiglas, rubber, textile and metal he was able to construct an accurate model representing all the components of his concept of proportioned and disproportional growth between different tissues. The dynamics of locomotion, but also of the intrinsic tension by balancing or produced by growth were visualised in all sorts of mechanical models. Roth created all his models himself. He fully realised in accordance with the gross morphologists like Volkmann, Hueter, Nicolodani, that there were changes in form of bones and joints between the embryological stages and the later adult state just because of the always present patterns of locomotion in the womb and in postnatal life. And that all these changes are reflecting the individual development of the phenotype, our ontogenesis.

Radiographs were made of these models in different stages of applied forces of tension, using different planes in order to demonstrate the close similarities with the radiographic images of living individuals. The model also explained the ascent of the conus medullaris during growth, widely seen then as a passive displacement. In some pathological conditions, like myelomeningocele, the ascent is said to be hindered by a tight string of fibrous tissue, the filum terminale, causing a "tethered cord". Roth claimed that the less intrinsic loss of stretch ability tense spinal cord and associated attached roots would explain the impossibility of it "ascending" properly into the position of the conus at the T12-L1 area whereas in other animals the conus still remains at a lower level in the lumbar spine. The ascent was thus seen as an adaptation to the prevailing upright position of the body in mankind. The so-called "tethering" is thus not a passive binding by strings, but an intrinsic quality of nervous tissue. The stressed lordotic component of the thoracolumbar spine required in order to create optimal biomechanical and neuromechanical conditions is also a very interesting aspect of his models.

For his concept of the osteoneural growth concept, Roth devised a very simple model, made from beads on a string. This "necklace" model, which can be easily copied today with materials such as slightly deformable beads, gives an insight in what can happen when nervous tissue is unable to keep up to the extending energy growing bone is delivering. The tension within the bones or the counteracting energy of muscle actions occurring as a result of activity act as supercharged engine dictated by nervous tissue itself.

Normal growth leads to the development of slender and long bones, but as the trend towards lengthening of bones takes place, the resulting retardation of extension of nervous tissue leads to the beads becoming compressed and thereby deformed.

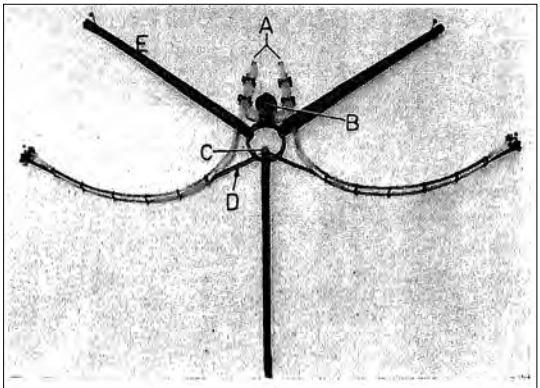


Fig. 1. A thoracic segment in the elastic model, viewed from above and slightly behind. A — vertebral body, B — longitudinal axis of spine, C — spinal cord, D — spinal nerve, E — rubber strip.

Fig. 5a. Photograph of a single segment of the thoracic spine in the transversal plane with modelling of the ribs, roots and cord. From: Roth M. [Models of vertebro neural relations]. Czesk Radiol 1970 Sep; 24(5): 189-94. (Courtesy of Roth's heirs).

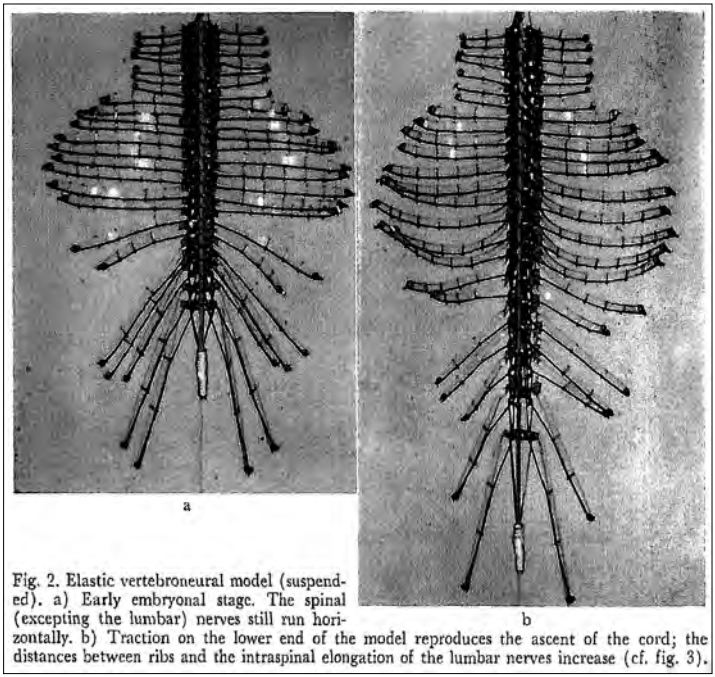


Fig. 2. Elastic vertebroneural model (suspended). a) Early embryonal stage. The spinal (excepting the lumbar) nerves still run horizontally. b) Traction on the lower end of the model reproduces the ascent of the cord; the distances between ribs and the intraspinal elongation of the lumbar nerves increase (cf. fig. 3).

Fig 5 b. The whole construct of spine, inhabitants and ribs in two different positions distinguished by a certain amount of tension in the combined system of different tissues. From: Roth M. [Models of vertebra-neural relations]. Cesk Radiol 1970 Sep; 24(5): 189–94. *(Courtesy of Roth's heirs).*

3.3 The concept of osteo-neural growth

The existence of scoliotic curves in the human spine, not encountered in other animals, puzzled him as much as it still does today, especially when he found out that the central cord was distorted too. Furthermore, the biomechanical adagio that form always follows or reflects function was a mainstay in his thinking throughout his published work. The attention was drawn to the relationship between nervous tissues and the spinal canal by his pioneering work as a neuro-radiologist, employing the techniques of pneumoencephalography, myelography and positive contrast examinations of the scoliotic spine.

Biological studies supporting these concepts

The comparison of the growth of animal nervous tissue by extension and the growth of central fibres in plants on the same mechanism has already been fully explained and is undeniable. It is also a well-known fact, that there is no cell proliferation by mitosis of nervous tissue after birth in animals. All the billions neurocytes are present about three months after gestation. Nervous tissue, in vertebrates as in all other animals, must possess an alternate pattern of growth, to reach its adult length than all other tissues in the body. Somatic tissues grow or renew themselves at all stages of life by rapid and intensive cell proliferation, especially during growth. "As in trees, the growth pattern is by extension of the cells (extensive growth; German: Streckungswachstum). Roth compared

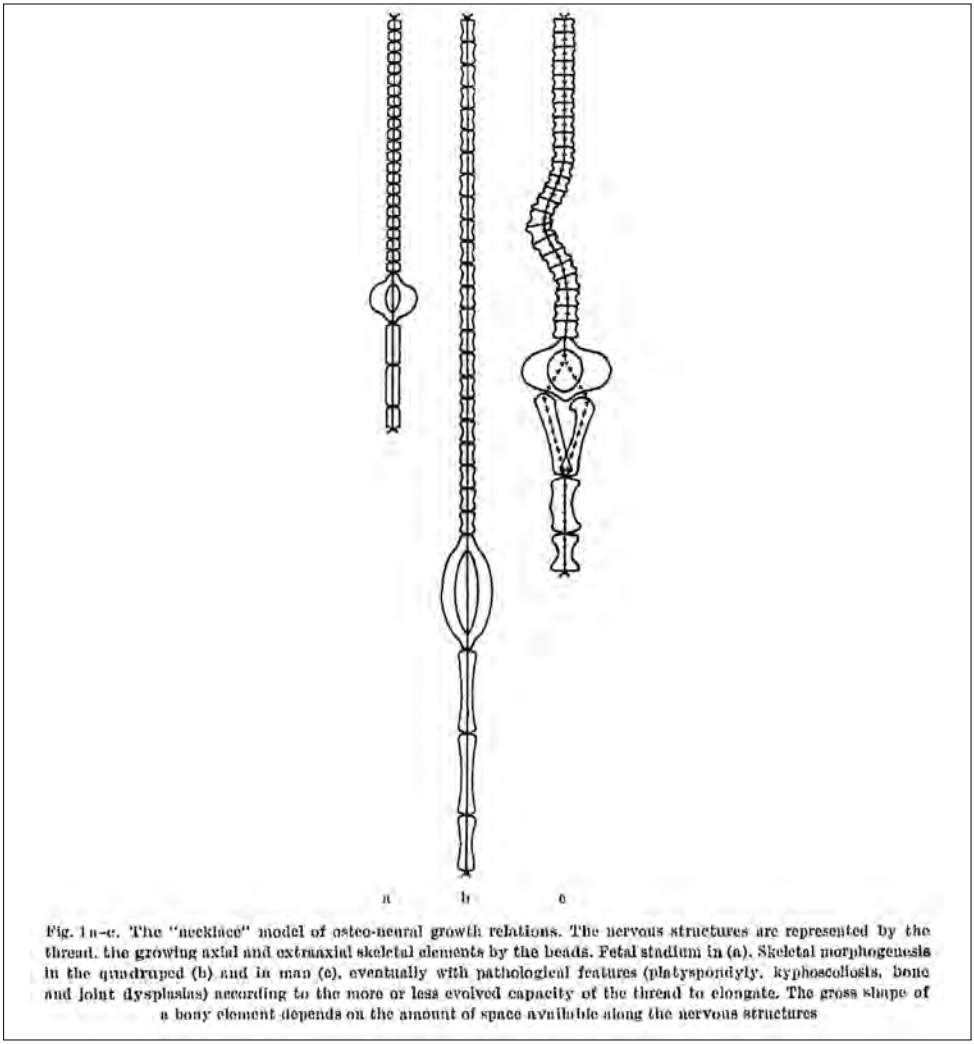


Fig. 1 a–c. The "necklace" model of osteo-neural growth relations. The nervous structures are represented by the thread, the growing axial and extraaxial skeletal elements by the beads. Fetal stadium in (a). Skeletal morphogenesis in the quadruped (b) and in man (c), eventually with pathological features (platyspondyly, kyphoscoliosis, bone and joint dysplasias) according to the more or less evolved capacity of the thread to elongate. The gross shape of a bony element depends on the amount of space available along the nervous structures

Fig 6. A schematic drawing of the necklace model in which prolonged or progressive tension on the string gives deformation of the vertebrate skeleton like beads. From: Roth M.: The relative osteo-Neural growth; a concept of Normal and pathological (Teratogenic) skeletal Morphogenesis. Gegenbaur morph. Jahrb. Leipzig 119 (1973)2, S.250–274 (courtesy of Roth's heirs).

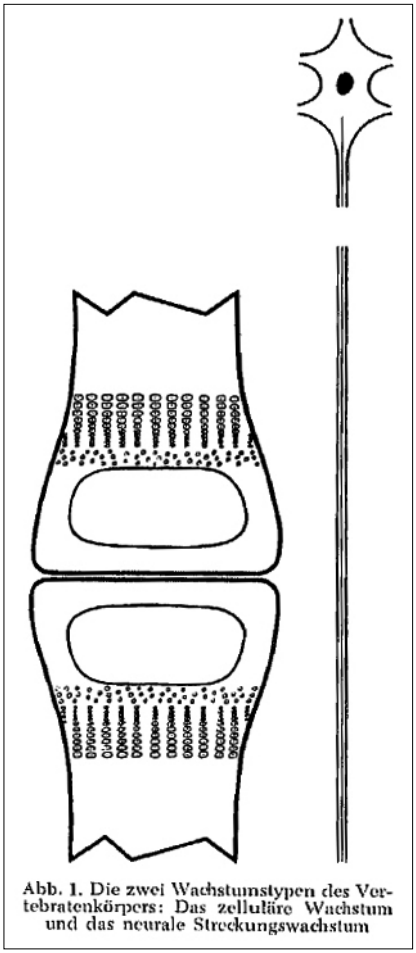


Fig. 7. A schematic drawing showing the difference in how tissues in vertebrate animals grow, namely by cell proliferation comparing the epiphyseal zones around a schematic joint at the left, and the elongation by stretching of a none proliferating nervous tissue cell. (From: Roth M. [Idiopathic scoliosis a special type of osteo-neural growth disproportion]. Z Orthop Ihre Grenzgeb 1969 Nov;107(1): 37–46). Courtesy of Roth's heirs.

the governing phytohormone auxin, a tryptophan derivate driving this type of growth in plants which is said to be highly susceptible to a number of growth inhibitors (Gutenberg, Lehrbuch der Botanik) with the role of serotonins in the growth of nerves in animals. The energy necessary to stretch cells is generated by tensile power in the surrounding tissues during growth. In the spine, the vertebrae and discoligamentary complex, growing by cell proliferation, is responsible for the energy needed to stretch associated nervous tissues: "tag on tow".

With great interest in biology and specially biological literature on plant and animal growth Roth adapted the law of cephalocaudal differential growth (Kingsbury) in which growth in animals, just as in plants is found to be directed from the first existing and central parts of a living creature, in the

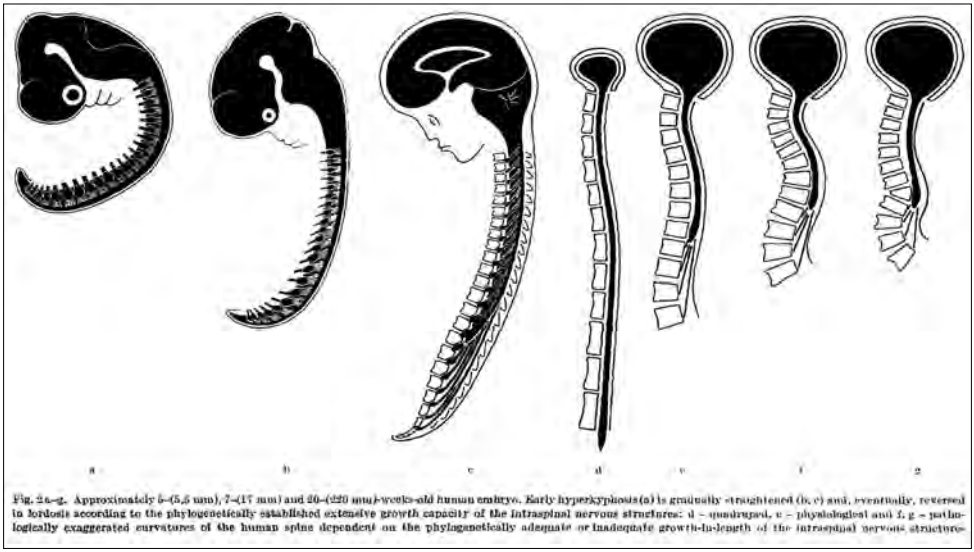


Fig. 2a–g. Approximately 5–(5,5 mm), 7–(17 mm) and 20–(220 mm)-weeks-old human embryo. Early hyperkyphosis (a) is gradually straightened (b, c) and, eventually, reversed to lordosis according to the phylogenetically established extensive growth capacity of the intraspinal nervous structures: d – quadruped, e – physiological and f, g – pathologically exaggerated curvatures of the human spine dependent on the phylogenetically adequate or inadequate growth-in-length of the intraspinal nervous structures.

Fig. 8. Schematic drawing of embryological stages in which the enormous relative volume of the nervous system and the comma like shape is depicted, gradually changing to a stretched and slenderer configuration, before the biomechanical needed cervical and lumbar lordosis is created. From: Roth M.: The relative osteo-Neural growth; a concept of Normal and pathological (Teratogenic) skeletal Morphogenesis. Gegenbaur morph.Jahrb., Leipzig 119 (1973)2, S.250-274 (courtesy of Roth's heirs)

vertebrate the central cord, in his early embryological stages being in advance of the first segmentations of surrounding tissues. Although describing a leading role the osseous structures play as an acting part in the lengthening of the central nervous structures, by subscribing that intriguing law of cephalocaudal differential growth he put the phylogenetically and embryologically oldest part of the nervous organ, the central cord and brainstem, in a initiating, architectural and controlling role of the lay-out or construction of their own house, the surrounding tissues that form the biomechanical even more intriguing spine.

The leading role of the nervous tissue in morphogenesis of the axial skeleton. Neurotropism explained.

Roth stresses that till his time, and not much changed since then (authors remark), the primary role and place of the nervous tissue in development and growth of the body with the other systems, like the vascular, gastrointestinal and musculo-skeletal systems, was apparently left out of consideration in scientific work on the very complex and interrelated stages of maturing a single diploid cell to a full-grown animal or man.

For showing the exaggerated ventral-concave curvature (hyperkyphosis) of the early embryonic body Roth refers and used schematic drawings with examples taken out of earlier work of Blechschmidt.

As is the so-called ascensus of the conus-cauda, until now seen as a passive event, also the lengthening of the spinal nerve roots is widely considered as dragging them along by the fast-growing spinal column. Roth stated the opposite and reveals that there is also a controlling function of the central nervous system on the final form of the spine in adulthood. It is the need for a child to create lordosis and the in human's unique possibility of torque and counter torque at the TL junction that is maximal at the thoracolumbar spine to perform upright walking. He compares it with the leading role unrolling of the growing brain substances control the form of the skull (calva) at the end of growth. It gives an understandable explanation why the conus in man is present at the thoracolumbar joint while it is in the lower lumbar spine in almost all quadrupeds.

As a Leitmotiv in all his argumentation he follows Němeček et al. (1972): *"The neuron has two main functions: First to maintain its own integrity as well as the integrity of the organism innervated cells by it. The neuron is one of the important regulators of growth of other organs, of their metabolism and function. The complex of these functional aspects is called the "trophic role" of the nervous system. The other part of the neuron's functions, in general more accentuated, consists in mechanisms which give origin to impulses, make their regulated propagation possible and account for the integrated function of the nervous system. The nervous system is extraordinarily sensible to oxygen supply. A lack of the latter lasting more than one-minute sets the nerve cells out of function. The main energetic substratum of the brain is glucose".*

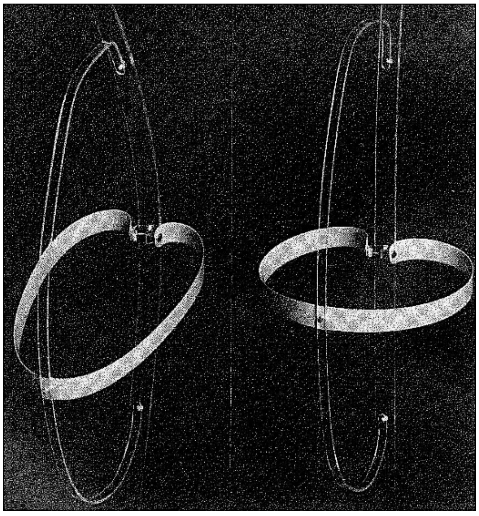


Fig. 9. A mechanical model showing the difference in shape of ribcage and diaphragm in a kyphotic posture and in full extension as in deep inhalation.

Chapter 4. Summary

It is clear that Roth missed feeling or constant practical experience with the complete clinical picture of children with and without deformations of the spine. He clearly stated that a lordotic form of the lumbar and thoracolumbar spine is of great importance for proper function of this complex area of the most mobile part of the spine in childhood. He described the needed functional possibility of the lower thoracic ribs to elevate, but also to retro-pulse themselves and helping by that the impressive bellow function of the diaphragm. That tension on neuromuscular structures can be measured and that most of the mechanical laws of Robert Hooke on properties of tensile bodies like springs are of value to understand the complex mechanism between controlling nervous system was not foreseen by Roth. The deformation of discs and osseous elements of the spine is created by the same sort of forces that makes the ability to stand, sit, balance and motion, which is delivered by the muscular system, possible. No muscle acts without instruction by neurogenous signalling.

The consequence: Roth on spinal and skeletal deformities during growth, the practical field of orthopaedics.

Roth was very consequent in applying his concepts in his explanation of the mechanism of the major deformity: scoliosis. The best we can do is citing Roth with his own words:

"There exists the most intimate interrelation between the rapid craniocaudal growth-in-length of the axial skeleton and the slower proceeding extensive growth of the spinal cord and the nerve roots. The latter type of growth requires a higher supply with energy and, consequently, is more vulnerable than the former one. The vertebro-neural growth relation is similar to that existing between the developing brain and its bony case. The growth in length of the individual vertebrae and of the spine as a whole is adapted to the growth-potentiality of the intraspinal nervous structures, viz.; the former is determined by the availability of space among the latter. Idiopathic scoliosis may be interpreted as an adaptive morphogenetic reaction of the vertebral column upon the growth insufficiency of the intraspinal nervous structures: The growth process of the vertebral column, though continuing undisturbed at the cellular level, is adapted at the organ level by "waves" to the growth-insufficient cord-nerve complex. Morphological features of the scoliotic vertebra together with the typical position of the spinal cord within the spinal canal speak in favour of the suggested vertebro-neural concept which offers a plausible explanation of the congenital and experimental scoliosis as well". End of quotation

Some of you might argue: what then about restoring the form e.g. by bracing where extension and lordosis are created instead of counteracted as in most available bracing techniques; isn't that harmful because it lengthens the spine, and thereby increases tension on the cord.

The answer comes again from Roth himself:
"Adjustment or rectification of the deformed structure like a scoliosis spine is not accompanied by lengthening, notwithstanding the fact that the scoliosis trunk is elongated; the curved spine is adjusted, not lengthened. The adjustment involves a contraction or reduction of the convex side of the intervertebral

discs. Consequently, in adjusting– paradoxally but irrefutably- the spinal canal is rather shortened." End of quotation (see bibliography no.15).

The work of Milan Roth: new challenges for future research

Science is an ongoing process with its own dynamics. In biomedical science clarification of etiology is of paramount importance for the right diagnostic conclusions and the therapeutic consequences that can be taken. Roth took the challenge for many ailments the human locomotion apparatus and the Central Nervous System can show, by opening the black box of Medicine: how is growth in Nature arranged?

We are convinced that full disclosure, study and understanding of the work of Roth will inspire many of our present colleagues to start new research in different biomedical fields and clinical specialities around the locomotor system and the nervous system in children and adults. We think the challenges will be taken in different fields of (medical) science in order to create solutions in prevention and therapy for man.

1. Reproduce and clarify several of his analytical studies (pneumoencephalography and - myelography) by using modern technologies (MRI, Spiral CT-scan). Also, neurophysiologic studies (like SSEP and surface EMG) can be performed in situations with clear higher tensions in the neuromuscular structures. For instance, a publication of Cheng et al 2008 in Spine on short spinal cord with scoliosis is evidence that this kind of work is already in progress.
2. Research on what can causes the suspected differences in (the quality of) stretch growth of the cord-roots system to understand at last if this is the background of the misunderstood variation of spinal forms (like curvature, disc-height, vertebral height and shape). Can the basic genetic background be investigated behind the basic difference in resilience towards external deforming forces (like spectrum of laxity in boys and girls) reflecting the basic difference in elasticity of the cellmembrane? Clinical detectable tension in growing children is never investigated in the light of their spinal curvature.
3. A new coordinated effort between biophysics, like biomechanics and biochemistry to clarify the mechanism behind and between the growth (proportionate or disproportionate) of bone and tissues in relation with the stretch growth of the neural tissues. For biophysics this means, following Roth, the role of tension, tension patterns and tension regulation. For biochemics thorough research on the role of the transmitters, like serotonin, nowadays apparently important in all sorts of processes and diseases. What is their role, how do they work in the period of growth and is their function altered in body with deformations, even "light" ones? How is the process of distribution of the lava-like material surrounding the notochord as Roth calls it is organised, because following Roth it can give the clues on the final form of the body and the organs.
4. New concepts for treating patients by conservative or operative treatments with emphasis on the requirements for the nervous system as part of the complex "game" of compressive and tensile forces. Specific stretching exercises and brace techniques that extend the spine and apply lordosis to the thoracolumbar joint rearrange the tensile forces into natural postures.

Bibliography of Milan Roth (incomplete list of his publications):

This bibliography with all relevant publications by Roth consists of publications we collected. Some of the articles were acquired through Roth's family. Until 2006 only very few publications could be found on PubMed.

The publications are presented in chronological order.

To allow maximum disclosure all articles are presented in the following way:

- An English version of the title
- Statement of the language in which the original was published
- An English summary or abstract (mostly original, sometimes extended) is added

1. Roth, M (1965), *Caudal end of the spinal cord*, Acta Radiologica Diagnosis Vol. 3 (1965)

Original Language: English
Abstract: The normal position of the spinal cord with special emphasis on the "dorsolumbar junction" as the part of the spine lacking a detailed knowledge of gross anatomic features as demonstrated at negative contrast myelography is discussed. Material consisted of 34 adults and 8 children

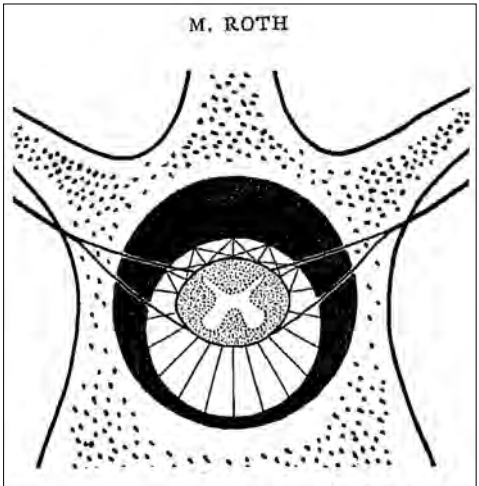


Fig. 1. Schematic illustration of the dorsal-eccentric position of the spinal cord and the ventral-eccentric position of the membranous sac due to the dorsally greater width of the extradural space (blackened) in the thoracic region.

Fig.10. The most normal anatomic configuration of calibre, position and radiant fibrous band stabilisation of the cord. Roth found in all deformations of the spine, that this optimal configuration was never present. Instead the cord can be firmly attached or easily in contact with bony boundaries of the canal. Anterior attachment in the thoracic spine and elongation and posterior attachment or contact at the lumbosacral area. The well-known Neuroprotective mechanism of Holzer means that all vertebrates do grow in such a way, that in adulthood all neural tissues have a distinct distance to bony structures in rest and in locomotion.

without symptoms in this part or known remote disorders. The variation in position, the calibre and the intrinsic curvature of the cord at the different levels is explained by developmental factors, among which the morphology of the vertebrae is stressed. A cadaver study with fresh spinal cords specimen hanging freely showed a constant intrinsic curvature in the distal cord as a "reminder "of the embryological existent complete kyphotic configuration. Also, the eccentric "lodgement" of the roots in the neuroforaminae is depicted as a consequence of the ascent of the cord, as seen in humans.

2. **Roth, M. (1966),** ***Vertebro-medullary interrelations as observed in gas myelography*****,** Acta Radiologica Diagnosis Vol. 4 (1966), p. 569–580

Original language: English
Abstract: The typical position of the spinal cord within the membranous sac, possibly derived from the close developmental relations between the neural tissue and the vertebral column, is described. The significance of the characteristic shape of the intervertebral foramina in predicting the depth of the ventral subarachnoid space is discussed. It is shown that small thoracic disk protrusions, with a narrow ventral subarachnoid space especially at the level of the lumbar intumescences, may give rise to myelopathy.

3. **Roth, M. (1968),** ***Idiopathic scoliosis caused by a short spinal cord*****,** Acta Radiologica Diagnosis Vol. 7 (1968), p. 257–271.

Original language: English
Abstract: An explanation of the pathogenesis of idiopathic scoliosis based on the disturbance of the relative vertebro-neural growth is presented. This concept is supported by neuroradiologic, experimental and clinical observations.

4. **Roth, M. (1969),** ***Models of vertebro-neural relations*****,** Acta Radiologica Diagnosis. Vol. 9 (1969)

Original Language: English
Abstract: The basic principles of vertebro-neural growth relations with special reference to the pathogenesis of idiopathic scoliosis are discussed. Plexiglas models, constructed to assist in the demonstration, are described. All models have in common that they do not only reflect a static three- dimensional condition but represent the incorporated forces in life and growth by visible movements and represent also a condensation of what happens in the fourth dimension: time.

5. **Roth, M. (1971),** ***The relative osteo-neural growth; some phylogenetic, ontogenetic and clinical aspects*****,** ad. Diagn. 1971, 1, p 81–97

Original language: German
Abstract: The growth in length of the nervous structures necessitates a higher energetic level than that of the bones. A harmonic side-by-side growth course of the growth rates, cellular-divisional

and neural-extensive, is indispensable for the normal body growth in length. Comparisons are made with features of growth in different animals and embryological knowledge. The relative osteo-neural growth represents therefore an important factor in the phylogenetic and ontogenetic development of the skeleton as well as in the pathogenesis of bone dysplasia's.

6. Roth, M., *The relative osteo-neural growth*

Part I: Gegenbaur Morph. Jahrb., Leipzig 117 (1971) 2, S. 232–255
Part II: Gegenbaur Morph. Jahrb., Leipzig 117 (1972) 3, S. 312–334

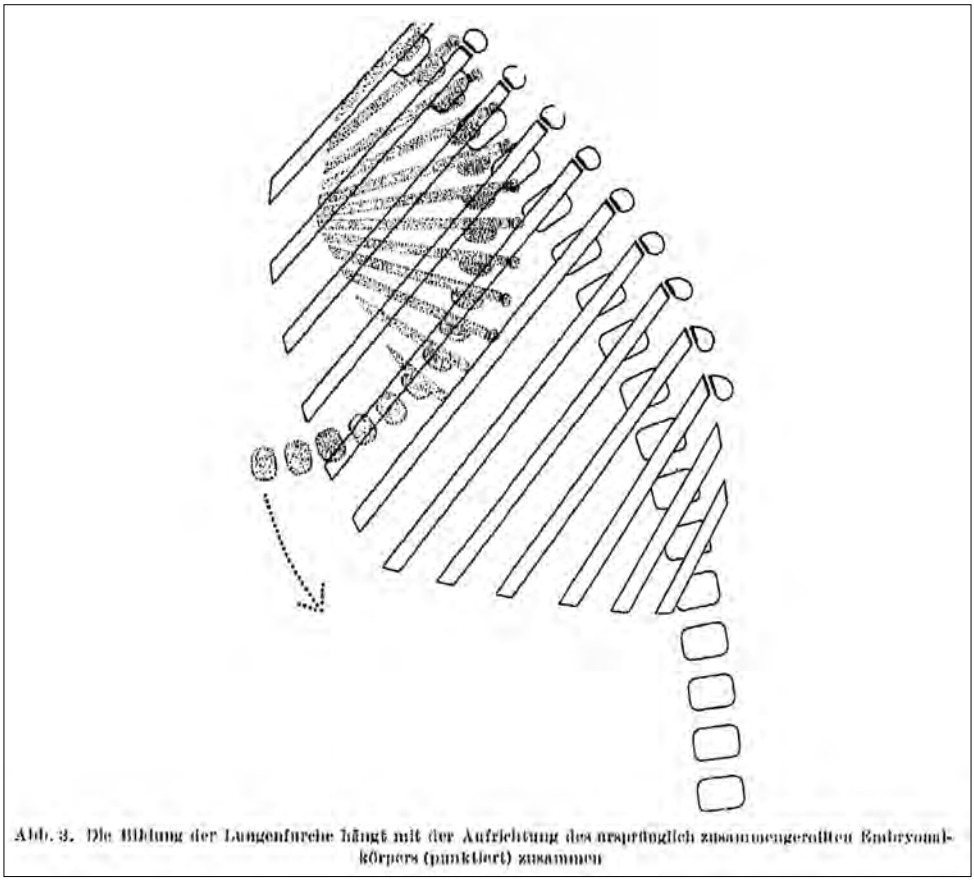


Abb. 3. Die Bildung der Lungenfurche hängt mit der Aufrichtung des ursprünglich zusammengerollten Embryonalkörpers (punktiert) zusammen

Fig. 11. The formation of the pulmonary groove depends on the extension of the completely kyphotic and rolled up configuration of the embryonic body. Roth created a beautiful mechanical model on the change of all dimensions and relationships initiated by the gradual extension of the body.

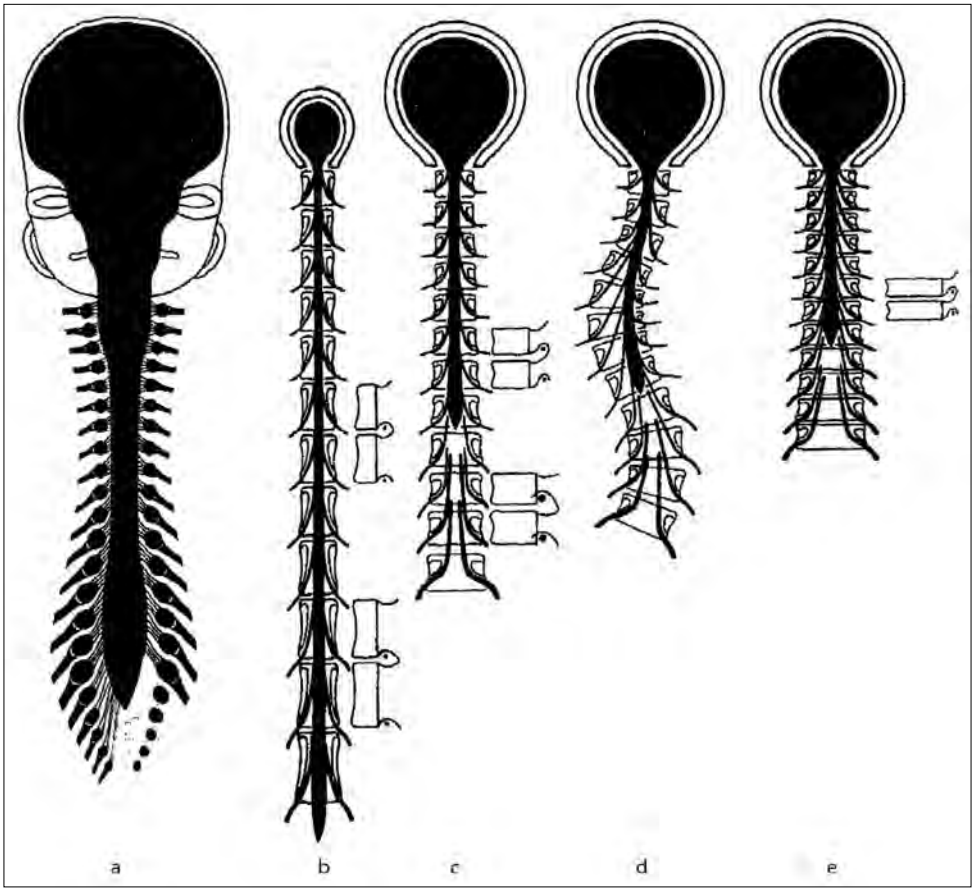


Fig. 12. The impressive relative change in proportions between cord and roots and vertebral bodies in animals, normal human spine, a scoliotic spine and a platyspondyly spine.

Part III:Gegenbaur Morph. Jahrb., Leipzig 117 (1972) 4, S. 421–440

Original language: German

Abstract: These three articles compose a total concept and explanation of the osteo-neural growth by extracting supporting evidence out of first class knowledge in biological, anatomical, embryological, histological and orthopaedic and neurological textbooks and literature. With own modelling, all sorts of research, and stepping over "scientific" boundaries, he tries to fit all visible formation and deformation of at least the skeletal development in his holistic explanation of how Nature "works". Skull and spine are in morphogenesis completely dependent on their neural countenances, but the spine and the bones of the extremities are "moulded" by the volume, condition and action of muscles in delivering 3-D movements.

In **Part I** the function of the Ascensus Medullae in Homo erectus is discussed. The inhibitive ("breaking") power of the more energy asking stretch type of growth of the neural system on the growth by mitosis of the osseous and arthrogenic skeleton gives an insight in the complex system of tension regulation and strive for optimisation, that growth in nature should always be. The earlier discovered and described craniocaudal and posteroanterior directed growth in ante- and postnatal growth in animals (Kingsbury) is completely incorporated in Roth's conceptual thinking. The change in relative size of the primitive neural structures from huge to small is depicted and discussed as is

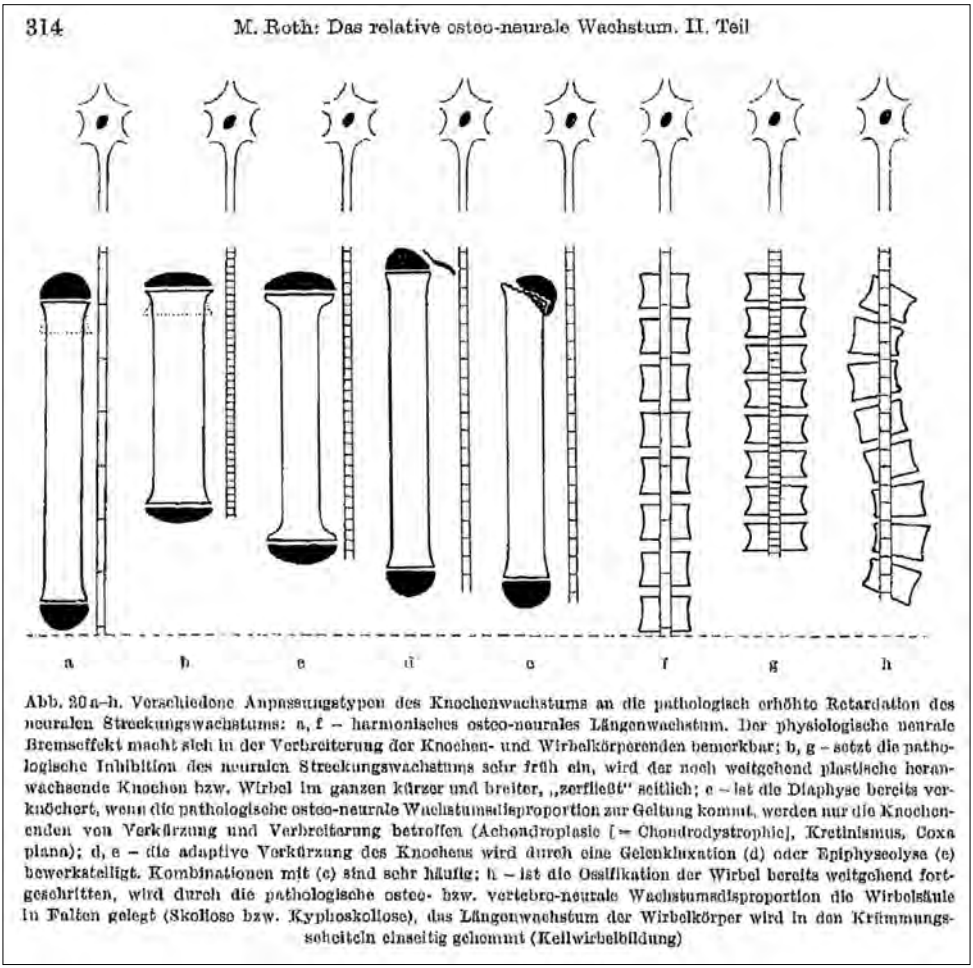


Fig. 13. Schematic drawing of different skeletal deformities with the suspected relation with the concomitant, but primary events in the stretching type of growth of the central cord.

the very clear present brachy-or Platyspondyly in siblings. The position, direction and calibre of the nerve roots in the neuroforaminae found at earlier pneumoencephalographic studies at all different levels are made understandable. Different morphologic features only present in the human spine, especially the caudalis (roof of the foramen) are clarified. Different affections like Scheuermann, Platy- (or better: brachy-) spondylie, Dysplasia spondyloepiphyseal tarda are according to Roth examples of clear "braking" power on growth in length by contracting muscles ordered in reflex by the neural cells that protects itself to overstretching. The formatted bone is like the narrow disc spaces diverged in horizontal directions.

Roth distilled out of his daily practice, that the thoracolumbar junction is the most inflicted in flattening of the discs and vertebrae in adolescent kyphotic deformities. Therefore, he ends with the statement that the length of the total spine is fixed by the capacity in growth by stretching of the intraspinal nerve structures.

Part II. Roth tries to come to a complete system of growth and formation of the body especially the complete skeleton based on earlier work of scientists and own studies. What seems true for the vertebra seems true for every piece of bone. It is the stretching forces and the stretch hindering forces that moulds the young bone in its cartilaginous stadium

Part III. On the form of the body and the physiological curvatures of the spine out of animal experiments in rats and frogs: "The nervous structures exert an influence on the morphogenesis of the skeleton even for the very reason of their existence in space, by their mass of a certain size and shape. The surrounding and /or accompanying skeletal masses adapt their general shape to that of the nervous structures. obviously under mediation of a "trophic" neural effect. Through this primary neural influence, the gross shape of the skeleton most appropriate for the given species in a given environment is elaborated. The stimuli and information reaching the organism by neural pathways are thus reflected in the morphogenesis of the skeleton. The role of the blood and the vessels (hormones-authors), of the physical stresses and of the hereditary (genetics- authors) appear only of secondary importance only in the light of osteo-neural growth relations".

7. **Roth, M. (1973),** ***The relative Osteo-Neural growth: a concept of normal and pathological (Teratogenic) Skeletal Morphogenesis,*** Gegenbaur Morph. Jahrb. Leipzig 119 (1973) 2, S. 250–274

Original Language: German

Abstract: A concept of skeletal morphogenesis is proposed which is based on the existence of 2 different types of growth in the vertebrate body, viz., the cellular-divisional bone growth and the extensive (stretch-) growth of the nervous structures. The latter type requires a higher energy and oxygen supply than the former. Consequently, the neural extensive growth proceeds at a slower rate than the bone growth. Which is manifested most conspicuously in the ascent of the spinal cord. The slower growth rate, however, is a general feature of the nervous structures throughout the vertebrate body. A number of normal as well as pathological features of the skeletal morphogenesis-above all the gross deformities of the body-parts which grow rapidly in length such as the spine,

the extremities or the facial skeleton – can be readily explained by the disturbed relation of the two growth types caused by an insufficiency of the vulnerable neural extensive growth.

8. **Roth, M. (1975),** ***Spinal cord and Scoliosis. The cause and the Effect,*** Acta Chir. Orthop. Traumas. Czech. 42, 1975, no. 6, p. 507–517.

Original language: Czech
Abstract: There exist the most intimate interrelation between the rapid craniocaudal growth-in-length of the axial skeleton and the slower proceeding extensive growth of the spinal cord and the nerve roots. The latter type of growth requires a higher supply with energy and, consequently, is more vulnerable than the former one. The vertebro-neural growth relation is similar to that existing between the developing brain and its bony case. The growth in length of the individual vertebrae and of the spine as a whole is adapted to the growth-potentiality of the intraspinal nervous structures, viz.; the former is determined by the availability of space among the latter. Idiopathic scoliosis may be interpreted as an adaptive morphogenetic reaction of the vertebral column upon the growth insufficiency of the intraspinal nervous structures: The growth process of the vertebral column, though continuing undisturbed at the cellular level, is adapted at the organ level by "waves" to the growth-insufficient cord-nerve complex. Morphological features of the scoliotic vertebra together with the typical position of the spinal cord within the spinal canal speak in favour of the suggested vertebro-neural concept, which offers a plausible explanation of the congenital and experimental scoliosis as well.

9. **Roth, M.,** ***The vertebral groove*****, Acta Radiol.9; 1965 p. 740-745.**

Original language: English
Abstract: Roth shows the presence, and gives name to the peculiar anatomical bilateral groove at the posterior surface of the bony spine of the human adult. The development of the vertebral groove at the posterior side of the lamina as a unique feature in the human skeleton, absent in quadrupeds, is explained and its influence via the spinal nerves on the shape of the intervertebral foramina is described. It fits in Roth's view about the supposed working of the musculature to provide forces on bony structures that will add in their final shape as form is dictated by functional request. In the axiom that form follows function it is the far more posterior presence of the facet joints and processi mammillaria in human that is specific for the species and originates from the tremendous greater pulling forces of the musculus Erector Trunci in the osseous insertions in the upright man. The upright posture and the early development of a long lordosis let the extensor muscles "create" these grooves, at the TL-area very shallow or even absent if its stays kyphotic. The upright position creates thus a gutter or pulley-groove, in which a muscle can increase its pulling force by acting against a fulcrum.

10. **Roth, M. (1969),** ***Idiopathic scoliosis- A special form of osteo-neural growth disproportion*** Z Orthop Ihre Grenzgeb 1969 Nov;107(1):37-46)

Original language: German

Abstract: Idiopathic scoliosis is explained as a pathological increase of the vertebro-neural growth disproportion, the physiological degree of which is reflected in the ascent of the spinal cord. This disproportion roots in the two different types of growth occurring in vertebrates, viz., the cellular-divisional and the neural-extensive. The latter is generally encountered in plant-kingdom, where spiralization in case of tethering of a central structure is a very common morphologic feature. The morphological findings on scoliotic vertebrae as well as model experiments point to the primary growth insufficiency of the intraspinal nervous structures as the actual cause of the idiopathic scoliosis.it can be seen as a biomechanic solution to choose for the shortest distance between skull and sacrum by inducing spiralization with the locked thoracolumbar joint as a starting point.

11. Roth, M., ***The experimental Teratogenesis of the skeleton. An experimental disturbance of the relative osteo-neural growth.*** Gegenbaur Morph. Jahrb., Leipzig 122 (1976) 5, S. 686–730

Original language: German

Abstract: The previously suggested concept of the closest growth relations existing between the bony and the nervous tissue at the organ level of the spinal cord and the peripheral (including the facial) nervous trunks is experimentally buttressed. It is shown that the normal gross-morphological features of the vertebrae as well as of the tubular bones (viz., their length, physiological curvatures and terminal expansions) result from the adaptation of the bone growth to the slower proceeding and vulnerable neural extensive growth, viz., from a physiological osteo-neural growth disproportion. The more or less conspicuous growth in the length of the facial skeleton depends upon the phylogenetically established, more or less evolved extensive-growth potentially of the facial nervous trunks as well.

The growth relation existing between the developing brain and its bony case applies essentially even for the axial organ, the extremities as well as for the facial skeleton.

The experimental findings speak in favour of the theoretical expectation that the typical teratogenic deformities of the extremities (micromelia), of the spine (scoliosis, defects of the vertebrae and of the ribs) as well as of the beak (jaws) which may be produced by a great number of most diverse teratogens, result from the adaptation of the bone growth to the growth-insufficient nervous trunks, viz., from the pathologically enhanced osteo-neural growth disproportion. The cleft palate and the digital defects (syndactyly, oligodactyly) may be readily explained by the growth-inhibition of the palate and digital nervous structures as well.

The vertebrate body may be thus conceived as composed of 2 growth types, viz., the neural-extensive and the cellular-divisional (mitotic). The former is represented by an extremely dense felt work of nerve fibres and trunks (the Donaldson's "nervous skeleton"), which is "stuffed "with the other, mostly mitotic growing tissues. The 2 growth types are closely related partly at the macro-(organ-) level concerning the normal and teratogenic morphogenesis of the skeleton, partly at the micro-level of the utmost periphery, viz., of the terminal extensive meshwork and the individual cells or groups of cells. The cells which escape from the extensive felt work (i.e. from the "nervous skeleton") such as the superficial cells of the epidermis or mucous membranes and, in all probability,

the elements of the haemopoietic organs, perish under normal conditions, suffer a planned, highly purposeful death. With regard to the lack of normal nerves within malignant tumors, the malignant cell may be conceived as the one escaped from the limiting confines of the extensive felt work and, in spite of that, continues to live instead of "committing suicide".

12. Roth, M., J. Krkoška and I. Toman *Morphogenesis of the spinal canal, normal and stenotic*, Neuroradiology 10, 277–286 (1976)

Original language: English

Abstract: The shape of the canal in transverse view, the shape and the position of the facet joints and the foraminate are discussed in normal and pathological conditions, like the developmental of lumbosacral stenosis (Verbiest) and degenerative stenotic and degenerative changes are explained by the conductive role the neural tissues play in growth. In malignement of the spine the osseous structures of facet joints and laminae will be overloaded with hypertrophy and condensation (sclerosis) of bone as consequence, leaving the neural structures decreasingly less space to pass. Histological specimens are used. New models of the relationship between roots and vertebrae are introduced (fig). But nevertheless, the base of the early base of any deformation seems still orchestrated by the necessary normal or disturbs the developmental balance between the two tissues (neural and osseous- discoligamentary). Roth states firmly in this paper that the role of the Notochord, a prominent structure in fishes, amphibians and reptiles is vestigial in higher mammals and its morphogenetic role in the developmental events of the axial skeleton is grossly overestimated (The Dispensability of the Notochord).

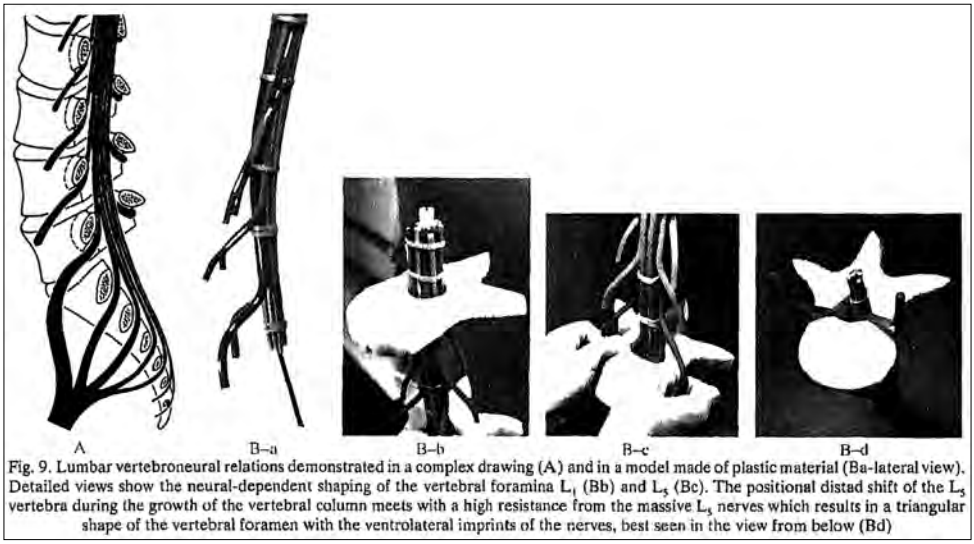


Fig. 9. Lumbar vertebroneural relations demonstrated in a complex drawing (A) and in a model made of plastic material (Ba-lateral view). Detailed views show the neural-dependent shaping of the vertebral foramina L_1 (Bb) and L_5 (Bc). The positional distad shift of the L_5 vertebra during the growth of the vertebral column meets with a high resistance from the massive L_5 nerves which results in a triangular shape of the vertebral foramen with the ventrolateral imprints of the nerves, best seen in the view from below (Bd)

Fig. 14. Modelling of the relationship of the roots, their directions and the presumed tight contact between the roots and the bony surroundings in the lumbar spine.

13. **Roth, M. (1981),** ***Idiopathic scoliosis from the point of view of the neuroradiologist*****,** Neuroradiology (1981) 21: 133–138

Original language: English
Abstract: There is a simple morphological interrelation between the growing spinal cord-nerve root complex and the vertebral column, not unlike that between the growing brain and the skull. The shape of the enveloping vertebral skeleton mirrors the anatomical features of the enclosed neural contents. During the cranio-caudally directed growth, spurts of elongation of the vertebral column may be too rapid for the slower growth rate of the spinal cord and nerve roots. The smaller caliber and the conclusion, the cord root-system must be under increased tension are well described and explained. By this the Arnold Chiari malformation is made an understandable pathoanatomic feature and the serious complaints coming with the malformation can be explained. The resulting disproportion of growth between spine and nervous system can compensated for by adaptive scoliotic curvature of the otherwise normally growing spine. The proposed pathogenetic concept readily explains the main clinical features of the deformity and is supported by a spring model experiment.

14. **Roth, M. (1981),** ***Idiopathic scoliosis and Scheuermann "disease": Essentially identical manifestation of neuro-vertebral growth disproportion*****.** Radiol. Diagn. 22 (1981), H.3, 380–391

Original language: German
Abstract: With the knowledge postulated on the disproportionate growth between the nervous tissue and the spine, Roth gives with his spring models a true to nature morphological presentation of the proportioned relations of the (tight or generally tethered) cord and roots and the deformed vertebrae (compression of the spring windings at the concavity, rope in the concavity). As the eccentric position of the cord and cauda was already known in literature (Lindgren 1941, Jirout 1964) Roth reverses this with arguments as it was seen as a secondary effect of the deformity towards a primary position with the deformity of the spine as a nervous tissue conducted developmental feature of the surrounding bony tissue. To Roth's finding the lower thoracic and thoracolumbar spine function as the most predilected area for the first dicongruencies between the two types of growth in otherwise healthy children in their growth. In his view the modificated muscular activity to keep the new posture with its relocated axial loading and unloading.

He also gives an understandable discussion in his concept of the existence of congenital scoliosis and kyphosis. More or less, he proposed scoliosis occurring mostly in flexible girls as an escape of becoming more and more kyphotic.

15. **Roth, M. (1985),** ***Once more spinal cord and scoliosis*****,** Acta Chir. Orthop. Traum. Czech. 52, 1985, no. 6, p. 532–543

Original Language: Czech
Abstract: Morphogenesis of the spine as well as of the neurocranium cannot be understood from the growing bone tissue alone, regardless of the morphology and growth peculiarities of the neural content, the brain and the spinal cord-nerve roots complex. Idiopathic scoliosis may be explained as

a consequence of excessive discrepancy between the neural and the vertebral growth rates which will give especially the girl with more laxile joints the possibility to "escape" in a shortening, spiralizing way. Growth rate differential is a well-established factor of morphogenesis resulting, among others, in curvature of two adjacent structures growing in length at different rates. The periods of growth spurt are particularly prone to neurovertebral growth disproportionateness since the spinal cord-nerve roots complex may be unable to keep pace with the too rapidly growing spine. The latter is then laid in adaptive kyphoscoliotic curvatures along the growth insufficient neural content. The relative growth deficit of the "Wirbelbogenreihe" as compared with the "Wirbelkörperreihe", a feature characteristic for idiopathic scoliosis seems to result from the primary retarding effect of the spinal nerves, which run reins like along the pedicles. This neural retarding effect may be elicited either by excessive stimulation of the vertebral growth or by inhibition of the spinal neural growth, or by combination of both. The basic gross features of idiopathic scoliosis including the deformity of the thoracic cage and the concave sided eccentric position of the spinal cord may be reproduced by means of a neuro-costo-vertebral model.

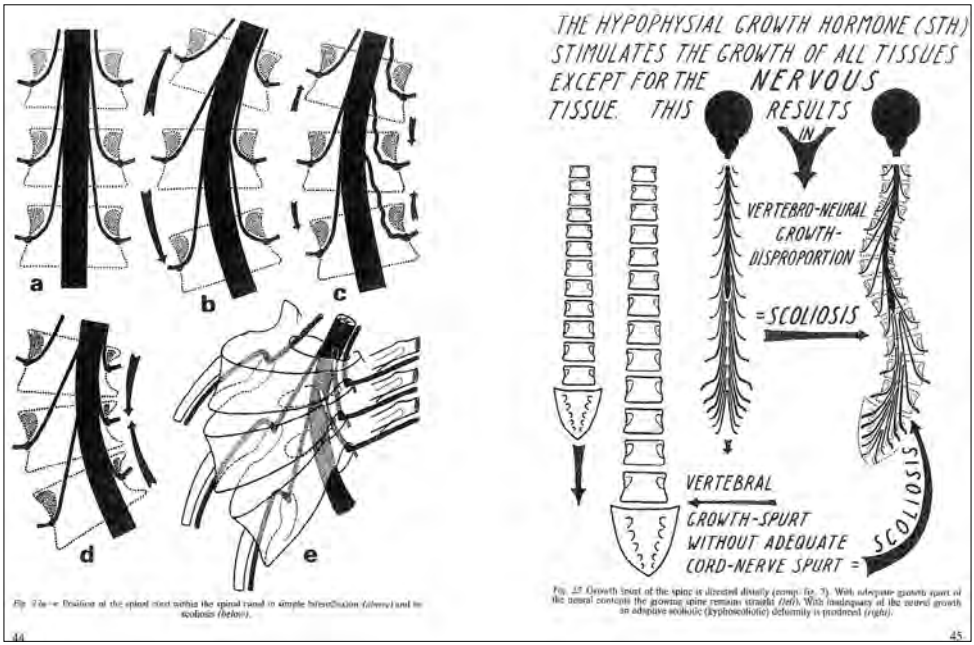


Fig. 15. Left: Drawing of the observations Roth did in bending a post mortem normal spine in which he removed all laminae and below the findings you can see in scoliosis in pneumomyelography (and MRI!!; PvL). Right: The schematic drawing of the result of growth spurt in normal and in scoliotic spines. He was not aware, that scoliosis always starts in spines with early kyphosis at the thoracolumbar spine and slight asymmetry at the TL spine because of asymmetric forces by the diaphragm (according to Murk Jansen, 1912)

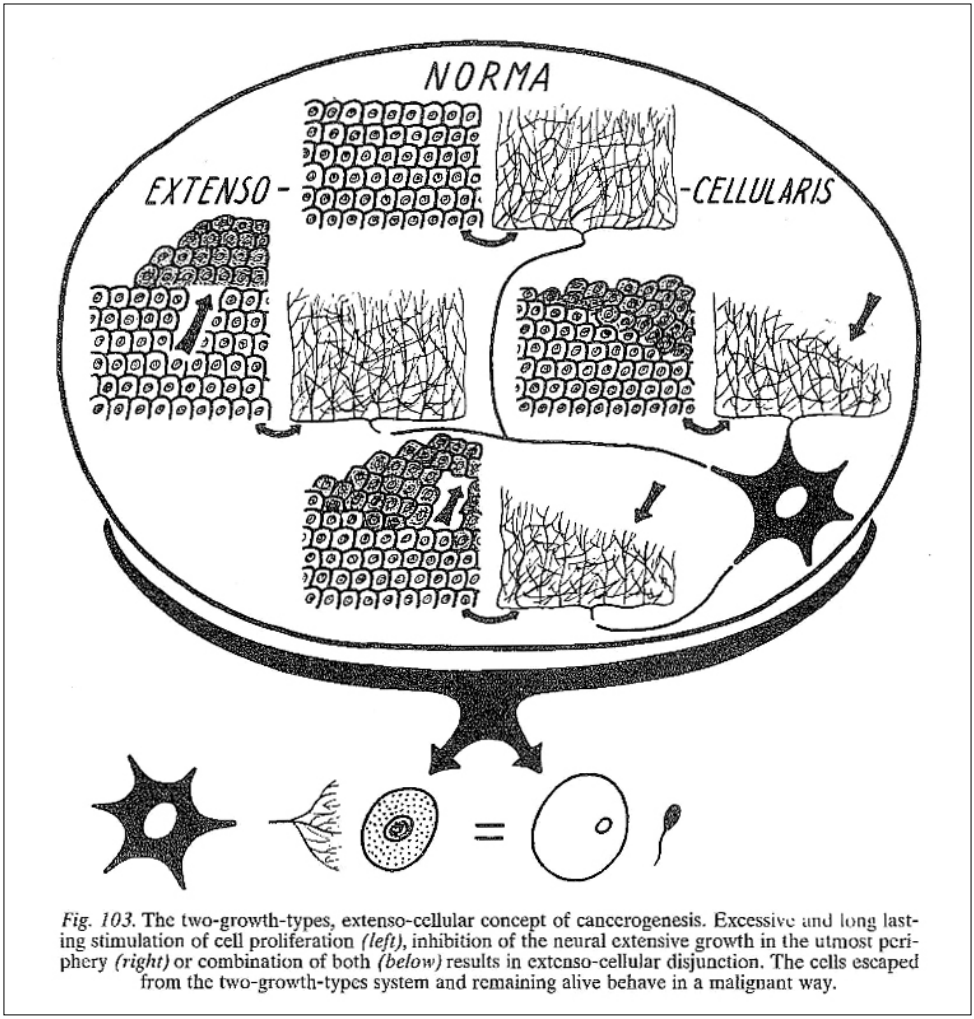


Fig. 103. The two-growth-types, extenso-cellular concept of cancerogenesis. Excessive and long lasting stimulation of cell proliferation *(left)*, inhibition of the neural extensive growth in the utmost periphery *(right)* or combination of both *(below)* results in extenso-cellular disjunction. The cells escaped from the two-growth-types system and remaining alive behave in a malignant way.

Fig. 16. Schematized origin of groups of cells, not attached or controlled by the nervous system (no connection nervous cells and new formed somatic cells during growth) and their capability to form tumours with malignant growth after initialization of cell proliferation by different types of exogen factors (tobacco, virus, mechanical forces, drugs, radiation etc.).

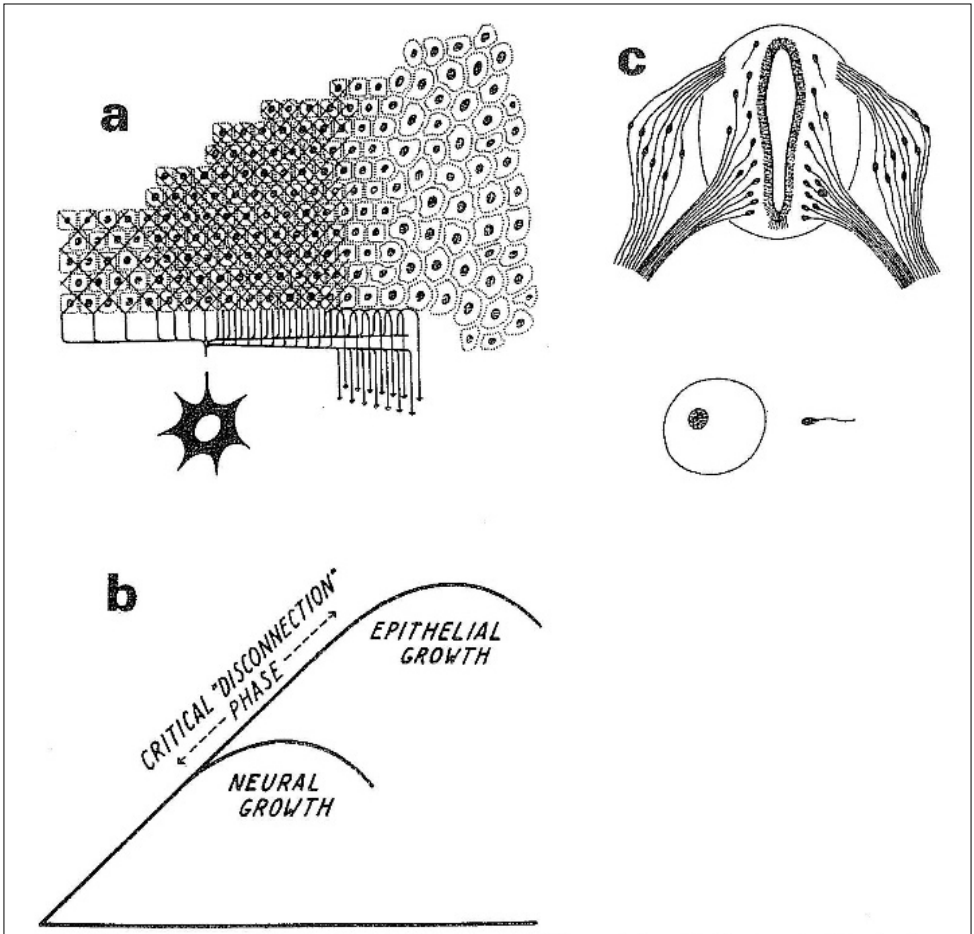


Fig. 104a–c. Schematic illustrations of the extenso-cellular relations in the tarred skin of mice. (Drawn according to *Julius'* findings (1930)) (a). Differential sensitivity of the epithelial and of the neural-extensive growth to stimulative factors: The vulnerable neural growth is impaired at concentrations of the cancerogenic agent still stimulating the epithelial growth (b). Schematic cross section of the human embryonic spinal cord with individual neuroblasts indicated (*above*—redrawn from *Villiger E. and Ludwig E.:* Gehirn und Rückenmark (Fig. 26). 14. Aufl., Benno Schwabe, Basel 1946). The outer resemblance, motility and some other features suggest a developmental relationship between the sperm *(below)* and the neuroblast (c).

Fig.17. Schematic drawings, based on earlier biomedical research on the neurotrophic background of malignant tumour growth.

There prevails a widespread tendency in cancerology to apply the *principle of infectiology*, viz., the penetrance of a pathogenic agens from outside into the body to the pathomechanism of tumours. According to the proposed concept and in sharp contrast to the principle of infectiology, the *principle of cancerogenesis* seems to consist, however, in *disconnection of the cellular-divisional and of the neural-extensive type of growth.* In addition to many other cancerogens, this fatal event may be brought about even by an infectious agens, above all by the oncoviruses which chronically and excessively stimulate cell proliferation and, possibly, impair the extensive neural growth. By both these effects the cellular "escape" is instigated.

As a matter of fact, the extenso-cellular concept of cancerogenesis postulates a *disturbance of the mechanism of physiological cellular death.* A cell, for instance the superficial cell in the epidermis or in any mucous membrane, when leaving the confines of the respective nervous skeleton, appears to be provided with something like *"lethal information"* by which the further existence of the cell is rendered

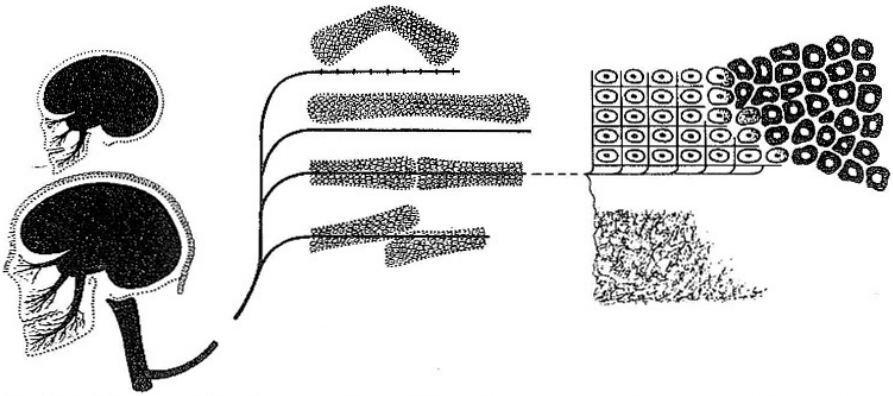


Fig. 106. Diagram of the "non-escape" *(middle)* and "escape" *(right)* extenso-cellular pathology. Both are based on a generalization of the neurocranial developmental relation *(left)* and result from the reduced availability of space—for individual bones or for epithelial cells—along or within the growth-insufficient nervous *macroskeleton* (scoliosis, bone deformities) or *microskeleton* (cancerogenesis).

impossible, the cell "commits suicide". Cancerogenesis means a *failure* of that mechanism, viz., the cell escaped from the confines of the nervous skeleton has "forgotten" or "refused" its physiological duty to die. The knowledge of this lethal mechanism possibly would make feasible to remind the malignant cell of its duty to die and to compel it to "commit suicide" by setting in function its own intrinsic lethal mechanisms.

Fig. 18. Part of the conclusive remarks of the chapter on carcinogenesis with its illustration on the way Roth concepted his idea's on how, by escaping of mitotic growing somatic cells to the individual but necessary synaptic attachment of every cell to a nervous cell or its dendrites. When these "escaped cells" in isolated groups are urged to proliferate to renew tissue, they stay uncontrolled by the nervous system and will behave in a malignant way.

16. **Roth M. (1985), Neurovertebral and Osteoneural Growth Relations. A concept of normal and pathological development of the skeleton,** Opuscula Radiologika; Acta facultatis medicae Universitatis Brunensis; Univerzita J.E. Purkyně v Brně

Original language: English
This **opus magnum reflects all his research** till then, brings his concepts of growth and discongruent growth under various experimental conditions and proposes well understandable etiologic pathways of many conditions that will have their origin in the period the organism forms itself by growth.

The designation "extenso-cellular escape growth pathology" that he proposed for the origin of cancer or malignant cell proliferation is discussed by Roth in the light of earlier "attempts at a neural explanation of cancerogenesis". In the Chapter: "The nervous skeleton- the missing link between skeletal teratogenesis and cancerogenesis? "

The complete summary of this book and summed up in 25 items of interest by Milan Roth himself is the best way to give an oversight of his thoughts, research and concepts.

1. There exist two diametrally different types of growth in vertebrates, viz., the *cellular-divisonal (mitotic)* and the *neural-extensive.* The latter, occurring otherwise in plants, requires a high supply with energy and oxygen. This accounts for its higher vulnerability as compared with the mitotic type of growth.
2. The notion is advocated that the neurocranial developmental relation (with the growing brain determining the gross shape of its skeletogenic envelope) represents just the most striking example of an *universal* osteoneural growth relation working throughout the entire body, viz., in the axial organ, in the limbs as well as in the facial area between the corresponding gross nervous structures and the respective skeletal parts.
3. Under normal conditions the spinal cord—nerve roots complex lags to a distinct degree behind the faster growing vertebral column. The growth in length of the axial organ proceeds in the *cranio-caudal* direction. Consequently, the neurovertebral growth differential is manifested in obliquity (caudal slanting) of the spinal nerve roots and in the cranially eccentric position of the spinal ganglia within the intervertebral foramina.
4. It has been shown (*Holtzer,* 1952) that skeletogenic tissue maintains a distinct distance from the surface of a nervous structure, probably by mediation of a negative chemotactic effect. By this *"neuroprotective mechanism"* the integrity of the neural contents is safeguarded, viz., its direct contact with the skeletogenic envelope is avoided. The formation of the subarachnoid space with the cerebrospinal fluid in the embryo appears to represent, among others, Holtzer's neuroprotective mechanism of the developing spinal cord.

5. By mediation of the neuroprotective mechanism, the vertebral skeletal envelope, not unlike the neurocranial, mirrors the anatomical features of the enclosed neural contents both in the embryo and in the adult, despite the important quantitative increase of the vertebral bone tissue and the relative decrease of the central nervous system taking place in the course of development. A vertebra is *"normal"* because it envelops a portion of the *normal* neural contents.

6. According to the more or less evolved phylogenetic capability of the spinal cord–nerve roots complex to grow extensively in length, the individual vertebrae grow either long and slender (dolichospondyly in quadrupeds) or short and broad (brachyspondyly in man). The craniocaudal length ("thickness") of the vertebral arch depends upon the length of the craniocaudal distances between the spinal ganglia. The caudal vertebral incisura (determining the shape of the intervertebral foramen) is produced by "cutting in" of the spinal ganglion (spinal nerve) from below into the vertebral arch.

7. Running ahead of the vertebral column in respect to the spinal cord–nerve roots complex means that every individual vertebral body disposes of a certain surplus of growth-energy which is realized in the transverse direction, viz., in spreading laterally of the skeletogenic material accumulating in the vicinity of the cranial and caudal growth plate. This transverse overgrowth, the onset of which fairly coincides with the first sings of the neurovertebral growth differential, remains lifelong manifest in the girth concavity of the vertebral body.

8. Concerning the "genetics" of the vertebral shape, it is under an indirect genetic control associated with the neural contents. The skeletal vertebral envelope is "carried with" and assumes the corresponding basic "neurovertebral" shape. The surface relief of the latter is just modified by the effect of muscles.

9. The rapid growth of the neural primordia is responsible for the kyphotic curvature of the early embryonic body. With the onset of the neurovertebral growth differential the spinal cord–nerve roots complex (from now on lagging behind the vertebral growth) imparts to the developing axial skeleton a tendency to straightening and, later, to lordotization, lumbar and cervical: The growing vertebral column is "laid in curvatures" along the somewhat shorter neural contents. Spinal curvatures established in this "neurovertebral" way are just modified by muscular action.

10. A disturbance of the relative neurovertebral growth, viz., an abnormally high difference between the neural and the vertebral growth rates may result from impairment of the vulnerable neural growth or from excessive stimulation of the vertebral growth or, possibly, from combination of both. The critical neurovertebral growth situation is then compensated for by adaptive deformities of the growing spine which has to "accomodate" along the inadequately growing, "too short" spinal cord–nerve roots complex. This adaptive reaction of the spine consists either in platyspondyly ("brachyspondyly", i.e. in formation of still shorter and still broader vertebrae than under normal conditions) or in abnormal kypho-lordo-scoliotic curvatures, isolated or in combination.

11. In contrast to a normal vertebra, specific features of the scoliotic vertebra result from its enveloping a portion of the more or less growth retarded spinal cord—nerve roots complex. Enhanced neurovertebral growth differential seems to account for other developmental spinal deformities as well, such as Scheuermann's kyphosis, deformities associated with dysraphic conditions and those occurring in various bone "dysplasias".

12. Primordial vertebral arch originates as a tongue-like process of skeletogenic tissue penetrating from in front into the interganglionic space. With an early coalescence of neighbouring ganglia this is rendered impossible and aplasia of the pedicle, usually considered as some primary derangement of the bone growth, results therefrom. A milder form of that abnormality, viz., an interganglionic space narrower than usual results in "dysplastic" thinning of the vertebral arch which is then predisposed to spondylolysis. Doubled spinal nerve roots often demonstrated by myelography in these conditions point to the early embryonic disturbance of neuromorphogenesis as the actual cause of them.

13. The vertebral body may be conceived as a very "short" long bone lacking the diaphysis. The neurovertebral growth differential should thus work—as osteoneural differential—even in the limbs where it is manifested in, essentially, the same features like in the spine, viz., 1. in physiological incurvations of long bones and 2. in terminal epi-metaphyseal widenings ("modeling") corresponding with the exuberant margins of the vertebral body.

14. The peripheral nervous system in its entirety represents an extremely dense feltwork of nervous trunks, branches and fibres, the "nervous skeleton" of Donaldson (1937) which is the product of postembryonic extensive neural growth of tremendous extent, which permeates throughout the entire body and forms, for instance, a feltlike neural envelope on the surface of every limb bone. Not unlike in the neurocranial area, various functional aspects of the peripheral nervous system should be disregarded in connection with the osteoneural relations: Just its *growth* should be taken in consideration.

15. Macromorphological osteoneural analysis of experimental deformities of the limb skeleton produced in rats, in chick and duck embryos and in frog tadpoles by various skeletal teratogens such as thallium, osteolathyrogens, cholinomimetics, hypothyroidism or roentgen irradiation and studied in specimens cleared with the Williams' technique (1943) suggests that the extensive growth of the limb nerves has been more severely interfered with by the administered teratogens than the bone growth in length. The produced skeletal deformities (bending, angulation, achondroplasia-like shortening, joint dislocations) appear as adaptations of the growing bones to the growth insufficiency of the nervous trunks, viz., the former had to "accomodate", even at the cost of a deformity, along the "too short" nervous trunks.

16. Two different "neural" mechanisms of the experimental and clinical developmental deformities of the limb skeleton are suggested. 1. The *early embryonic,* related to a disturbance of the primordial neuroskeletal relations within the forming limb bud and resulting in defects of whole bones or of their greater parts and in bone fusions. The sequelae of thalidomide disaster or of early irradiation of the pregnant uterus represent classic examples of that early neuroskeletal damage. 2. The *postembryonic,* resulting from enhancement of the physiological osteoneural growth rate differential to pathological levels and leading not to defects but just to adaptive deformities of otherwise normally growing limb bones.

17. The neurovertebral and osteoneural mechanism of the experimental deformities appears to work even in the analogous clinical deformities such as those of the spine mentioned above as well as in achondroplasia, in congenital dysplasia of the hip and in other bone "dysplasias" the causative mechanism of which is searched for in vain within the involved skeletal parts proper.

18. Micromelia in the chick embryo with characteristic "buckling" of the tibia, i.e. with its excessively sharp angulation resulting from treatment with the most variable teratogens, is associated with bones of essentially normal length, just with the distal (postperoneal) portion of the tibia growing in an opposite (proximal) direction. This specific osteoneural growth feature accompanied by hyperextension in the knee joint is analyzed and applied to explanation of clinical conditions associated with increased excursibility of joints such as the Marfan and the Ehlers-Danlos syndromes. The hyperextensibility of joints and of the skin together with increased length of bones (arachnodactyly) in these conditions appear to be related to the primary enhancement of the extensive neural growth.

19. "Curled toes" in the duck embryo treated with syntostigmine or with thallium show a striking outer resemblance with the "flaglike" deformity of the human hand in chronic rheumatoid arthritis. The possible relation of that mysterious condition to an osteoneural disturbance is discussed.

20. Facial skeleton and corresponding nerves do not escape from the universal osteoneural growth principle. Shortening of the mandible with production of the chin is related to a primary reduction of growth of the mandibular nervous skeleton which took place in the course of hominization. The classic experimental-teratogenic deformities of the beak in the chick embryo ("parrot" upper beak, shortening and angulation of the lower beak) are related, not unlike the deformities of the limb bones, to a primary growth impairment of the maxillo-mandibular nervous trunks.

21. Micrognathia and cleft palate are characteristic features of the Pierre-Robin syndrome. Micrognathia may be referred to a growth insufficiency of the mandibular nerves, the inability of the palatal shelves to grow adequately towards the midline to a primary growth insufficiency of the palatal nervous skeleton.

22. Osteolathyrism, a laboratory condition of growing animals produced by ingestion of peas of Lathyrus odoratus or by chemical osteolathyrogens, is held for a primary disorder of the skeleton in contrast to neurolathyrism characterized by spastic spinal paralysis. Osteolathyrogens have been shown, however, to work by the same indirect osteoneural mechanism upon the growing skeleton as the classic skeletal teratogens, viz., by a primary growth impairment of the spinal cord—nerve roots complex and of the peripheral nervous trunks. Accordingly, disturbances of collagen maturation and structure typical of osteolathyrism represent nothing but a secondary finding without any direct bearing upon the origin of skeletal deformities. Osteolathyrism represents just a variety of neurolathyrism: Whereas in the latter the neural *functions* are compromised, the former interferes with the neural *growth.*

23. The limiting role of the gross neural growth upon the growth in length of bones should apply to the entire nervous skeleton including the utmost neural periphery. Isolation ("carving") of individual digits from the compact hand or foot plate in the embryo may be conceived as related to the early nervous skeleton established for every individual finger and toe. The cells lying outside the nervous skeleton, i.e. those occupying the prospective interdigital spaces, succumb to necrosis, they "commit suicide". In webbed limbs the nervous skeleton extends into the interdigital spaces so that the cells occupying them remain viable. Polydactyly and syndactyly appear to represent the sequel of the primarily faulty arrangement of the digital nervous skeleton.

24. Taking into account the utmost peripheral nervous skeleton within the mucosal and cutaneous coverings of the body as limiting—under normal intravital conditions—the proliferation of epithelial cells, the malignant cell may be conceived as an essentially *normal* cell which escaped from the limiting feltwork of extensive neural growth and, instead of obeying the physiological duty to die, continues with its one-growth-type existence and proliferation autonomously, i.e. without any relation to the other, extensive type of growth. Various facets of malignant growth may be readily explained by the two-growth-types concept of cancerogenesis.

Lack of adequate "availability of space" *along* the nervous macrostructures and *within* the utmost microstructural nervous skeleton is advocated as the common pathogenetic denominator of skeletal teratogenesis and of cancerogenesis. In the former instance, the shape of otherwise normally growing bones is just adapted to the inadequately growing nervous macrostructures (the spinal cord and/or the spinal nerves) without any disjunction of the two tissues closely interrelated at the organ level. Scoliosis and various "dysplastic" conditions of the skeleton are typical examples of what has been designated *"non-escape extenso-cellular growth pathology"*. In the latter instance, the individual epithelial cells escape from the extensive neural feltwork, continue proliferating outside its limiting confines and acquire malignant features. A fatal disjunction of the two growth types takes place resulting in the *"escape extenso-cellular growth pathology"*, viz., in the nerveless malignant growth. Cancerogenic factors seem to influence upon the two-growth system in the most variable combinations of stimulation and inhibition with unpredictable sequelae for their cohesivity.

25. The striking outer resemblance of the sperm and of the neuroblast together with some other features common to both (concerning the motility and, above all, the resistance of the embryonic cell once innervated to further innervation suggestive of the egg-sperm interaction) point to some phylogenetic relationship established probably at the very beginnings of the animal kingdom. The nervous system of animals would arise as a branch of the pre-existent plant (''archplant'') kingdom and this initial event were recapitulated in the egg-sperm interaction at the onset of every individual ontogenesis as well as in the identical growth type of plants and of nervous structures, viz., in the extensive growth following after the embryonic stage of mitotic proliferation of cells. The purpose of fertilization were not only to bring together the maternal and paternal genetic equippment but also to induce the ''two-growth-types'' composition of the animal and human body.

17. Roth, M. (1986), *Cranio-cervical growth collision: another explanation of the Arnold Chiari malformation and of basilar impression*, Neuroradiology (1986) 28: 187–194

Original language: English

Abstract: Analysis of neuro-cranio-spinal development suggests a cranio-cervical growth conflict as the cause of the Arnold Chiari malformation and of basilar impression. Impaired cantilevering of the skull to accommodate the enrolling content and the hindered growth of the cervical skeleton gives rise the a "pulled out" configuration of brainstem and cerebellum that comes easily in contact with bony boundaries, giving rise to painful conditions and neural dysfunction. In gross (Meningomyelocele) and slight (adolescent deformities) impairment of distal spinal growth, a reversal of cervical growth occurs, the initial descent (uncoiling) of the primordial brain curvatures is compromised owing to the growth collision with the ascending cervical spine. The availability of space is subject of the struggle in which the cervical spine stays shorter and the foramen magnum relatively smaller, whilst the stem-cerebellum complex is pulled against it because of the tightness of the cord-roots complex in the vast growing axial skeleton.

18. Roth, M (1989), *The `Enveloping` versus the Biomechanical function of the spine*, Cs. Radiology 43, 1989, No. 1, c. 1–13.

Original language: Czech

Abstract: As a continuation of argumentation presented in a number of previous communications, the author advocates the view according to which the developing spine and its neural content ("spinal cord-nerve roots complex") are linked by an equally intimate morphogenetic relation like that existing between the brain and its skeletogenic envelope. A specific feature of the neurovertebral developmental relation consists in the fact that the elongated spinal cord-nerve roots complex is enveloped by its skeletogenic case both in the transversal and in the longitudinal direction. The matter is further complicated by lagging of the spinal neural growth behind that of the vertebral column. The development of the basic anatomical features of the individual vertebrae such as their length and width, the girth of the vertebral body as well as the shape of the intervertebral foramina

cannot be understood without taking into account the gross developmental dynamics of the two main components of the axial organ, viz., of the spinal cord-nerve roots complex and of the vertebral column.

19. Roth, M. (1994), ***Traumatic Spondylolysis in the hedgehog. A contribution to the Problem of Dysplasia of the Isthmus,*** Z. Orthop. 132 (1994), p. 33–37

Original language: German
Traumatic Spondylolysis in a hedgehog is reported. On the basis of that rare thinning of the vertebral isthmus frequently associated with Spondylolysis in man is claimed to be related to the "neuro-enveloping "function of the spine shared with that of the neurocranium. Dysplasia of the isthmus results from abnormal ganglio-foraminal interrelation in the embryo rather than from any primary derangement of the proper vertebral bone growth. In humans the compressive forces on

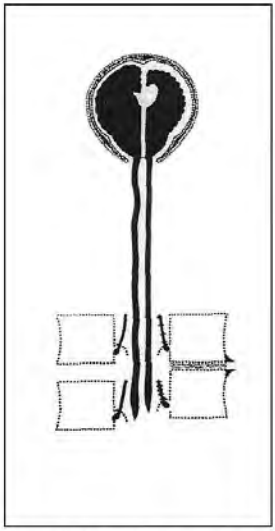
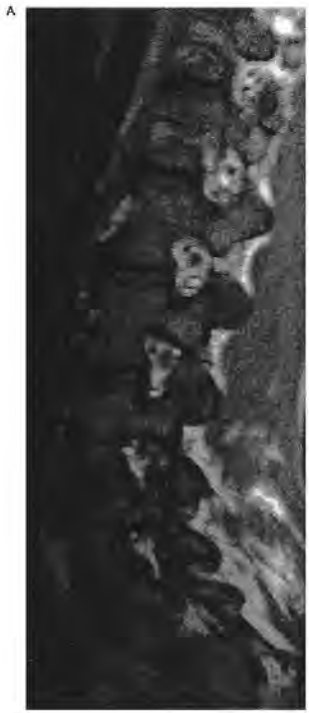


Figure 9 Concept of neuroadaptive "degeneration" of the disc (Roth [11]). Involutional atrophy of the brain is paralleled by atrophogenic shortening of spinal nerve roots which is compensated for by neuroadaptive shortening of the spine "from below" accomplished at the expense of "degenerative" nerrowing (i.e. craniocaudal shortening) of the intervertebral disc space(s).



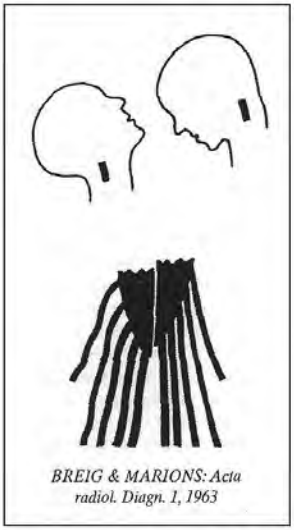


Figure 10 Different relation of spinal ganglia to the roof of intervertebral foramina (left): Ganglia L4,5 adhere more tightly to the roof so that the corresponding nerve roots (including S1) are in a less slackened condition than the L1-3 roots (shown by Breig and Marions[1] - right). Lumbar spinal nerve roots thus have a different "length reserve" in respect to the rigid vertebral envelope.

Fig.19. Schematic drawing of the obviously always present concomitant involution of cerebral volume (atrophy) and shortened tight cord and roots in the degenerative process that at the same time occur in the spine. A sedentary lifestyle and heavy labour can enhance these degenerative changes in case of already discongruent osteoneural growth.

the posterior elements in case of a low ending (hyper-) kyphosis can give rise to stress fractures of the pars intra-articularis.

20. Roth M. (1995) ***Role of neural growth in the pathomechanism of skeletal dysplasia's: an experimental study.*** Locomotor System, 2, 1995, No. 3, pp. 85–111

21. Roth M. (1996) ***Macroneurotrophic features of growth hormone effects upon the spine and hip.*** Locomotor System, 3, 1996, No. 2, pp. 72–108.

22. Roth M. (1998) ***Rheumatoid Deformities of the Skeleton: Animal Models and Neuroadaptive Pathomechanism.*** Locomotor System, 5, 1998, No. 1–2, pp. 40–49.

23. Roth M. (1998) ***Neuroadaptive Pathomechanism of Bone Dysplasia's.*** **(in Czech).** Locomotor System, 5, 1998, No. 3–4, pp. 127–132
In a number of instances experimental "osteoneural" findings pattern what happened in the course of evolution and hominization, viz., primary shortening of the nervous skeleton reflected in corresponding transfonnations of the bony skeleton. Shortening of the human mandible with appearance of the chin is one of the most striking examples of such an (experimentally reproducible) "phylogenetic neuroadaptive deformity".

24. Roth M. (1998*) Morphology and Development of the Spine: Plea for a doubt.* Rivista di Neuroradiology 11:313–320.

Against the evident present "macroneurotrophism" effect that can be seen in the period of growth of both skeleton and nervous tissue, leading to gross morphological changes in the skeleton (deformities) he places the more "microneurotrophisme" effects, that can be seen in adulthood. This can explain the "degenerative" shortening of the spine and structural chances as seen in the lower spine can be related to similar degenerative (involution) processes that at the same time takes place in the neurocranium.

25. Roth M. ***Disc Degeneration: A Sort of Neuroadaptive Skeletal Dysplasia in the Adult and Aged Essay on "Macroneurotrophism" of the Skeleton, Pathology and Developmental Biology of Gross Neural Growth,*** April 1, 1999 Research Article, Volume: 12 issue: 2, page(s): 281-302
Radio diagnostic Clinic, Medical Faculty Hospital, Masaryk University; Brno-Bohunice, Czech Republic

Owing to the craniocaudally proceeding bodily growth, "neuroadaptive" shortening of the skeleton is accomplished as though "from below" since the too short spinal nerve roots and/or peripheral nerves hinder the spine and /or limb bones from growing straight forward in length. The concept is buttressed by experimentation on laboratory animals which suggests a common neuroadaptive pathomechanism of experimental as well as clinical skeletal "dysplasia's". Vertebroneural and/or osteoneural length disproportion may take place even in the adult and aged as a result of

involutional-atrophogenic shortening of spinal nerve roots and/or of peripheral nerves. Also, that disproportion must be compensated by the skeleton since otherwise the shortened nervous elements would be exposed to undue stretching. In the spine this "neuroprotective" measure is accomplished by degenerative narrowing (i.e. shortening) of the disc comparable with "cerebroprotective" dehiscence of cranial sutures under the effect of the expanding brain in obstructive hydrocephalus. Herniation of the disc is just a mechanical complication of the essentially purposeful "degenerative" process. Degenerative "arthrotic" narrowing (shortening) of the joint spaces in the limbs may be ascribed to analogous primary atrophogenic shortening of peripheral nerves.

25. Roth M. ***Macroneurotrophism in the development of the vertebrate skeleton.*** Anthropology XXXII/1 (1994) 1-24

Motto: "It is sometimes held that no real progress has been made until a biological mechanism is placed on a firm molecular basis. Such a view denies the existence of different levels of organization at which one can meaningfully investigate biological processes."

Abstract: … Against the petrified belief that the growth of the extracerebral nervous structures is mere passive "innervation follower" of the other tissues to be innervated, the view is defended and experimentally supported that growth in length of the bony skeleton depends upon and is governed by the active co-growth of the nervous skeleton (ten by Donaldson 1937). Variable length of the vertebral column as well as of the limb bones in animals and man mirrors the variable growth-in-length potentiality of the spinal and peripheral nervous structures. The nervous skeleton perceives, along exteroceptive and proprioceptive path ways, the conditions prevailing in the environmental niche and provides, by mediation of the more or less extensive neural growth, for the appropriate shape and length of the bony skeleton. Impairment of the vulnerable neural growth results in "neuroadaptive" deformities of the skeleton consisting in various types of its shortening, i.e. accumulation of the proliferating skeletogenic material along and within the too short nervous skeleton. If the two types of growth evolve in a congruent way than you can speak (in accordance with Holzer) of the Neuroprotective mechanism: The indispensable "Osteoneural balancer".

It is argued that egg and sperm appear to be sources of the two basic growth types of the vertebrate body, the cellular-divisional and the neural-extensive. The possible repercussions of that developmental interrelation upon some problems of general biology are discussed.

Acknowledgments

We thank Milan Roth's widow, the late Mrs. Milada Rothova and their sons Tomas and Michal for their initial help in providing his biographical material and photographs and their approval to use all his published work to be brought under attention of the present medical world interested in unanswered questions on skeletal growth and spinal deformities as scoliosis.

Also, thanks to Dr. Kayo Styblo PhD, now orthopedic surgeon in Zaandam the Netherlands, who originates from Czechoslovakia, for translating the Czech articles of Milan Roth into Dutch.

Thanks to Prof. Ivo Marik and the Czech Society for Connective tissues J.E. Purkynë to give us the opportunity at the different Prague-Lublin-Sydney-St. Petersburg Symposia to bring our knowledge on the importance of the concepts of Roth in the light of many ailments modern man has to suffer.

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The PDF of his book is placed under the Research Gate profile of Piet van Loon https://www.researchgate.net/publication/23275347 The_central_cord-nervous_roots_complex_and_the_formation_and_deformation_of_the_spine_the_scientific_work_on_systematic_body_growth_by_Milan_Roth_of_Brno_1926–2006

List of articles with reference to spinal growth and Roth's work

1. GUO,X. CHAU W.-W., CHAN Y.-L., CHENG J. C.-Y. **Relative anterior spinal overgrowth in adolescent idiopathic scoliosis. Results of disproportionate endochondral-membranousbone growth** J Bone Joint Surg [Br] 2003;85-B:1026–31
2. PORTER RW: **The pathogenesis of idiopathic scoliosis: uncoupled neuro-osseous growth?** Eur Spine J**(**2001Dec)10 (6): 473–81
3. PORTER R. W. **Comment to "The pathogenesis of idiopathic scoliosis:uncoupled neuro-osseous growth?"** ;Eur Spine J (2001) 10 :482–487
4. CHU WC et al. **A detailed morphologic and functional magnetic resonance imaging study of the craniocervical junction in adolescent idiopathic scoliosis**. Spine (Phila Pa 1976). 2007 Jul 1; 32(15):1667-74.
5. CHU WC, LAM WW, CHAN YL, NG BK, LAM TP, LEE KM, et al. **Relative shortening and functional tethering of spinal cord in adolescent idiopathic scoliosis?: study with multiplanar reformat magnetic resonance imaging and somatosensory evoked potential**. Spine 2006 Jan 1;31(1):E19–E25.
6. CHU WC, MAN GC, LAM WW, YEUNG BH, CHAU WW, NG BK, et al. **A detailed morphologic and functional magnetic resonance imaging study of the craniocervical junction in adolescent idiopathic scoliosis.** Spine 2007 Jul 1;32(15):1667–74.
7. GIGLIO CA, VOLPON JB**: Development and evaluation of thoracic kyphosis and lumbar lordosis during growth**. J Child Orthop**.** 2007 Sep; 1(3):187-93. Epub 2007 Jul 28

8. VAN LOON P.J.M., VAN RHIJN L.W.; **The central cord-nervous roots complex and the formation and deformation of the spine; the scientific work on systematic body growth by Milan Roth of Brno** *(1926–2006)*. Stud Health Technol Inform 2008; 140:170–86.
9. CHU WC et al: **Morphological and functional electrophysiological evidence of relative spinal cord tethering in adolescent idiopathic scoliosis**. Spine *(2008): 33*; 6(673–680)
10. VAN LOON PJM; **Clinical detectable tension in the growing body**. Stud Health Technol Inform 2008; 140:52-8
11. KOUWENHOVEN JW, CASTELEIN RM. **The pathogenesis of adolescent idiopathic scoliosis: review of the literature**. Spine (Phila Pa 1976). 2008 Dec 15;33(26):2898–90
12. VAN LOON PJM et al.: **Forced Lordosis on the Thoracolumbar Junction Can Correct Coronal Plane Deformity in Adolescents With Double Major Curve Pattern Idiopathic Scoliosis**. Spine(2008)33;7(797-801)
13. NI HAIJIAN et al**: An *Increased Kyphosis of the Thoracolumbar Junction is Correlated to More Axial Vertebral Rotation in Thoracolumbar/Lumbar Adolescent Idiopathic Scoliosis.*** Spine (2010) 35; 33(1334-1338)
14. VAN LOON P.J.M; Roukens M; Thunnissen FB; Munneke J. (†).**A new brace technique for adolescent scoliosis and kyphosis based on restoration of thoracolumbar lordosis.** Radiological and subjective clinical results after one year of treatment. Scoliosis 2012, 7:19
15. DUDIN, M. G., & PINCHUK, D. Y. (2009). **Idiopathic scoliosis:. Diagnostics, Pathogenesis** (in Russian). St. Petersburg: Čelovjek. 335 p.
16. DUDIN, M. G., & PINCHUK, D. Y. (2013). **Idiopathic scoliosis. Neurophysiology and neurochemistry** (in Russian). St. Petersburg: Čelovjek. 303 p.
17. DUDIN, M. G. (2017). **Idiopathic scoliosis: prevention, conservative treatment**; Monography (in Russian). St. Petersburg: Čelovjek. 223 p.
18. DUDIN, M. G. (2018). **Reflections about the perspectives of scoliosology**. Locomotor system, 25(2), p. 61–65.

OPAKOVANÉ PUBLIKACE PŮVODNÍCH PRACÍ
REPEATED PUBLICATIONS OF THE ORIGINAL PAPERS

Next two original papers of Milan Roth were published in the journal Locomotor System – Advances in Research, Diagnostics and Therapy in 1995 and 1996 (ROTH M. Role of neural growth in the pathomechanism of skeletal dysplasias: an experimental study. Locomotor System, 2, 1995, No. 3, pp. 85–111 and ROTH M. Macroneurotrophic features of growth hormone effects upon the spine and hip. Locomotor System, 3, 1996, No. 2, pp. 72–108).

Repeated publication of these outstanding papers were offered and approved by Editorial Board of the Locomotor System journal because of the Locomotor System journal Archive is available for download in PDF format from 1997.

OPAKOVANÁ PUBLIKACE PŮVODNÍ PRÁCE
REPEATED PUBLICATION OF THE ORIGINAL PAPER

ROLE OF NEURAL GROWTH IN THE PATHOMECHANISM OF SKELETAL DYSPLASIAS: AN EXPERIMENTAL STUDY

Originally published in Locomotor System, 2, 1995, No. 3, pp. 85–111

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SUMMARY

The author continues his polemic with the current belief that the growing nervous structures just passively follow the outgrowing non-nervous tissues for the sake of innervation. Nervous system, in addition to its intricate functions, represents the extensive type of growth consisting in sprouting of innumerably branching processes from the nerve cell body. The vertebrate body is thus composed of products of two basic growth types, the cellular-divisional and the neural-extensive. The latter represents in its entirety an ubiquitous, cotton-wool-like feltwork, the "nervous skeleton" (Donaldson 1937). Growth in length of the bony skeleton, embedded within the periosteal and endosteal nervous skeleton, cannot proceed without adequate co-growth of that neural feltwork which shares with the cerebral growth its high demands on supply with energy and oxygen and, consequently, its high vulnerability. Skeletal dysplasias and their experimental models, characterized by shortening as though "from below" of the involved bones, may be explained as "neuroadaptive" response of the growing bones lo insufficiency of the vulnerable neural growth.

Keywords: bony skeleton and nervous skeleton, extracerebral neural growth, insufficiency of vulnerable neural growth, neuroadaptive skeletal deformities, skeletal dysplasias.

SOUHRN

M. Roth: Úloha neurálního růstu v patomechanismu kostních dysplazií: pokusná studie.

Práce je pokračováním autorovy polemiky se současným názorem, že rostoucí nervové struktury pouze pasivně sledují z důvodu inervace ostatní rostoucí ne-nervové tkáně. Nervový systém kromě svých složitých funkcí představuje dlouživý typ růstu, který se skládá z pučících bezpočetně se

větvících výběžků těla nervové buňky. Tělo obratlovce je tvořeno produkty dvou základních typů růstu, a to buněčně dělivého a neurálně dlouživého. Neurální dlouživý růst představuje ve svém celku všudypřítomnou vatovitou síť, tzv. nervový skelet, popsaný v r. 1937 Donaldsonem. Růst do délky kostry, která je uložena uvnitř periostálního a endostálního nervového skeletu, nemůže pokračovat bez adekvátního současného růstu neurální sítě, která sdílí s růstem mozku jeho vysoké nároky na zásobení energií a kyslíkem a následně i jeho snadnou zranitelnost. Kostní dysplazie a jejich experimentální modely, charakterizované zkrácením postižených kostí jakoby „zespodu", mohou být vysvětlovány jako „neuroadaptivní" odpověď rostoucích kostí na insuficienci zranitelného neurálního růstu.

Klíčová slova: kostní a nervový skelet, kostní dysplazie, extracerebrální nervový růst, insuficience zranitelného neurálního růstu, neuroadaptivní deformity skeletu.

Motto

We must attempt to derive the different shapes of metazoan organisms in terms of some gross, macroscopical principles.
N. Rashevsky: Organic form as determined by function. Ann. N. York Acad. Sci., 63, 1955, pp. 442–453.

It is sometimes held that no real progress has been made until a biological mechanism is placed on a firm molecular basis. Such a view denies the existence of different levels of organization at which one can meaningfully investigate biological processes.
L. Wolpert: Pattern formation in biological development. Scientific American, 239, 1974, pp. 154-165.

Introduction: Macroneurotrophism versus microneurotrophism

The undeniable effect of the nervous system upon the developing and adult bone is searched for in the "neurotrophic" function, viz., in some extremely intricate, so far poorly understood interaction between the nervous fiber and the individual tissue cell or group of cells in the utmost periphery. The term "microneurotrophism" has been coined to designate that cellular-level effect in contrast to "macroneurotrophism" (**22**) dramatically evident, at the organ level, in the moulding effect of the growing brain upon the shape and size of its neurocranial bony envelope. In connection with this self-evident process the intricate cerebral functions as well as histobiological details of neurocranial bone growth are entirely disregarded: The brain is viewed upon simply as a lump of growing nervous tissue moulding the gross shape of its bony envelope. Since long ago the author has tried to find out whether or not the cerebrocranial developmental interrelation patterns the existence of the same relation between the entire developing extracerebral nervous tissue (spinal, peripheral and facial) and the extracranial skeleton. The aim of the present communication is to recapitulate the problem and to justify a positive response to the posed question, viz. to document that morphogenesis of the axial and limb skeleton is equally dependent upon neural growth like that of the neurocranium upon the cerebral growth.

Results – hypotheses on the basis of experimental studies.

Activity of cerebral growth confronted with the presumed passivity of extracerebral neural growth: A grossly paradoxical today's view

In diametral contrast to the highly active and vulnerable brain growth (1,2 a.o.) that of the extracerebral nervous tissue is held for a passive process that just follows the outgrowing non-nervous tissues for the sake of "innervation". Embryonic spinal nerve roots and/or peripheral nerves invading the early limb bud are said to be "taken in tow and dragged along" by the other tissues with the tacitly accepted implication that definitive length of adult nerves depends upon the degree of outgrowth of the non-nervous tissues, above all of bones. Extracerebral neural growth should share with the brain, however, its high demands on supply with energy and oxygen and, consequently, its high vulnerability. "Axonogenesis puts great demands on the synthetic machineries of the developing neuron which have to produce protein, lipids and polysacharides of axonal components" (quotation from (**2**), p. 29).

Not unlike the brain the extracerebral nervous tissue develops and grows side by side in the most intimate interrelation with the skeleton, above all in the axial organ. Active cerebral growth in volume moulding its bony envelope patterns what is going on in length in the developing axial organ. Vertebral column, not unlike the neurocranium, represents a firm protective segmented envelope of the elongated spinal neural content and is moulded by that content, above al! as concerns its length, i.e. degree of vertebral outgrowth (**Fig. 4**). With insufficiency of spinal neural growth the vertebral envelope grows "neuroadaplively" shorter as well (**Fig. 2c**). The matter has been discussed in detail in (**20,22,25**), here only the limb skeleton will be treated from the "neuroadaptive" point of view.

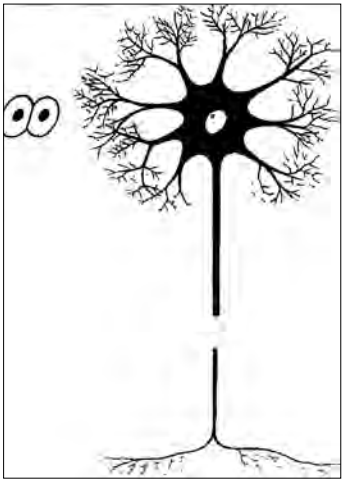
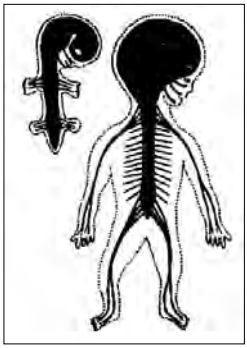


Fig. 1: Two growth types of the vertebrate body, cellular-divisional and neural-extensive proceeding at a different energetic level.



a, b

d

c

Fig. 2 a-d: Cotton-wool model of the "nervous skeleton" (**4**) (c). It originated by extensive peripheral growth from the meager embryonic primordia (a, b) and is "stuffed" with the non-nervous tissues. With insufficiency of the vulnerable neural growth bones grow "neuroadaptively" shorter, mostly with thickening and/ or bowing ("buckling"). Two main neuroadaptive deformities of the spine, scoliosis and platyspondyly are outlined. d: Sod-model of the nervous skeleton: Soil particles are held together by the root skeleton.

Cerebrocranial developmental interrelation extended to the limbs

It might seem hardly feasible to advocate the generalization suggested in the title since nerves run at a distance from the bone surfaces and it looks futile to credit them with any similar effect upon the developing skeleton comparable with that of the brain upon its bony envelope. It should be borne in mind, however, that the currently adopted schematization of the peripheral nervous system in form of simple branching lines represents but quite a small fragment of the system. In its organ entirety the peripheral nervous system (including the vegetative) represents an excessively dense, cotton-wool-like (**Fig. 2c**), ubiquitous feltwork of nervous twigs and fibers (the "nervous skeleton" of Donaldson (**4**)) permeating throughout the vertebrate body which all bodily tissues and organs are "embedded within" including the bony skeleton. The following comparison should prove useful for illustration of the proposed morphogenetic role of the nervous skeleton (**Fig. 2d**): When digging a grassy ground one perceives the visible roots without being aware of the fact that the "pure" soil between them is densely and diffusely permeated by the feltwork of the finest rootlets. In the isolated sod the soil particles are held together by the "rootlet skeleton", those that did not

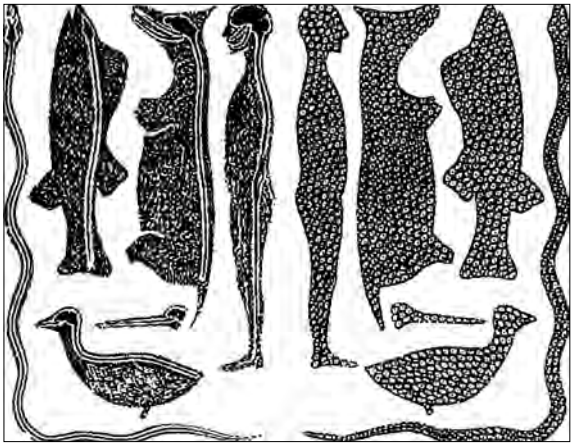


Fig. 3. Diagram of the two-growth-types composition of the vertebrate body, cellular-divisional (right) and neural-extensive (left) (to be viewed upon super-imposed). The shape and size (length) of the body is determined by the extent of the nervous skeleton.

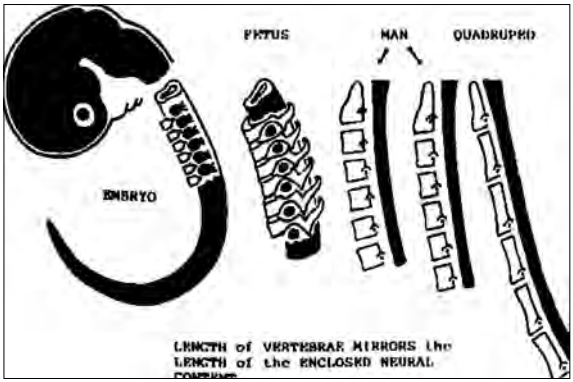
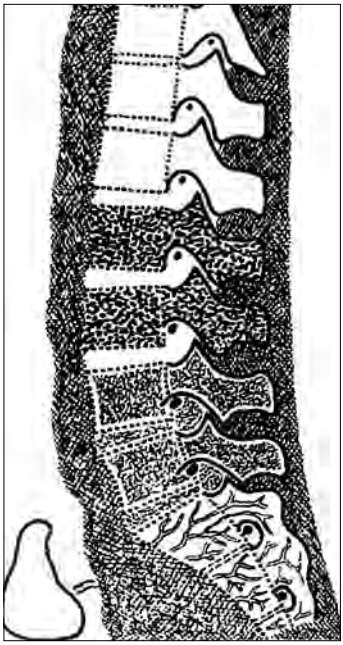


Fig. 4. "Neuroenveloping" function of the vertebral column, best evident in the embryo with its huge spinal cord. In the course of subsequent development length of the spine depends upon the degree of outgrowth of its neural content: Individual vertebrae grow accordingly longer and more slender in the quadruped or shorter and broader in man.

find any more place within the skeleton fall away. The sod thus appears to pattern another, highly elusive function of the nervous system, the morphogenetic one. The "nervous skeleton" is "stuffed" with the non-nervous tissues for proliferation of which it represents, in addition to innervation, an active "limiter" rather than mere passive "innervation follower". The entirety of the nervous skeleton implies that, in addition to the connective tissue periosteum, every bone is covered by a felt-like envelope ("bag") of periosteal nervous skeleton and, moreover, is permeated by the endosteal nervous skeleton within the meshes of spongiosa (**Fig. 5 a, b**).

What this amounts to is that 1/ the limb bones have a more intimate relation to the nervous system than the brain to the neurocranium from which it is separated by the subarachnoid space and meninges; 2/ the total amount of the nervous tissue present within the limb exceeds that of the bone tissue; 3/ every bone may be viewed upon, without much exaggeration, as a bony "cast" of the correspondingly shaped cavity within the nervous skeleton: The former is moulded by the latter



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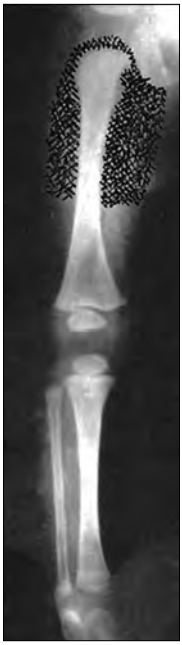


b

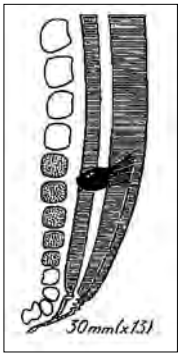
Fig. 5 a, b: a: Diagram of the lumbosacral spine: Current out-line (ThII-LI), with spongiosa (L2, 3) and blood supply (sacrum). In L4, 5 nervous skeleton, periosteal (perivertebral) and endosteal is indicated which the vertebral column is embedded within. In the roentgenogram of suckling's leg (b) the nervous skeleton is outlined in the proximal portion of the thigh.

not unlike the neurocranium by the brain. Any shape transformation of a bone, above all its growth in length, cannot take place without adequate co-growth of the periosteal and endosteal nervous skeleton as well as of the nearby nervous trunks, "macrorepresentatives" of the nervous skeleton. Schumacher (**28**) ascribed to the periosteum the role of a diffuse "growth center" represented, in the present author's opinion, above all, by the periosteal nervous skeleton.

With proceeding growth of a bone any individual of myriads of periosteal nervous fibres must be protected from any undue stretch, must preserve its "unloaded" condition. This is accomplished by the "neuroprotective" effect of the complex periosteal nervous skeleton upon the growing bone comparable with that of the growing brain upon the developing neurocranium. This seemingly outright speculation finds its striking support in gross morphological features of the skeleton to be discussed in the next paragraph.

Physiological vertebroneural and osteoneural growth differential

What is to be reckoned with may be demonstrated in the cotton-wool model (**Fig. 2c**): To pull out a single fibre does not require any appreciable effort but to do the same with a cluster of fibres means to overcome a rather strong mechanical resistance, i.e. neural-growth-resistance in vivo. The growing spine and limb bones meet a distinct resistance of the more energy demanding, slower neural growth. This "physiological neuroskeletal growth differential" must be compensated



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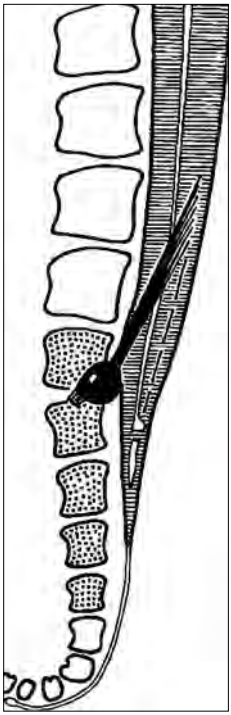
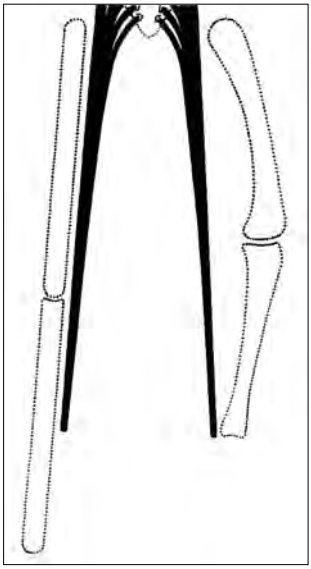


b

c

d



f

e

Fig. 6 a–f: Gross morphological manifestations of the physiological vertebroneural and osteoneural growth differential. "Waisting" of the early vertebral bodies (b – redrawn from (**29**)) reflects the beginning slowing down of the spinal neural growth (lumbosacral lordotization seems to be related to the slowness of spinal neural growth as well (**21, 23**). Limb bones (c – tadpole, d – adult frog in full ex-tension; specimens cleared by Freihofer-Compa-gno's (**6**) modification of Sihler's technique (further on (S)) are "accomodated" along the distinctly shorter nerves partly by terminal flaring (comp. **Fig. 16**), partly by angulated joint posture and incurvations of individual bones. Neuroadaptive "accomodation" by terminal broadening of phalangae (i.e. by transversal dissipation of bone growth) in the toes of a near-term duck embryo (e). Osteoneural interpretation is schematized (with some exaggeration) in (f).

for on the part of growing bones since otherwise the indispensable "unloading", i.e. slackedness of the nervous fibers and trunks would be compromised. Two types of that "neuroadaptive" compensatory reaction of the growing bones may be deciphered from gross skeletal morphology: 1/ Physiological curvatures, above all in form of physiological angulated posture of joints and incurvations of the limb bones; physiological curvatures of the spine may be also related to the effect of the vertebroneural growth differential (**20, 22**). 2/ Terminal epi-metaphyseal flare ("modelling") of the limb bones and its counterpart, "waisting" of the vertebral bodies appearing in the early embryo and persisting into adulthood. A gross-morphological, growth-dynamic view at **Figs. 6a–f** should save lengthy description.

Bone modelling, i.e. decreasing diameter of diaphysis at the same time that it flares toward metaepiphyses, a puzzling, diametrally anatagonistic behaviour of the growing bone is generally ascribed to the "pressure effect" of the periostcum. It seems reasonable, however, to attribute shaping of growing bone to the osteoneural growth differential and to the shape of the cavity within the nervous skeleton "filled in" with or "casted" by the bone tissue. Different size of that cavity accounts for the different thickness of bones, for instance, in the tree frog and in the common frog (**Fig. 13**, **14**). There can be little doubt that abnormal thinness of bones in some lethal syndromes (**14**) or "overtubulation" with exaggerated metaphyseal flare (**11**) are of the same origin.

Without any considerable stretch of imagination one is led to the conclusion that length of the vertebrate body is determined by the extent (degree of outgrowth) of the nervous skeleton, not by that of the bony skeleton (**Fig. 3**) which provides just for the indispensable stability of the body.

Exaggerated osteoneural growth differential: The causative factor in the pathomechanism of skeletal dysplasias

Among the "platoon" of tissues growing in length within the developing limb and/ or spine (bones, muscles, vessels, skin, nerves) neural growth has the highest demands on supply with energy and oxygen and, consequently, is more vulnerable than any other growing tissue. With neural growth insufficiency bones cannot grow in length adequately even though their proliferative growth process as such, at the cellular level, proceeds normally. What should ensue in that case is anticipated in the author's working hypothesis (**Fig. 2c**): Impaired growth of the brain ("micrencephaly") is manifested in "neuroadaptively" reduced size of the cranial vault ("microcephaly"). Growth insufficiency of the spinal neural content and/ or of peripheral nerves should be manifested in "neuroadaptive" shortening of the vertebral column and/ or of the limb skeleton. Since growth of the spine and limbs proceeds craniocaudally (proximo-distally) their neuroadaptive shortening will be accomplished as though "from below" because the too slow neural growth would hinder the spine and limbs from growing adequately in the distal direction (**23**).

Animal experimentation based on that working hypothesis fits well with theoretical expectations. Stereotyped bowing ("buckling"), shortening with thickening or dislocation of limb bones producible by a host of most heterogeneous "skeletal" teratogens (mostly respiratory inhibitors, neurotoxicants (thallium, organophosphorous compounds), cholinomimetics or neurotropic drugs, ionizing

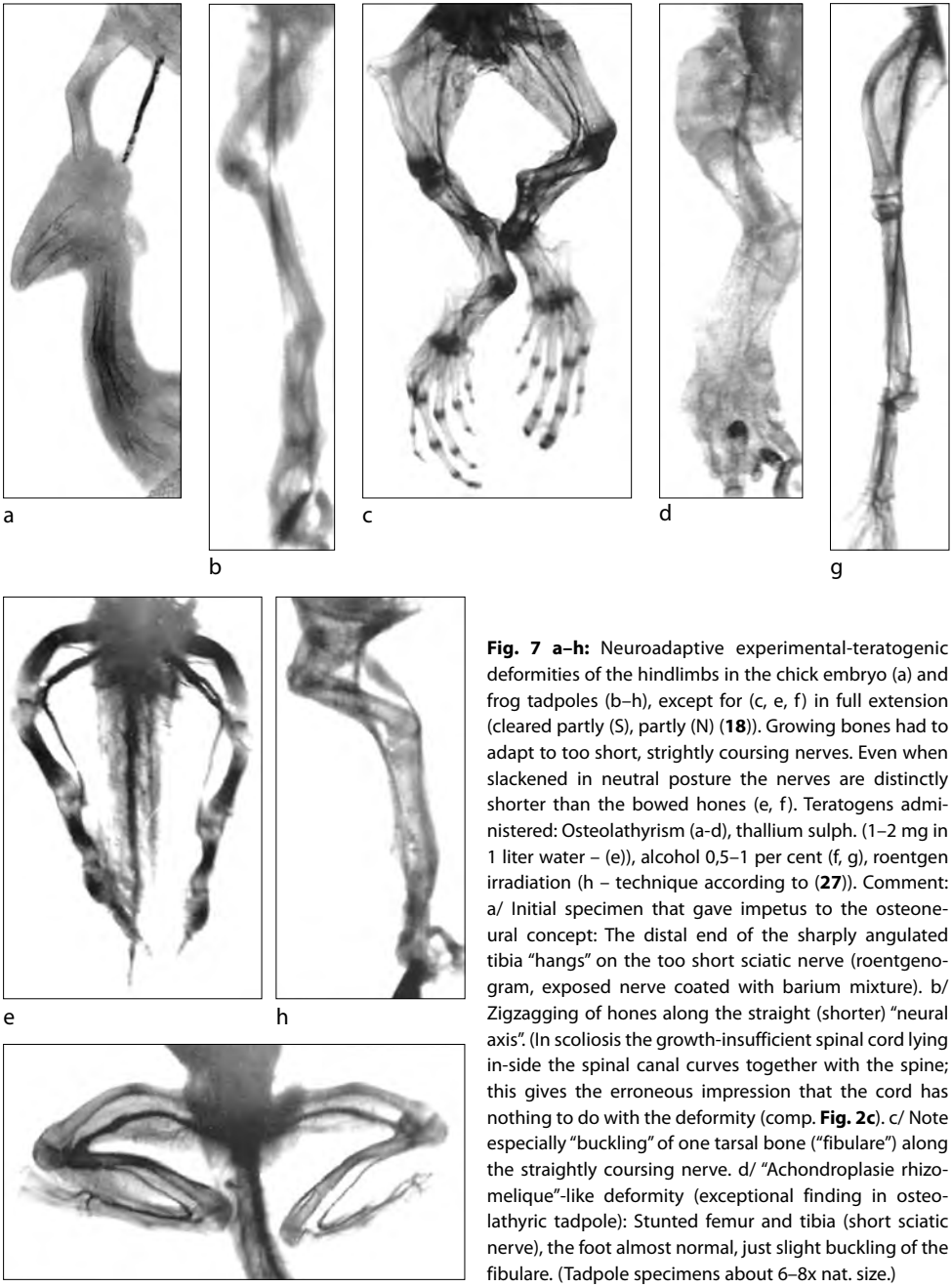
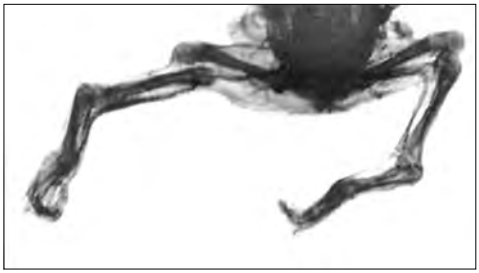


Fig. 7 a–h: Neuroadaptive experimental-teratogenic deformities of the hindlimbs in the chick embryo (a) and frog tadpoles (b–h), except for (c, e, f) in full extension (cleared partly (S), partly (N) (**18**)). Growing bones had to adapt to too short, strightly coursing nerves. Even when slackened in neutral posture the nerves are distinctly shorter than the bowed hones (e, f). Teratogens administered: Osteolathyrism (a-d), thallium sulph. (1–2 mg in 1 liter water – (e)), alcohol 0,5–1 per cent (f, g), roentgen irradiation (h – technique according to (**27**)). Comment: a/ Initial specimen that gave impetus to the osteoneural concept: The distal end of the sharply angulated tibia "hangs" on the too short sciatic nerve (roentgenogram, exposed nerve coated with barium mixture). b/ Zigzagging of hones along the straight (shorter) "neural axis". (In scoliosis the growth-insufficient spinal cord lying in-side the spinal canal curves together with the spine; this gives the erroneous impression that the cord has nothing to do with the deformity (comp. **Fig. 2c**). c/ Note especially "buckling" of one tarsal bone ("fibulare") along the straightly coursing nerve. d/ "Achondroplasie rhizomelique"-like deformity (exceptional finding in osteolathyric tadpole): Stunted femur and tibia (short sciatic nerve), the foot almost normal, just slight buckling of the fibulare. (Tadpole specimens about 6–8x nat. size.)



a

b

Fig. 8 a, b: Neuroadaptive dislocation at the knee in an osteolathyric tadpole: The dislocated tibia "hangs" on the too short sciatic nerve (a). In full extension (b – another animal) the bones, instead of zigzagging like in **Fig. 7h**, have "shifted over" with their ends along the too short "neural axis". Note also curled toes in (a). (Dislocation of the same nature may be brought about also by cholinomimetics (**21**). Comp. also **Fig. 13b**.)

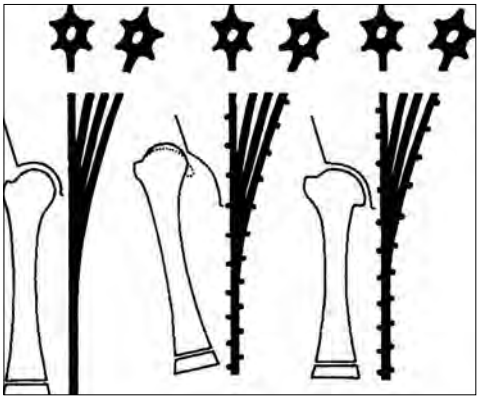


Fig. 9: Diagram of the same pathomechanism of congenital dislocation of the hip and of Perthes' disease, viz., skeletal response to growth impairment of the lumbosacral plexus. The causative exaggerated osteoneural growth differential sets in slowly in the former, more acutely in the latter instance (due probably to a too rapid growth spurt of the femur (**24**)).

radiation (to quote just a few) are accompanied by straightly coursing nervous trunks (**Fig. 7–9**). This finding proves at the purely macromorphological level (i.e. without knowledge of any histobiological details) that nerves have grown less in length as compared with bones in the course of limb development. Teratogenic dislocation means "shifting over" of bone ends otherwise normal along the too short nervous trunk(s).

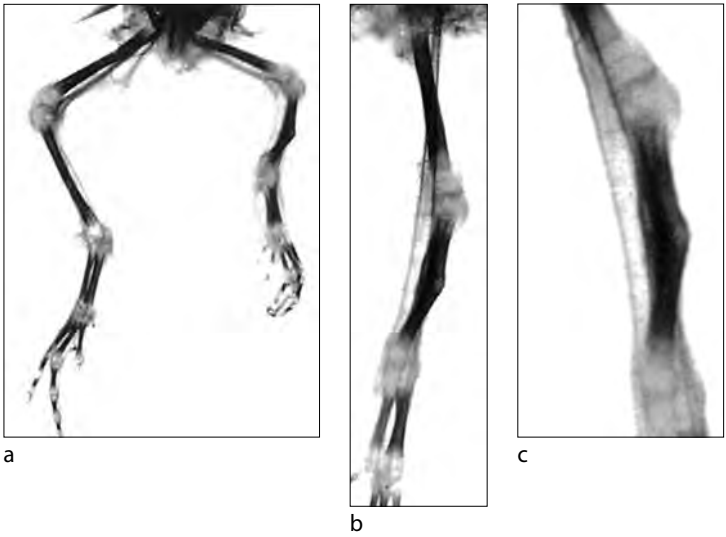


Fig. 10–18: Gross osteoneural (dysplastic) findings in postamputation regenerating hindlimb skeleton in frogs (common frog, toad, tree frog).

Fig. 10 a–c: Buckling of one compound of tibiofibula along the straightly coursing nerve (a), full extension (b), detail (c).

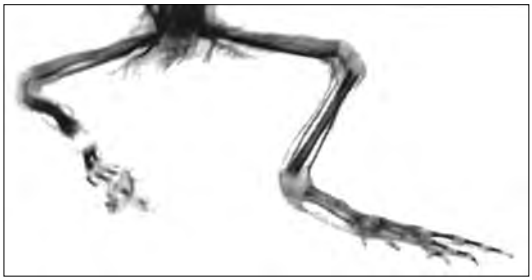
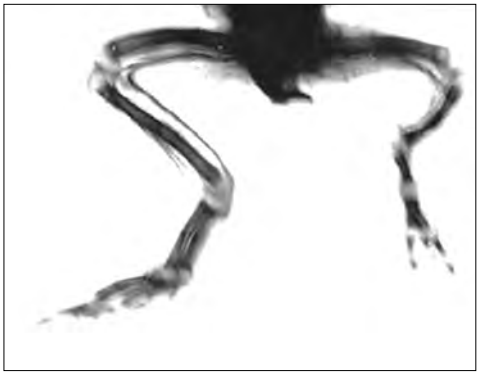


Fig. 11: Hypoplasia of the regenerating skeleton at left, oligodactylia. Dysplastic shortening, thickening and bowing of the tibia.

There is hardly any room left for doubt that clinical skeletal "dysplasias" characterized by dwarfing "from below" and reproduced in the model experiment are related to the same neuroadaptive mechanism though the causative inhibitor of neural growth is not so clearly defined. Elusive endogenous and often hereditarily transmitted disturbance of axonal growth appears to be primarily involved in these developmental disorders of the skeleton giving the seemingly clear-cut but misleading impression of some primary, damage of the bone growth proper. Histological abnormalities found in dysplastic bones reflect, in all probability, the "effort" and "inevitable task" of the growing bone to find place, to "accomodate" on the shorter space available along and within the too short nervous skeleton. In this respect skeletal dysplasias represent deeply purposeful transformations of skeletal



a

b

c

Fig. 12 a-c: Hypoplasia and zigzag arrangement (a), full extension ap view (b), lateral view (c). Oligodactylia, tarsal fusion, dysplastic thickening of the femur.

a

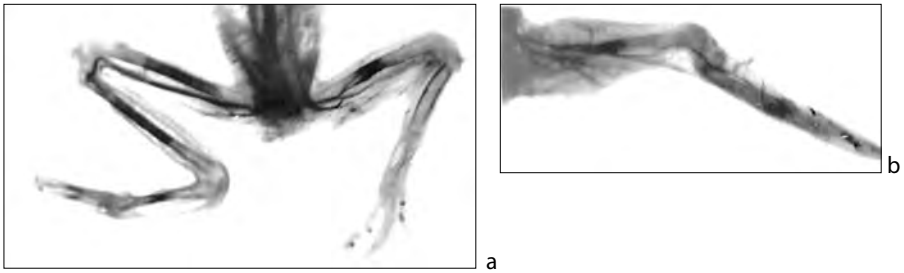
b

Fig. 13 a, b: Abnormal joint posture, a frequent finding in regenerating skeleton. In full extension (b) subluxation at the knee, viz., partial "shifting over" of bone ends along the somewhat shorter nerve (toad tadpole).

a

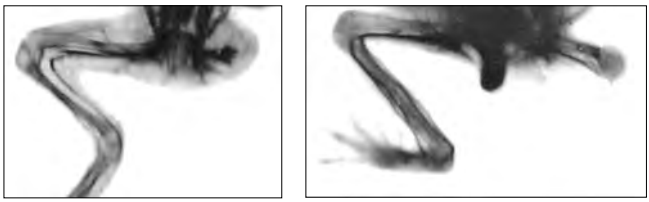
b

Fig. 14 a, b: Another finding of hypoplasia and "contracture" of the foot regenerated, the too short nerve courses arch-like in the concavity of the bony angle. In forced extension (b) the nerve, though still slightly arched, is the neurobiological "limited" of further extension (comp. **Fig. 19b**) (tree frog tadpole).



a b

Fig. 15 a, b: After bilateral amputation of the limb bud, note almost complete regeneration at left (though distal hypoplasia is evident), clear-cut hypoplasia at right. Impairment of ossification, more pronounced at right, with "anosteogenesis" in the distal portion of the limb. In full extension (b) subluxation at the knee with femoro-tibial deformity identical with that noticeable e.g. in osteolathyrism (**Fig. 7b**).



a b

Fig. 16 a, b: Club-like terminal expansion of the amputated femur (neuroadaptively bowed in (b)) looking like "stasis" of bone growth not "permitted" (owing to lack of neural regenerative growth) to extend in length (comp. Goss (**9**), his Fig. 68).

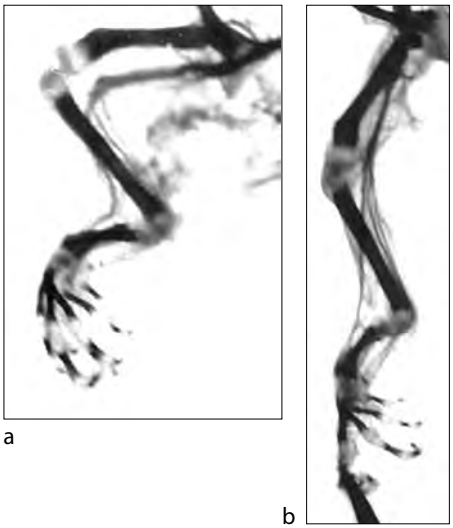
shape aimed at preservation of indispensable "unloading" of the nervous structures. Would the bones continue with their straightforward growth in length irrespective of impaired neural growth, stretch of nerves would ensue with neurological symptoms. Life quality of the involved subject would be much more seriously affected by impaired neural functions than it is the case by neuroadaptive bone deformity.

Osteolathyrism – a variety of neurolathyrism

Osteolathyric findings presented to buttress the advocated concept may throw doubt on it since osleolathyrogens are held for clear-cut bone-seeking factors believed lo elicit skeletal deformities by some direct effect upon the growing bone proper, above all by a disturbance of cross-linking of collagen. The decreased resistance of bones to mechanical stress would then result in deformities. Osteolathyrogens are patent respiratory inhibitors, however, so that vulnerable neural growth will be in the first place interfered with by them. Osteolathyrism thus appears to be just a variety of neurolathyrism: The latter interferes with neural functions, the former does this with neural growth. Hence, osteolathyrogens are nothing but a special group of teratogens producing the same "neuro-

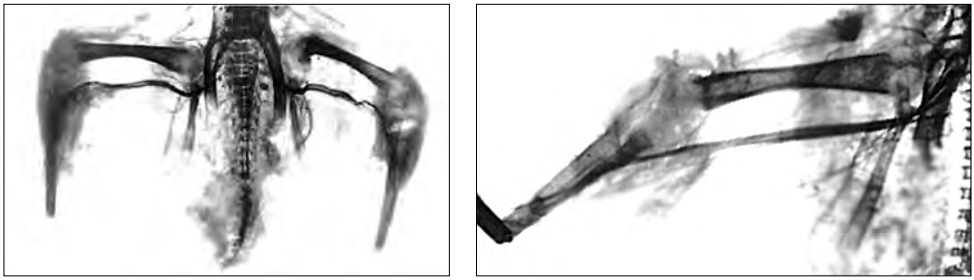
a b c

Fig. 17 a–c: Outer appearance of regenerated hindlimbs after bilateral (a) and unilateral (b, c) amputation.



a b

Fig. 18 a, b: Regeneration in combination with feeding osteolathyric diet in neutral posture (a) and in full extension (b) shows accentuated zigzagging of bones along the too short "neural axis".



a b

Fig. 19 a, b: Thallium-induced aplasia of the foot in a 25-day duck embryo (0,6 mg thallium nitrate into the yolk sac on the 4th day of incubation). Note also the limiting effect of the nerve upon the degree of extension at the knee in fully stretched limb b).

adaptive" skeletal deformities like many other "skeletal" teratogens of entirely different nature. By lathyric "weakening" of bones their neuroadaptive transformations are, as a matter of fact, facilitated.

Rachitic deformities of the limb bones deserve similar consideration. They seem to result simply from reduced mechanical resistibility of the rachitic skeleton. In the light of the critical role played by calcium in axonal growth it seems more likely that rachitic disturbance of calcium metabolism involves primarily the neural growth with associated neuroadaptive deformities of the bony skeleton the ossification process of which is naturally co-involved. Shortening and buckling of limb bones in osteogenesis imperfecta (above all of tibiae) is mostly so bilaterally regular and symmetrical that one is reluctant to interpret them as mere remnants of previous fractures. A primary "caleiogenic" disturbance of neural growth seems to offer a more plausible explanation (**23**).

Dysplastic features of the regenerating limb skeleton in frogs

The presented concept led the author to inquiry into the gross features of regenerating hindlimb skeleton following early amputation in frogs (common frogs, tree frogs, toads). Investigative efforts in this field are concentrated for the most part on histobiology of the regeneration blastema. Basic idea of author's experimentation emanated from presumption that regenerative growth of the nervous skeleton should be slower than that of bones so that osteoneural situation similar to that produced by skeletal teratogens should ensue. Following "neuroadaptive" features of the regenerating skeleton have been encountered (**Fig. 10–18**): More or less pronounced hypoplasia of bones (with coinvolvement of the soft parts), frequently with oligo- and hypoclactylia has been found without exception. Occasional failure to regenerate may be looked upon as excessive degree of hypoplasia.

While hypoplasia mirrors approximately equal impairment of bony and neural regenerative growth, osteoneural growth disproportion may occasionally take place resulting in "neuroadaptive" deformities such as achondroplasia-like shortening and thickening (**Fig. 10–12**), campomelic "buckling" (**Fig. 10**), dislocation of joints (**Fig. 13**) or abnormal joint postures ("contractures" (**Fig. 13–15**)).

What may we learn from regenerative skeletal findings?

Gross features of the regenerated limb skeleton yield a natural response to a number of enigmatic conditions in developmental skeletal pathology.

1. Congenital skeletal defects (hypoplasias, aplasias, oligodactylia, syndactylia)

Perusal of any manual of medical genetics reveals a number of hypoplastic conditions of the limb skeleton, mostly with abnormal joint postures ("contractures") identical with regenerative findings in frogs (**Fig. 17**) or with distal skeletal aplasia in a thallium-treated duck embryo (**Fig. 19**). Primary hypoplasia of the nervous skeleton with reduced or lacking "bone cavities" seems to be the common denominator of skeletal defects in man and in experimental animals. Nerves in tadpoles stain perfectly by the progressive Sudan B technique (**18**). Less perfect stainability·of regenerating nerves in a number of instances points to some neurobiological abnormality including obviously their regenerative potentiality.

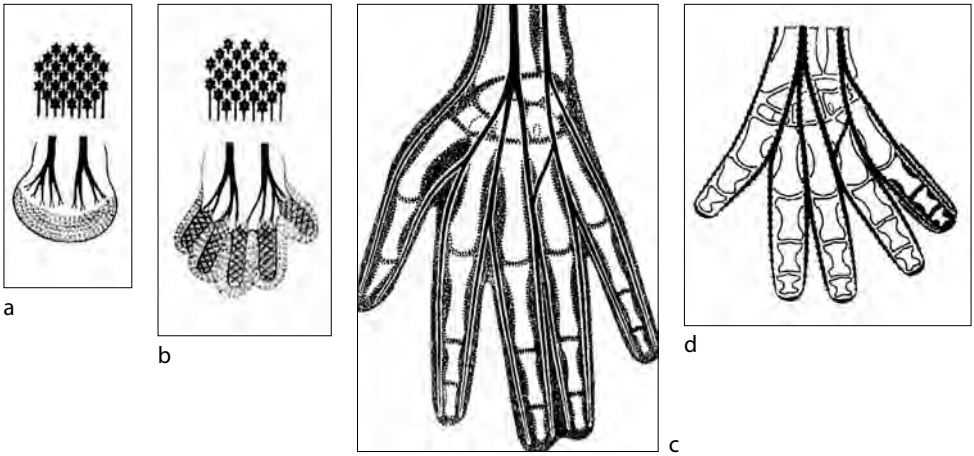


Fig. 20 a–d: The role of the nervous skeleton in digital individuation. Within the compact embryonic hand plate the individual fingers are demarcated by their own nervous skeletons. Cells lying outside are" doomed to death", above all those in prospective interdigital spaces (a, b). Syndactylia presented as resulting from faulty arrangement of the digital nervous skeleton (c). Accentuation of the physiological digital divergence associated with dysplastic neuroadaptive shortening "from below" of fingers (full extent of the nervous skeleton indicated in the 5th finger).

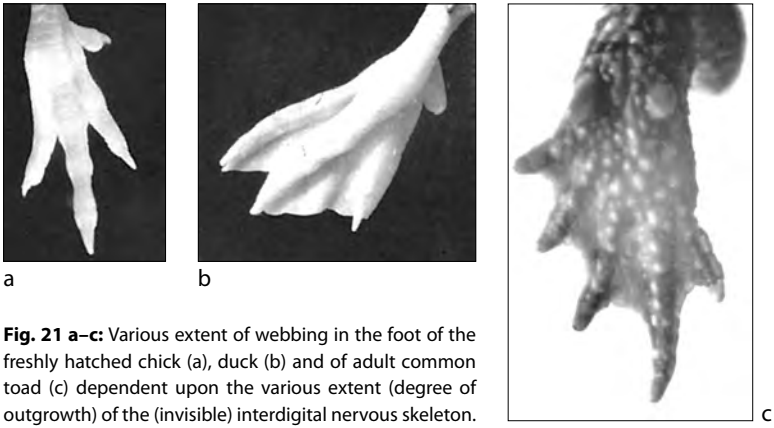


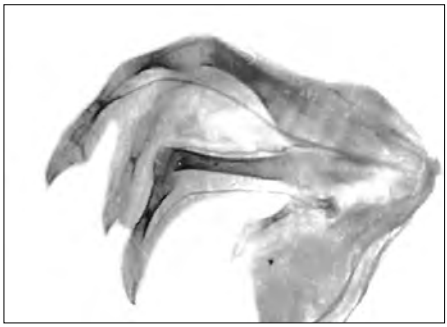
Fig. 21 a–c: Various extent of webbing in the foot of the freshly hatched chick (a), duck (b) and of adult common toad (c) dependent upon the various extent (degree of outgrowth) of the (invisible) interdigital nervous skeleton.

Abnormal numbers and fusions of digits, a frequent teratogenic finding, are related to a primary fault of the digital nervous skeleton. Within the originally compact band or foot plate individuation of fingers and toes is accomplished by installation of individual digital nervous skeletons. Cells lying outside that skeleton, above all those occupying the prospective interdigital spaces, are "doomed to death" since one-growth-type way of living is "forbidden" within the living body (**Fig. 20**). Where interdigital webbing appears purposeful in the given environment, the nervous

skeleton extends into the interdigital spaces so that the other "stuffing" tissue components remain viable (**Fig. 21**). Syndactylism in man would mean a pathological feature of that normal phylogenetic arrangement (**Fig. 20c**).

2. Joint posture, normal and contracted, osteoneurally established

Abnormal joint posture, mostly flexion "contracture" in form of "curled toes" and/or mediolateral deviations of toes is a very frequent finding in experimental and clinical teratogenesis. Normal semiflexion of fingers or toes assumed at rest may be ascribed to the physiological osteoneural


a


b

Fig. 22 a, b: Thallium-induced deformity of the foot in a duck embryo with flexion "contractures" of toes and buckling of the tarsometatarsus (cleared (S)). Note slackedness and stretch of the plantar digital nerve of the 2nd toe inflexion (a) and extension (b).

Fig. 23: Different posture of the toes in two osteolathyric chick embryos (1 mg semicarbazide hydrochloride into the yolk sac on the 5th day of incubation) with only partial stain (S) of chord-like (in geometric sense) coursing sciatic nerve. Position of the toes (including the exaggerated "hitchhiker" one in the upper specimen) should be ascribed to growth impairment of digital nerves.

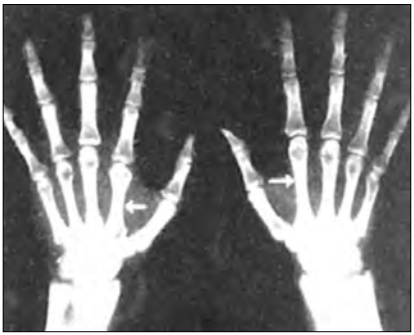


Fig. 24: Dysplastic shortening and terminal thickening of the 2nd left metacarpal bone associated with a lesion of the post-central cerebral cortex. (From (**19**) with permission of the Archives of Neurology and Psychiatry).

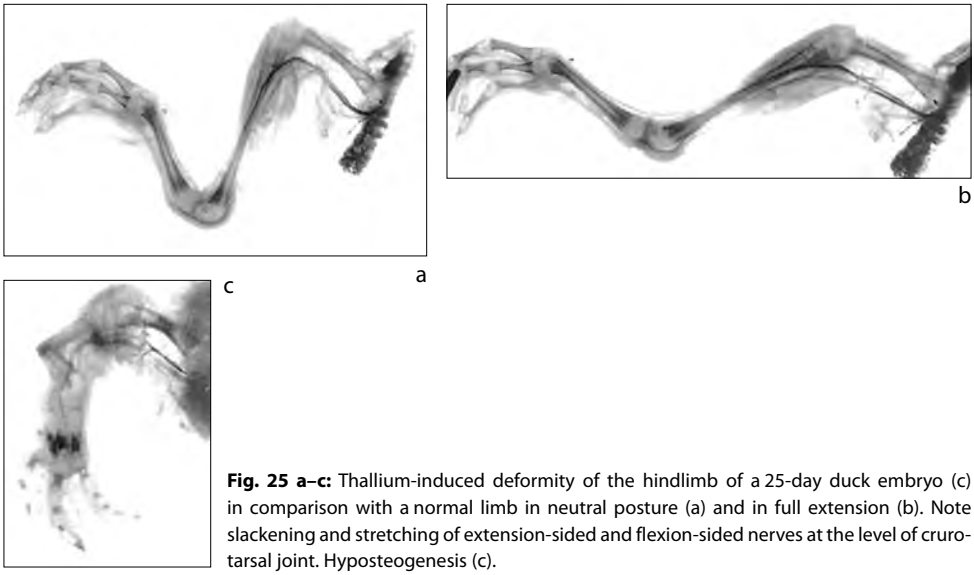


Fig. 25 a–c: Thallium-induced deformity of the hindlimb of a 25-day duck embryo (c) in comparison with a normal limb in neutral posture (a) and in full extension (b). Note slackening and stretching of extension-sided and flexion-sided nerves at the level of crurotarsal joint. Hyposteogenesis (c).

growth differential, viz., to physiological slowness of digital neural growth as compared with that of phalangae. In the neutral posture the digital nervous skeleton (above all that permeating the joint capsules) is not exposed to any tension, it is entirely "unloaded" with subjective feeling of "neural comfort". With physiological joint excursion the digital nervous skeleton is exposed to a distinct, still acceptable stretch whereas with a forced excursion, say, hyperextension the volar or plantar nerves become overstretched and pain is elicited which definitely limits joint excursion: Biomechanical limitation of joint excursion is subordinated to or governed by the neural limitation (**20**). In pathological impairment of neural growth the too short nerves promote another, abnormal resting posture looking like "contracture", viz., again a "neuroadaptive" posture where the digital nervous skeleton is unloaded (**Fig. 13,14,18, 22, 23**). It seems most likely that rheumatoid deformity of the hand has also something to do primarily with the nervous skeleton rather than with tendons and ligaments (**20**).

3. Anosteogenesis

Delayed and impaired ossification is another feature common to experimental-teratogenic and post-amputation regenerative findings (**Fig. 15, 25**) hardly to explain by "microneurotrophism". "Macro-neurotrophism" offers a natural explanation (**Fig. 26, 27**): Growth in length of a bone cannot proceed without adequate co-growth of the corresponding portion of the nervous skeleton. This implies, at the same time, dependence of the longitudinal extent of ossification accomplished within the growing bone upon adequacy of neural growth. With its inadequacy growth in length of the bone is compromised and so is also the longitudinal progress of ossification. Hyposteogenesis and anosteogenesis frequently accompanying experimental-teratogenic deformities and post-amputation regenerates doubtlessly represent neuroadaptive models of analogous human conditions (**24**).

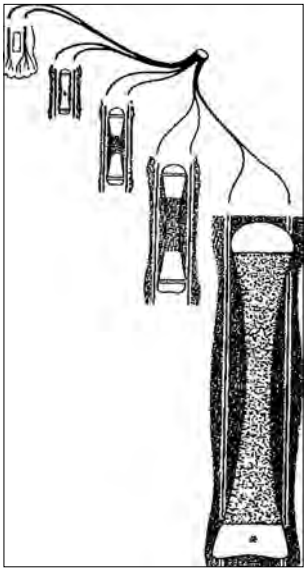


Fig. 26: Growth-dynamic diagram (from (**23**) illustrating dependence of skeletal growth (including the longitudinal extent of ossification) upon the vulnerable co-growth of the nervous skeleton. With impairment of the latter, toxic or regenerative ossification "stops" neuroadaptively at an earlier stage (comp. **Fig. 15** and **22c**).

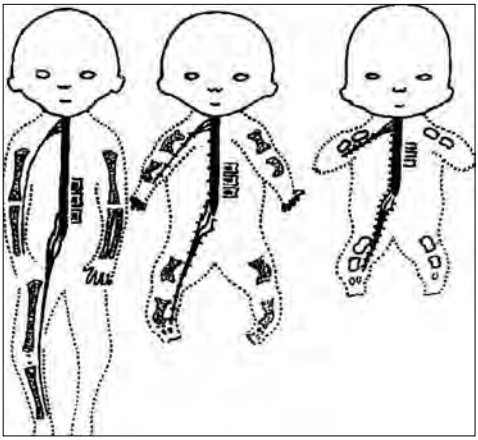
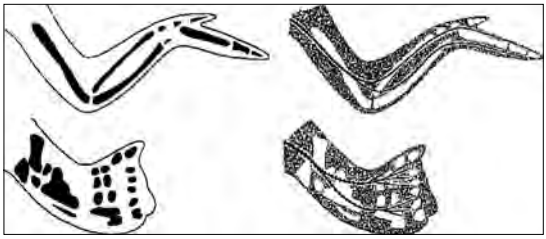


Fig. 27: A concentrated diagram of neuroadaptive transformations of the skeleton: Physiological terminal flaring and slight incurvations of long bones (a), exaggeration of those features with insufficiency of neural growth together with neuroadaptively defective ossification (b). The most severe degree of neural growth insufficiency results in anosteogenesis (c).

4. Skeletal abnormalities associated with clinico-neurological conditions in the light of teratogenic and regenerative findings

A number of chronic neurological conditions such as heredodegenerative diseases (m. Friedreich a.o.), dysraphism, cerebral palsy or post-poliomyelitic conditions are usually associated with skeletal abnormalities such as kyphoscoliosis, foot deformities, dislocation of the hip and/or hypoplasia of bones. As regards explanation the effect of paralytic or spastic muscles together with "micro-neurotrophism" are held for self-evident causative factors. In view of the dependence of axonal growth upon the machinery of the nerve cell body, impairment of that growth associated with central pathology (in addition to strikingly evident functional manifestations) is most probably the true cause of accompanying gross skeletal deformities and defects.

A remarkable finding by Penfield and Robertson (**19**) deserves mention in this connection, viz., "dysplastic" shortening and terminal thickening of the first metacarpal bone accounting for shortening of the index finger in a patient with a lesion of the postcentral cerebral cortex (**Fig. 24**). Central lesion has led obviously to growth impairment of the nervous skeleton in the target areas with



a

b

Fig. 28 a, b: Role of the nervous skeleton in the production of skeletal defects in the wing of telpid2 mutant of the chick (bones redrawn according to Goetinck and Abbot (**7**)). Abnormal shortness of the main nervous trunks with "crowding" of bones along them (and within the hypoplastic nervous skeleton), "reciprocal" (term see in (**23**)) hyperplasia of the digital nervous skeleton resulted in polydactylia (below, norm above) (a). One may conclude by interpolation that a still more severe disturbance of neural growth would result in phocomelia, b – accidental spontaneous finding from a pond near Brno.

selective accentuation in the area of the 1st metacarpal. Reduced extent of the nervous skeleton is clinically manifest in correspondingly reduced extent of the "stuffing" tissues, viz., in hypoplasia of the left upper limb and left thoracic wall and in shortening of the left index finger (reading of the original report is warmly recommended (**19**)).

"Projection" of a central lesion into hypoplasia of the corresponding bodily part and reference to **Fig. 3** should suggest that undersized body sometimes associated with microcephaly (**8, 11**) and frequently accompanying dysplastic conditions, clinical as well as experimental, might be related to a primary hypoplasia of the peripheral nervous skeleton which offers only limited amount of space within its meshes for proliferation of non-nervous tissues.

Craniofacium – another site of relative osteoneural growth effects

1. Cranial base

Basicranium is another object of purely osteological, "one-growth-type" research efforts. The profound increase of sagittal and transversal diameters of the base between the embryonic stage and adulthood depends, however, upon adequate increase of the brain size, viz., increase of interdistances between the cranial nerves piercing the base. Blechschmidt (**3**) emphasized that cranial nerves do not pass through preformed foramina since they become established by accumulation of skeletogenic tissue around the individual nervous trunks (Tondury's (**30**). Comparison "enclosed as though by lava" concerning the "neuroenveloping" function of the embryonic vertebral column, is most telling (also in this instance). In the light of neuroadaptive findings in the limbs, "depressed"

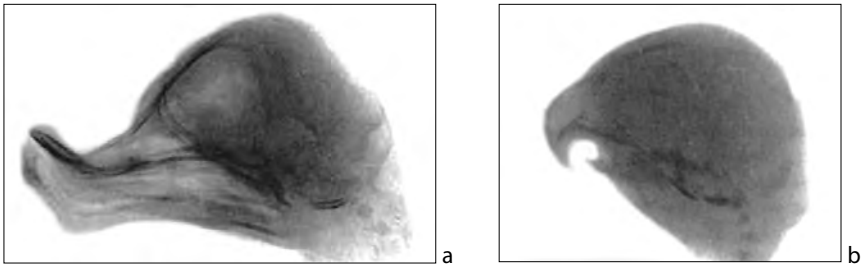


Fig. 29 a, b: Common experimental-teratogenic deformities of the beak in osteolathyrism (roentgenograms): Angulation in the duck (a) and parrot-beak in the chick (b – 1,5x nat. size).

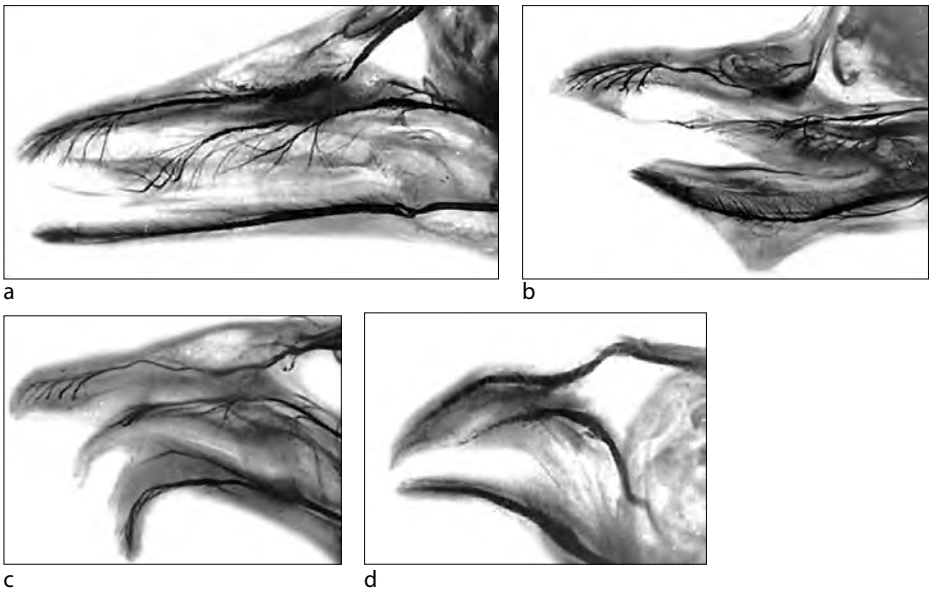


Fig. 30 a–d: Neuroadaptive pathomechanism of beak deformities in duck embryos (cleared (s)): Norm (a); chin-like appearance of the lower beak angulated along the too short nerve (b); eversion of the lower beak, the causative role of the growth insufficient nerve is reflected in its caudally eccentric course (c); severe thallium-induced growth impairment of the facial nervous skeleton with resulting facial hypoplasia (d). Not unlike in **Fig. 28b**, a still more severe depression or neural growth would result in excessive hypognathia (comp. **Fig. 29b**) or agnathia. (cca 2x nat. size).

bridge of the nose (i. e. shortening of the anterior fossa of the cranial base) so characteristic for a number of dysplastic conditions, should be related to growth impairment of the corresponding neural components, above all of fila olfactoria.

2. Orofacium

The host of most variable degrees of facial (maxillo-mandibular) hypoplasia associated with all possible developmental disorders of the skeleton or of the brain should be related to the primary, experimentally reproducible growth impairment of the facial nervous skeleton (**Fig. 29, 30**). Slowing down of growth of the viscerocranium following selective irradiation of the neurocranium (**5**) can be readily explained by slowing down of growth of the facial nervous skeleton due to radiation injury of its intracranial centers. Ionizing radiation is a potent skeletal teratogen capable of producing, together with other teratogens, neuroadaptive deformities of the limb skeleton (**21, 27**) (**Fig. 7h**).

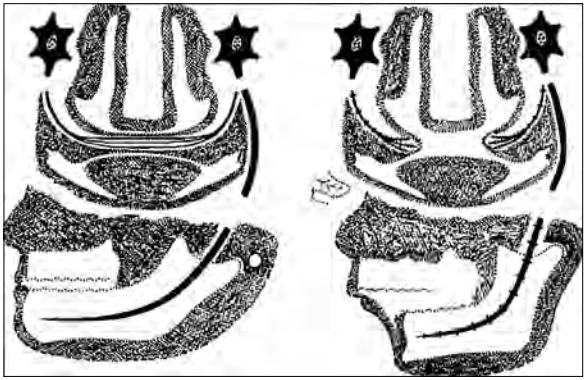


Fig. 31: Cleft palate due to growth insufficiency of the palatal nervous skeleton in Pierre-Robin syndrome associated with micro-retrognathia, i.e. with a slight dorsal neuroadaptive subluxation of the mandible (impinging upon the external auditory meatus) due to growth slowness of the mandibular nerve.

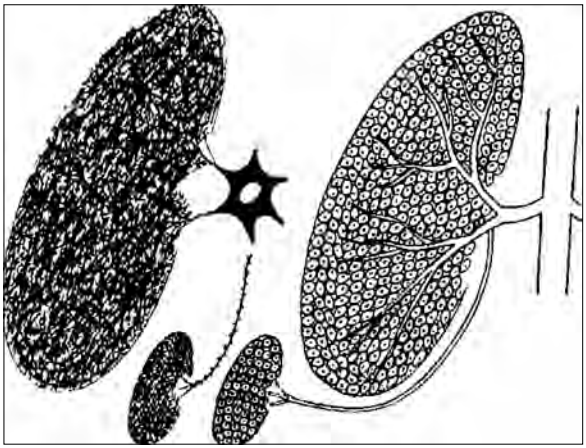


Fig. 32: Hypoplasia of the kidney, currently considered under the viewpoint of its cellular composition and blood supply (right), related to the primary hypoplasia of its very rich nervous skeleton (left).

3. Cleft palate

A very frequent defect, isolated or accompanying various malformation syndromes, fits well with the neuroadaptive mechanism. By growth in-sufficiency of the palatal nervous skeleton the palatal shelves, otherwise entirely normal, are hindered from adequate extension towards the midline (**Fig. 31**). Palatal clefting finds its unexpected counterpart in the above mentioned individuation of digits from the compact embryonic hand or foot plate. Individuation of digits would learn what underlies palatal clefting, syndactylism would pattern "synshelvism" in normal development of the palate (**Fig. 20**).

DISCUSSION

The presented argumentation and experimental findings seem to warrant the following conclusions:

1. The universal belief in passivity of neural growth roots in the early embryonic period when growing nervous fibres seem to be "attracted" by cells and organs to be innervated, viz., the impression is evoked of subordination of neural growth to that of non-nervous tissues in the sense "We, cells, have established ourselves here so that you, nervous substance, are obliged to grow out in our direction for the sake of innervation!". Growth of a nervous fibre is, however, a highly active process aimed, in addition to innervation, at maintenance of non-nervous cells within the confines of the nervous skeleton. It is rather the nervous substance which "holds the speech" in the sense "You, cells, have established yourselves there? This cannot happen without me, it is imperative to enclose you into the feltwork of nervous skeleton produced by me!". Author's approach is based upon the latter interpretation which fits much better with the spirit of neurobiology than the former.

2. Continued proliferation of denervated or explanted tissues (including primordial bone) seems to point to a far reaching independence upon the nervous system. Denervation and explantation are, however, gross artifacts, within the intact living body the existence of tissues, including the bones, is strictly confined to the two-growth-types complex, viz., they cannot and do not exist outside the nervous skeleton. The elusive aspect of explantation in respect to the nervous system may be illustrated as follows: Continued normality of the clog released from the lead does by no means justify the inference of independence of the animal upon the lead. It has an important limiting effect upon the animal so far it is lied on it, the untied clog escapes that effect. Nervous trunks, twigs and fibres of the nervous skeleton represent, as a matter of fact, innumerable "leads" "curbing" the developing nonnervous tissues.

Strenuous and ingenious efforts have been devoted lo trials to elucidate the role of the nervous system in normal and pathological skeletal development. Untiring endeavours by, among others, McBricle and McCredie (**15, 16**), most prominent pioneers in this field, based on "microneurotrophic" approach to thalidomide disaster, have aroused heavy objections based on "denervation" and "dog-released-from-the-lead" type of argumentation. Their findings of abnormal nerve cells in the spinal

ganglia of thalidomide subjects suggest, however, that axonal growth, rather than functions, has been interfered with by the toxic drug with the corresponding "macroneurotrophic" effect upon the skeleton. Defects of individual bones, partial or total, characteristic for thalidomide intoxication appear to result from lack of "cavities" within the hypoplastic nervous skeleton. It seems most likely that factors capable to produce peripheral neuropathy (with insulin, at the head well-known skeletal teratogen) are prone to interfere also with neural growth.

Macroneurotrophism yields also an acceptable explanation of malformations of other organs than bones, for instance aplasia of the kidney, not quite rarely associated with congenital defects of the skeleton. "Relative to its size the kidney receives a more profuse and widespread nerve supply than almost any other viscus". The quotation from (**17**), translated into terms of neural growth should point to a high vulnerability of the growing neural component of the developing organ. Hence, renal hypoplasia and aplasia should be related to the inadequate extent or absence of the renal nervous skeleton (**Fig. 32**).

3. The term "congenital malformation" seems to imply automatically that its pathomechanism cannot be searched for but at the very beginnings of development, for instance in the early bone primordium, in some derangement of the intricate cellular events taking place within that primordium, at first without participation of the nervous system. Naturally, a gross experimental injury (say, a mechanical one) of a primordial organ can jolt the developmental process out from its accustomed groove. Nevertheless, the truly critical situation sets in with ingrowth of nerves into the limb bud (or any other organ), viz., with the shift of the so far "one-growth-type" process to a "two-growth-types" one. From that moment on two entirely different growth types proceed side-by-side within the developing limb (or any other organ) at a different energetic level. Contemporaneous research efforts are based on the assumption that following correct installation of the initial morphogenetic processes further development of the spine or limbs proceeds automatically by unfolding of the initially established primordia. Interrelation of the two growth types and its disturbances in the course of development are responsible, however, for gross skeletal deformities. In man the causative exaggeration of the osteoneural growth differential may start working as late as during infancy and childhood, e.g. in idiopathic scoliosis. Should some fault really arise at the very beginning then it would be a genetically established disturbance of neural growth which, not immediately but in the course of further development will be manifested in neuroadaptive skeletal deformity.

4. The latter point concerns successful efforts of osteogenetics to identify a number of genes responsible for various dysplastic conditions of the skeleton. The cardinal question remains unanswered, however, what is the dysplaslic bone shortened, thickened, buckled or dislocated. Grüneberg's statement (**10**) is still true that "genes influence the bones in some round-about way" which consists, in all probability, in "macroneurotrophism". Irrespective of the definition of the morphogenetic system (26) it cannot escape the closest link with the "network" of the nervous skeleton. The basic triad of molecular biology is DNA-RNA-protein (**13**). Correct coding and structure of the latter is indispensable for normal course of both skeletogenesis and neurogenesis. Investigation of genes "responsible" for skeletal dysplasias as to their role in neurogenesis might prove more fruitful for explanation of skeletal malformations than their relation to the growing skeleton proper.

5. Last but not least it should be emphasized that the intricate phenomena of functional adaptation of bone associated with its manifold functions and stresses it is exposed to and realized seemingly without participation of the nervous system should by no means be questioned. What we learn from the osteoneural concept is, however, that the adaptive changes of the bony skeleton should be "approved" by and not in conflict with the neurobiology of the nervous skeleton, periosteal and endosteal. Should such a conflict set in, pain would result therefrom.

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Experimentation in tadpoles has been approved by the Ethical Committee of the University Hospital, Jihlavská 20, Brno-Bohunice on June 7, 1994.

REFERENCES

1. BENESOVA, O., PETOVA, J., VINSOVA N.: Perinatal distress and brain development. Prague, Avicenum 1981.
2. BENESOVA, O., PETOVA,J., PAVLIK, A.: Brain mal-development and drugs. Prague, Avicenum 1984.
3. BLECHSCHMIDT, M.: The biokinetics of the basicranium. In: Symposium on development of the basicranium (pp. 44–55). Ed. J. F. Bosma. National Institutes of Health, Bethesda 1976.
4. DONALDSON, H.H.: The nervous skeleton. Trans. Amer. neurol. Ass., 63, 1937, pp. 1–9.
5. ENGSTROM, H., ENGSTROM, C., HOLLENDER, L. et al.: Effect of local irradiation on cranial skeletal growth sites in the rat. In: Normal and abnormal bone growth. Basic and clinical research (pp. 109–124). Progress in clinical and biological research, vol. 187. Eds. Dixon A.D., B.G. Sarnat. New York, Liss 1985.
6. FREIHOFER, W.C., COMPAGNO, L.J.V.: Additional notes on the use of the Sihler technigue of staining nerves of small, whole specimens of fishes and other vertebrates. Copeia, 1977, No. 3, pp. 587–588.
7. GOETINCK, P.F., ABBOTT, U.K: Studies on limb morphogenesis. I. Experiments with the polydactylous mutant, talpid2.J.exp.Zool., 155, 1964, pp. 161–170.
8. GORDON, R.R., COOKE, P.: Ring-I chromosome and microcephalic dwarfism. Lancet, 2, 1964, pp. 1212–1213.
9. GOSS, RJ.: Principles of regeneration. New York and London, Academic Press 1969.
10. GRUNEBERG, H.: How do genes affect the skeleton? In: New approaches to the evaluation of abnormal embryonic development (pp. 354–359). Eds. Nubert D., HJ. Merker. Stuttgart. Thieme 1975.
11. HERSH, J.H., JOYCE, M.R., SPRANGER, J. et al.: Microcephalic osteodysplastic dysplasia. Amer. J. med. Genet., 51, 1994, pp. 194–199.
12. JURAND, A.: Malformations of the central nervous system induced by neurotropic drugs in mouse embryos. Develop. Growth Differ., 22, 1980, pp. 61–78.
13. KRAML, J.: Concerning the problem of origin of life: prebiotic synthesis of coenzyme? (In Czech) Vesmír, 74, 1995, pp. 371–372.

14. MAROTEAUX, P., COHEN-SOLAL, L., BONAVENTURE, J. et al.: Syndromes letaux avec gracilité du squelette. Arch. franc. Pediat., 45, 1988, pp. 477–481.
15. MCBRIDE, W.G.: Fetal nerve cell degeneration produced by thalidomide in rabbits. Teratology, 10, 1974, pp. 283–292.
16. MCCREDIE, J.: Embryonic neuropathy, a hypothesis of neural crest injury as the pathogenesis of congenital malformations. Med. J. Aust., 1, 1974, pp. 159–163.
17. MITCHELL, G.A.G.: The nerve supply of the kidneys. Acta anat., 10, 1950, pp. 1–37.
18. NISHIKAWA, K.C.: Staining amphibian peripheral nerves with Sudan black B: Progressive vs. regressive methods. Copeia, 1987 (2), pp. 489-491.
19. PENFIELD, W., ROBERTSON, J.S.M.: Growth asymmetry due to lesions of the postcentral cerebral cortex. Arch. Neurol. Psychiat., 50, 1943, pp. 405–430.
20. ROTH, M.: Die Neuromorphologie der Gelenk-bewegungen. Gegeng. morph. Jb., 126, 1980, pp. 900-948.
21. ROTH, M.: Neurovertebral and osteoneural growth realations. Acta Facult. Med. Univ. Brunensis, Brno 1985.
22. ROTH, M.: Neurovertebral developmental morphodynamics and degeneration of the disc: a suggestion. Neurology in Europe I. (pp. 632–636). Eds. Bartko, D., Gerstenbrad, F. London, Libbey 1989.
23. ROTH, M.: Macroneurotrophism in the development of the vertebrate skeleton. Anthropologie (Brno), 32, 1994, pp. 1–24.
24. ROTH, M.: Bone dysplasias - neuroadaptive deformities characterized by "shortening from below".(In Czech) Čes. Radiol., 48, 1994, pp. 215–232.
25. ROTH, M.: Congenital vertebral block and degeneration of the disc: Common osteoneuroradiological interpretation. (In Czech) Čes. Radiol., in press.
26. RYCHTER, Z., JELINEK, R.: Foundations of experimental teratology. (In Czech) Praha, Avicenum 1978.
27. SCHINZ, H.R., FRITZ-NIGGLI, H.: Missibildungen adulter Krallenfrosche (Xenopus laevis Daud.) nach Rontgen-Bestrahlung im Embryonalstadium. Strahlentherapie, 94, 1954, pp. 147–151.
28. SCHUMACHER, G.-H.: Factors influencing craniofacial growth. In: Progress in clinical and biological research, vol. 187: Normal and abnormal bone growth (pp.3-22). Eds. Dixon, A.D., Sarnat, B.G. New York, Liss 1985.
29. STREETER, G.L.: Factors involved in the formation of the filum terminale. Amer.J. Anat., 25, 1919, pp. 1–11.
30. TÖNDURY , G.: Entwicklungsgeschichte und Fehlbildungen der Wirbelsaule. Stuttgart, Hippokrates-Verlag 1958.

MACRONEUROTROPHIC FEATURES OF GROWTH HORMONE EFFECTS UPON THE SPINE AND HIP

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SUMMARY

An inquiry into the problem is put forward whether or not the developmental cerebro-cranial relation between the growing brain and its bony envelope (the saucer-like shape of which is "neuroadaptively" determined by the "macroneurotrophic" effect of the brain) applies also for the analogous neurospinal relation between the spinal cord with the nerve roots and its spinal envelope. This would be in line with the statement of osteology that, in addition to biomechanics and haemopoesis, the bone tissue provides a firm protective covering of the delicate central nervous system, i.e. of the brain and of the spinal cord. Comparison of macromorphological features of quadrupedal and human vertebrae points to validity of that statement even as concerns the axial organ.

Development and growth of the vertebral column is inseparably linked with adequate co-growth of its neural content. Its growth is a highly demanding process as concerns supply with energy and oxygen. Consequently, neural growth is more vulnerable than bone growth. There exists reasonably buttressed evidence that a number of developmental deformities of the spine, above all idiopathic scoliosis and Scheuermann's disease the pathomechanism of which has not been disclosed within the vertebral envelope proper, represent "neuroadaptive" response of that envelope to exaggerated slowness of spinal neural growth. The striking tendency of the two abovenamed deformities to involve the lower thoracic spine may be readily related to the fact that Th5–10 spinal cord segments are by far the longest so that their growth is more energy-consuming and more vulnerable than that of the other segments. The lower thoracic spinal cord is thus prone to undue growth slowness which becomes manifest in neuroadaptive deformity of the growing vertebral envelope.

Osteoneural developmental interrelation applies also to the limbs. Congenital "dysplasia" of the hip, Perthes' disease and slipped femoral capital epiphysis may be interpreted as various types of neuroadaptive response of the growing femur to growth insufficiency of the lumbosacral plexus.

Degenerative conditions of the skeleton such as degeneration of the intervertebral disc, arthrosis and spondylosis may be related to involutional atrophogenic shortening of aging spinal and

peripheral nervous structures. Even that type of neural shortening must be compensated for by neuroadaptive shortening of the bony skeleton. Degenerative narrowing (i.c. shortening) of the disc space or of the joint space (i.e. of the respective cartilages) appears to represent such a reaction to extremely slowly, in course of long years and decenniums established atrophogenic shortening of the spinal nerve roots and/or of peripheral nerves, a process parallel, in all probability, to that involving the aging brain.

Growth hormone is especially considered since by its stimulatory effect on bone growth the osteoneural length balance, viz., the length relation between bones and nerves may be disturbed. The well-known effects of growth hormone upon the spine and hip joint in acromegaly or in connection with its therapeutic administration fits well into the advocated osteoneural growth concept.

Keywords: growth hormone, macroneurotrophic effect, neuroadaptive bone deformities, osteoneural growth concept

SOUHRN

M. Roth: Makroneurotrofické aspekty působení růstového hormonu na páteř a kyčel

Předkládá se k úvaze otázka, zda vývojový vztah cerebrokraniální mezi rostoucím mozkem a jeho kostěným obalem (jehož miskovitý tvar je dán „neuroadaptivně" či „makroneurotroficky" rostoucím mozkem) neplatí i pro obdobný vztah mezi míchou s kořeny a jejím páteřním obalem. Odpovídalo by to známému osteologickému konstatování, že úlohou kostní tkáně je vedle biomechaniky a krvetvorby též vytvářet pevný ochranný obal delikátního ústředního nervového systému, tj. nejen mozku ale i míchy. Srovnání makromorfologických rysů zvířecích a lidských obratlů ukazuje na platnost této poučky i pro osový orgán. Vývoj a růst páteře je nerozlučně vázán na současný adekvátní nárůst jejího neurálního obsahu, jenž je energeticko-metabolicky a kyslíkově podstatně náročnější, a tudíž i vulnerabilnější nežli růst kostní. Lze dovodit, že řada vývojových malformací páteře, na prvém místě idiopatická skolióza a Scheuermannova „choroba", jejichž patomechanismus se marně hledá v páteřním obalu samotném, představuje „neuroadaptivní" odpověď tohoto obalu na nedostatečný, příliš zaostávající růst neurálního obsahu. Vyložená afinita uvedených deformit k dolní hrudní páteři vyplývá z okolnosti, že míšní segmenty Th5–10 jsou daleko nejdelší a tudíž růstově náročnější nežli všechny ostatní, takže v tomto úseku neurální růst nejsnáze zaostává, což se projeví neuroadaptivní deformitou rostoucího páteřního obalu.

Osteoneurální růstový vztah může platit i pro končetiny, kde z něj lze vyvodit výklad vrozené dysplazie kyčle, Perthesovy choroby či epifyzeolýzy jakožto různých typů neuroadaptivní odpovědi rostoucího femoru na růstovou nedostatečnost masivního lumbosakrálního plexu.

I degenerativní stavy kostry, tj. degeneraci meziobratlové ploténky, artrózu a spondylózu, lze vztáhnout k involučně atrofogennímu zkracování spinálních a periferních nervových struktur s pokračujícím věkem, jemuž se i dospělý skelet musí přizpůsobit „neuroadaptivním" zkrácením. „Degenerativní" zúžení (= zkrácení) disku či kloubní chrupavky končetinového kloubu představuje takovou neuroadaptivní reakci na nesmírně zvolna, v průběhu let a desetiletí nastávající atrofogenní zkracování spinálních nervových kořenů či periferních nervů, dle všeho paralelně všeobecně známého involučního procesu stárnoucího mozku.

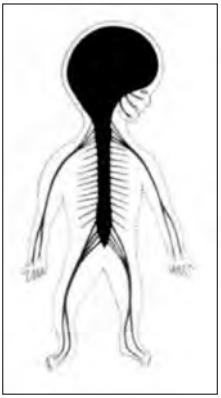
Zvláštní pozornost je věnována růstovému hormonu, který svým stimulačním vlivem na růst kostí rovněž narušuje osteoneurální rovnováhu, tj. délkový vztah mezi kostrou a nervstvem. Jeho známé působení na páteř či kyčelní kloub při akromegalii nebo během léčebného podávání zapadá do obhajovaného „ostconeurálně vztahového" pojetí.

Klíčová slova: růstový hormon, makroneurotrofické působení, neuroadaptivní deformity kostí, koncepce osteoneurálního růstu

INTRODUCTION: GROSS NEURAL GROWTH INSEPARABLY LINKED WITH GROSS SKELETAL GROWTH

In addition to its extremely intricate functions the nervous system represents the extensive type of growth consisting in sprouting of innumerably branching processes from the nerve cell body. The vertebrate body thus consists of products of not one but of two basic growth types, the cellular-divisional and the neural-extensive. Gross ("macroneurotrophic" (**27**)) interrelation of the two growth types is strikingly manifest in the neurocranial developmental events, viz., in the moulding effect of the growing brain upon the shape and size of its neurocranial bony envelope. The latter behaves "passively-neuroadaptively" in respect to the actively growing "leading" brain. In diametral contrast to the highly active, energy-demanding and vulnerable cerebral growth that of extracerebral nervous structures (both of the "spinal cord nerve root complex" (CNRC) and of peripheral nerves) is held for an essentially passive process which just follows the "towing" effect of outgrowing non-nervous tissues for the sake of "innervation". The basic idea put forward by the present author is that developing extracerebral nervous structures, spinal and peripheral, should share with the brain its growth activity and vulnerability and that they should be viewed upon as "limiters" of growth of non-nervous tissues rather than mere passive "innervation followers". Though explanted bone tissue is capable of proliferation independent upon any nervous influence, within the intact living body gross organ growth of the skeleton, axial as well as appendicular, is inseparably linked with adequate cogrowth of the respective nervous structures, i.e. of the CNRC and of peripheral nerves. With insufficiency of vulnerable neural growth that of bones cannot proceed normally in length since this would result in undue tension of nervous structures the normal condition of which is a distinct degree of slackedness ("unloading"). Preservation of that condition is the very purpose of "neuroadaptive" skeletal deformities the common feature of which is shortening as though "from below": Exaggerated slowness of neural growth hinders the skeleton, axial and/or appendicular, from growing normally in

a



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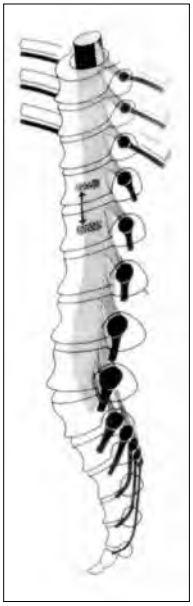

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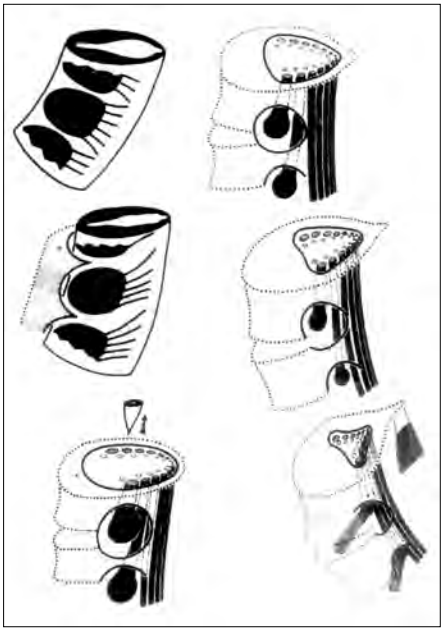
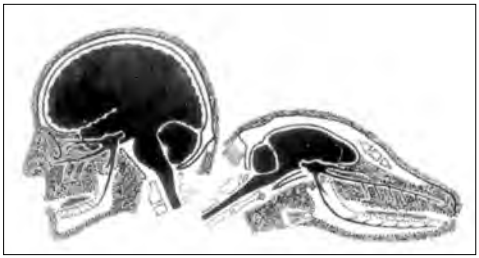


c

Fig. 1A a-e: Neuroenveloping function of the spine reflected in its gross morphology, embryonic and adult. Embryo consists for the most part of central nervous tissue (a), outgrowth of peripheral nervous system as though "at the expense" of the (relatively decreasing in size) central nervous system (b). -cl-6: Neurovertebral morphogenesis of the L4, 5 vertebrae including the "neuroadaptive" installation of lumbar lordosis. Schematic drawing c-2 shows what may be noted in (d) from Sensenig (34 – by permission of Carnegie Institution of Washington), viz., tongue-like projections of primordial vertebrogenic tissue (= primordial pedicles) into the interganglionic spaces. Spinal neural content is enveloped by the spine both transversally and longitudinally (e neurovertebral appearance of the thoracolumbosacral axial organ in an 80 mm human fetus (reconstructed according to (**36**)). Arrowed "total disc".



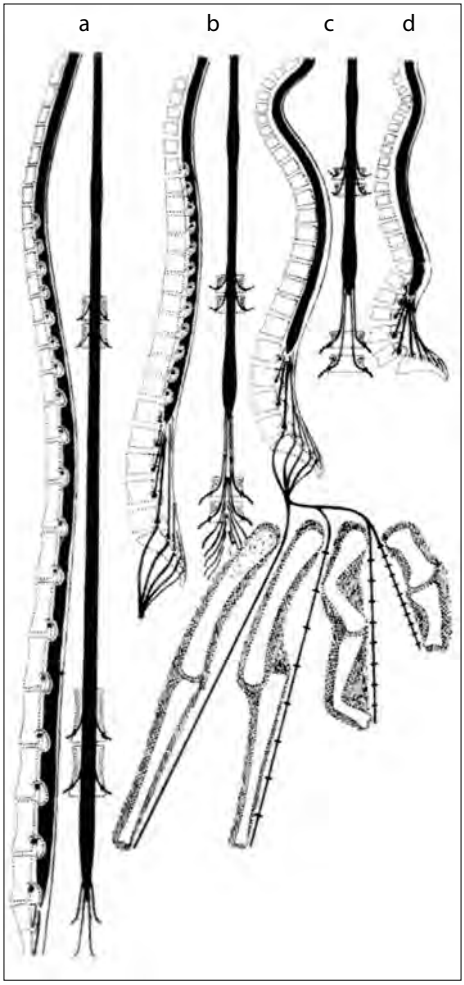


Fig. 1B: Neuroenveloping function of the spine reflected in its gross morphology, embryonic and adult.
Hominization of the spine involves primary shortening (i.e. phylogenetically decreased growth potentiality) of the spinal neural axis with "neuroadaptive" shortening of the vertebral envelope as though "from below" together with lumbosacral lordotization (a, b). Scheuermann's hyperkyphosis (c) and "dysplastic" features of the spine (d) interpreted as neuroadaptive response of the vertebral envelope to exaggerated, pathological degree of growth impairment of the spinal neural content. Analogous neuroadaptive deformities of the "shortening-from-below" type of the limb skeleton indicated (bottom right) together with the nervous skeleton (including partially also the endosteal in the proximal femur on the left) the bones are embedded within. "Reciprocity" of cerebrofacial neural growth in man and dog at the top.

distal direction. The most common types of neuroadaptive shortening are abnormal curvatures (i.e. bone ends nearer to each other), achondroplasia-like shortening and thickening (i.e. transversal dissipation of bony material hindered from normal growth in length) or dislocation (shifting over of bone ends) (**Fig. 1B**). (Detailed argumentation and experimentation see in (**28**)).

Peripheral nervous skeleton and neuroprotective mechanism

The two in the biomedical literature unknown terms must be preliminarily explained because of their profound importance in "neuroadaptive" behaviour of the bony skeleton.

1. Nervous skeleton: The factual organ extent of the peripheral nervous system

Peripheral nerves are currently schematized in form of simple branching lines. In its organ entirety, however, the peripheral nervous system represents an extremely dense, cotton-wool like (**30, 31**), ubiquitous feltwork of nervous twigs and fibers, the "nervous skeleton" (NS) (**4**) permeating

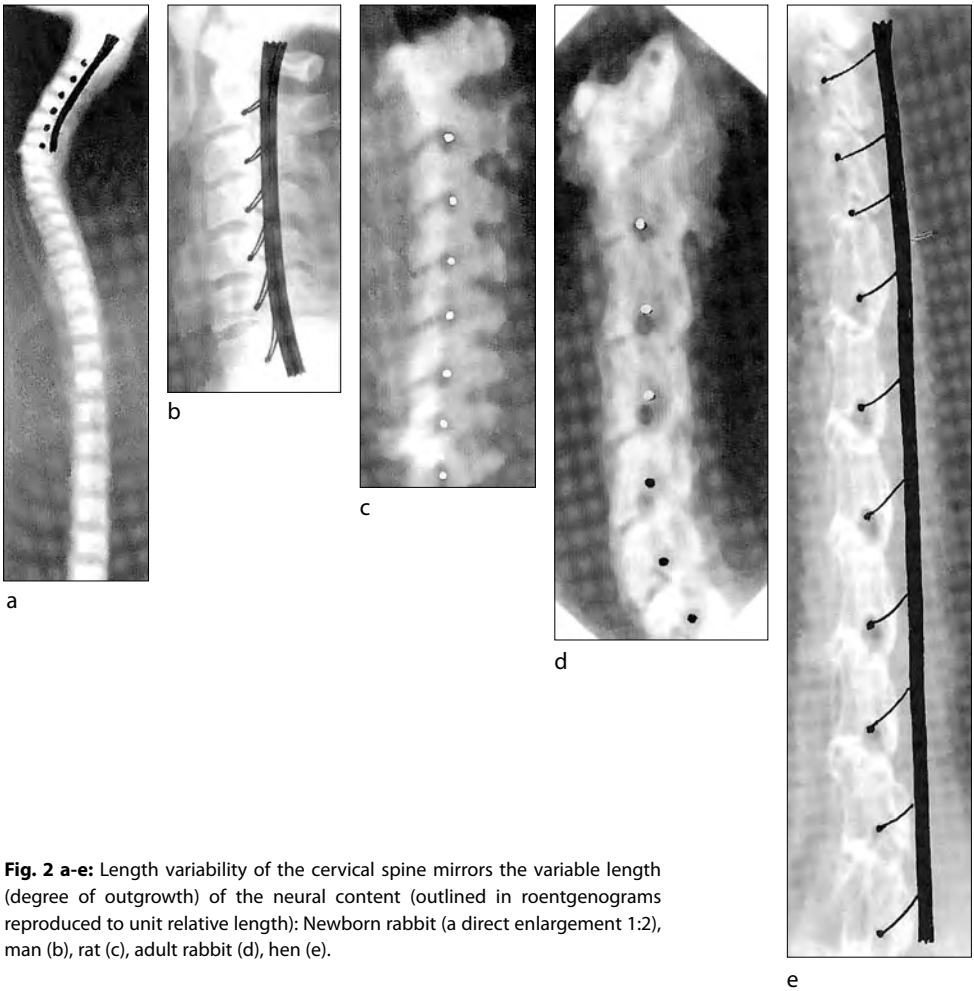


Fig. 2 a-e: Length variability of the cervical spine mirrors the variable length (degree of outgrowth) of the neural content (outlined in roentgenograms reproduced to unit relative length): Newborn rabbit (a direct enlargement 1:2), man (b), rat (c), adult rabbit (d), hen (e).

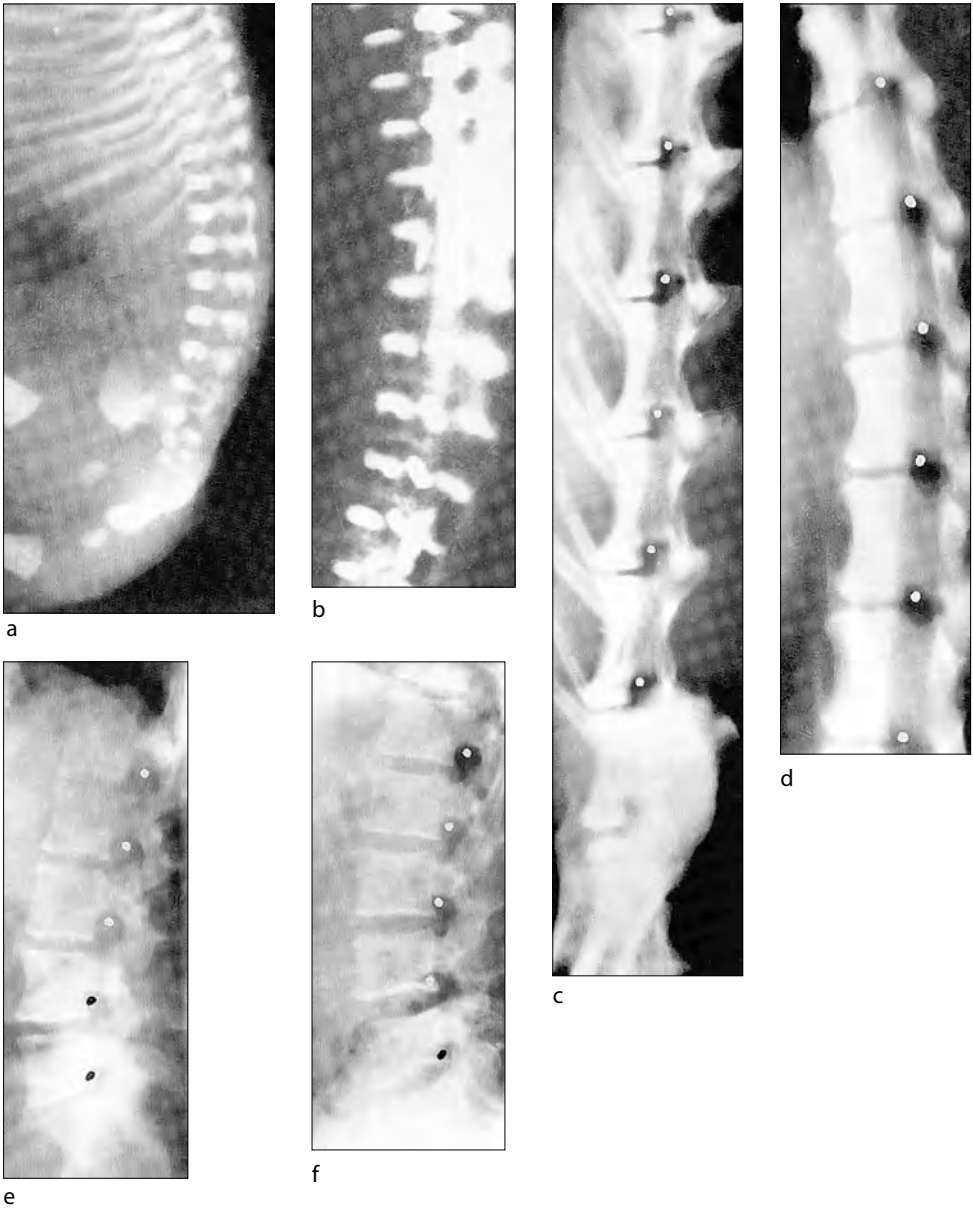


Fig. 3 a-f: Lumbar spine: 200 mm human fetus, roentgenogram (a - note the very beginnings of caudal vertebral incisura) and cleared specimen (b) showing "total disc" in the lumbar area. Rabbit (c), dog (d), man dolichospondylic (e) and normospondylic (f). Spinal ganglia indicated by white spots.

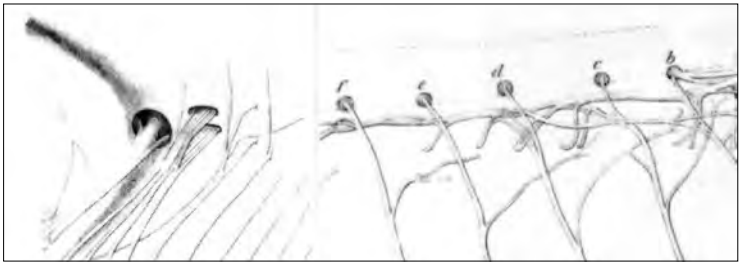
throughout the body including the surface of bones: Any individual bone is covered, in addition to the periosteum, by the feltlike "bag" of the periosteal NS and, moreover, is permeated by the "inner", endosteal NS. Limb bones as well as vertebrae may be viewed upon, without much exaggeration, as bony "casts" of the correspondingly shaped cavities within the NS. Any shape transformation of a bone or of a vertebra cannot take place without adequate cogrowth of the periosteal and endosteal NS as well as of the nearby nervous trunks, its "macro-representatives" (**Fig. 4d.9**). It is self-evident that growth of such a huge mass of nervous tissue requires a rich supply with energy and oxygen and is more vulnerable than the process of bone growth. Experimental findings point to the vulnerable neural growth as the primary target of "skeletal" teratogens (**30**).

2. Neuroprotective mechanism the indispensable osteoneural "balancer"

That is going on in the developing axial organ has been specified in the clear-cut statement by O'Rahilly and Benson (**24**): "The vertebral canal and intervertebral foramina are specially adapted to contain the structures of the central nervous system ... As the nervous system grows, vertebral column grows to accomodate it". 2. The "leading" role of the neural content in the morphogenesis of the vertebral column could be hardly more explicitly indicated. The indispensable balance of the two growing structures, the neural-enveloped and the bony-enveloping, viz., adequate "receding" "giving way" of the skeletogenic envelope to the rapidly enlarging and elongating neural content is provided for by the property of the nervous tissue to maintain the surrounding skeletogenic tissues in a "respectful" distance, probably by mediation of some metabolic product released from the neural surface to which precartilage cells react in a negative chemotaxic manner (**10**). This "neuroprotective mechanism" (NPM term coined by the present author) may be compared with the "halo" produced around a redhot wire pushed into a plate of readily melting metal. Owing to the NPM every nervous structure piercing a cartilaginous or bony structure is surrounded by a free "protective" space, due to a basic neurobiological mechanism common to all vertebrates (**Fig. 4**) including man. In this way, as a sort of "instinct of selfpreservation", the nervous tissue defends its integrity and at the same time moulds the shape of the encasing bones. Appearance of the subarachnoid space in the early embryo represents, according to all appearance, the first manifestation of the NPM arising with the first signs of stiffening in the so far of primordial vertebrogenic envelope.

Ganglioforaminal developmental interrelation

Not unlike the brain even the spinal ganglion, in addition to its intricate functions, mould the shape of its bony envelope, i.e. of the intervertebral foramen. The primordial vertebral arches are laid down in form of tongue-like projections of vertebrogenic tissue from in front into the narrow embryonic interganglion spaces (**Fig. 1A**). As concerns the subsequent development one should by no means adhere to the idea as though the ganglia were passively pushed apart by the accumulating vertebrogenic tissue since this tissue behaves passively "neuroadaptively": With craniocaudally proceeding growth in length of the axial organ the actively elongating (growing) interganglionic spaces become filled, "casted" with skeletogenic tissue. Spinal ganglia, rather than being passively pushed apart, play the role of "pacemakers" of vertebral growth since definitive length of the vertebral arch, together with that of the vertebral body, depends upon the definitive length of the interganglionic



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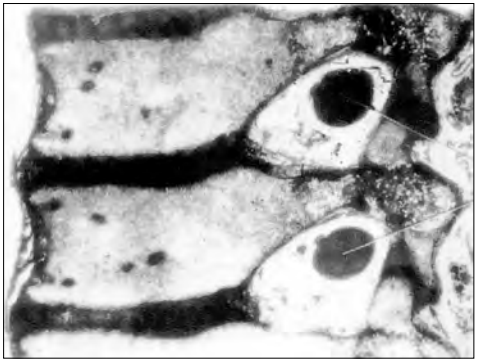

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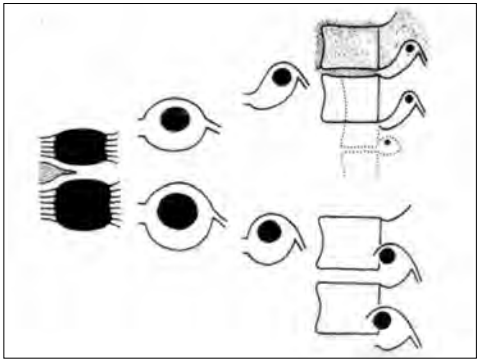

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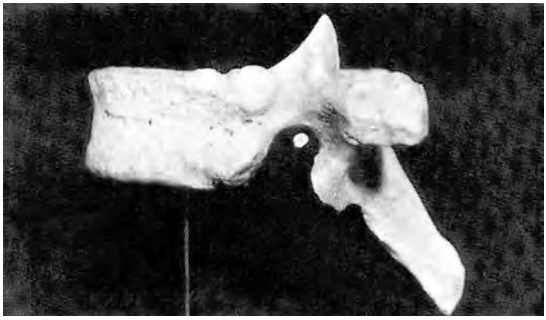
Fig. 4 a–c: Neuroprotective mechanism and its role in the ganglio-foraminal morphogenetic interrelation. – Spinal nerves in fish (a – from (**2**)). Parasagittal section through the thoracic spine of an 80 mm human fetus (b – from Tondury and Theiler (**36**) by permission of Hippokrates Verlag, Stuttgart). Cranial eccentricity of spinal ganglia is due to the beginning slowness of spinal neural growth in respect to the faster (distally directed) growth of the vertebral envelope. The eccentric ganglion moulds the shape of the caudal vertebral incisura (comp. **Fig. 3a**). – Dynamic developmental diagram of the ganglioforaminal interrelation, thoracic and lumbar (c). Vertebral nervous skeleton indicated at top right.

distance, i.e. upon the degree of outgrowth of the CNRC in whole. According to the length of the interganglionic distances the vertebral envelope grows longer and more slender in the quadruped, shorter and broader in man. In those features is enciphered the basic rule of neuroadaptive transformation of bones, viz., longer and thinner, shorter and thicker (**Fig.1–3, 8, 10**).

Platyspondyly evokes, of course, the intrusive impression of some causative axial "compression". It is, however, a common normal feature of, for instance, reptilian vertebrae (**22**) where hardly any axial loading is at work. Behind "platyspondyly", i.e. shorter and broader vertebrae one should recognize the very short, shorter than usual, interganglionic distances.

Transversally oval shape of the embryonic intervertebral foramen reflects the shape of the embryonic spinal ganglion (**Fig. 1A**). Soon, however, the foramen becomes changed under the effect of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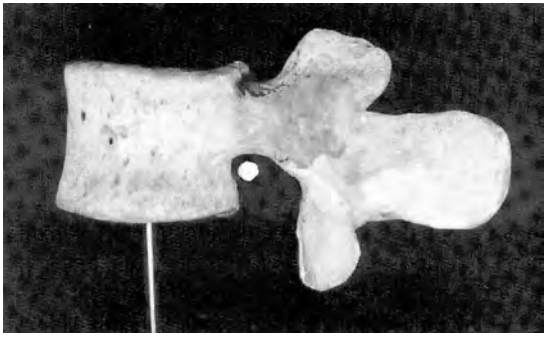
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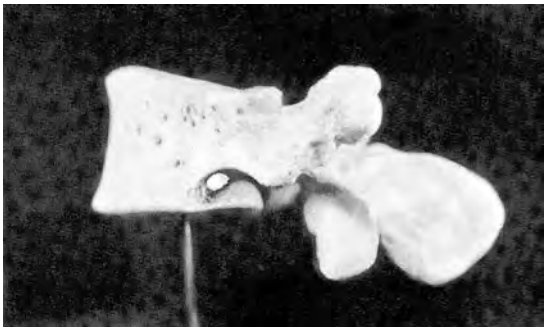
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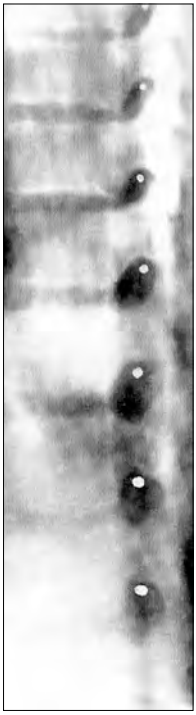
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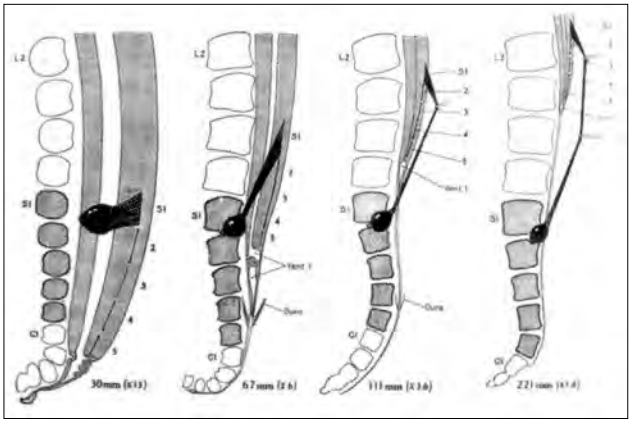
Fig. 5 a–d: Macerated Th8, L3 and L5 vertebrae in lateral view showing the different "ganglioadaptive" shape of the caudal vertebral incisura (a-c). Its "drawning out", craniodorsal in the thoracic and cranioventral in the lumbar portion is due to the direction of spinal nerves when leaving the spinal canal. Lateral roentgenogram (tomogram) of the thoracolumbar spine showing the different shape of inter-vertebral foramina (d). (Spinal ganglia indicated by white dots).

gradual eccentricity of the ganglion due to slowing down of spinal neural growth or to ever faster distally directed growth of the vertebral column. The distance between the ganglion and the dorsocaudal border of the vertebral body (about 10–15 mm in the adult (**Fig. 3e, f**)) means that the entire nervous tissue tract above that level has grown somewhat less in length than the vertebral column. This is the reason why intervertebral foramina are not circular but drawn out cranially (**Fig. 4, 5**). Shallow cranial vertebral incisura is, on the other hand, remnant of imprinting embryonic ganglion (**Fig. 4, 5**).



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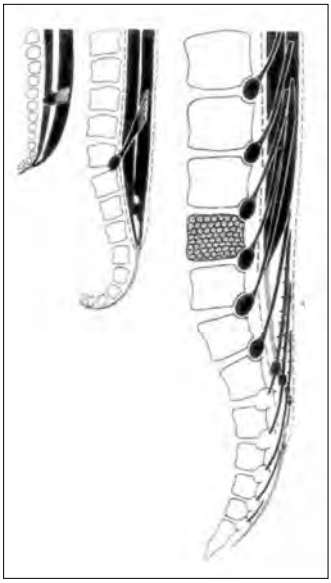

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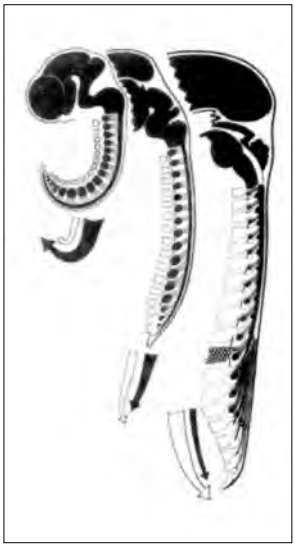

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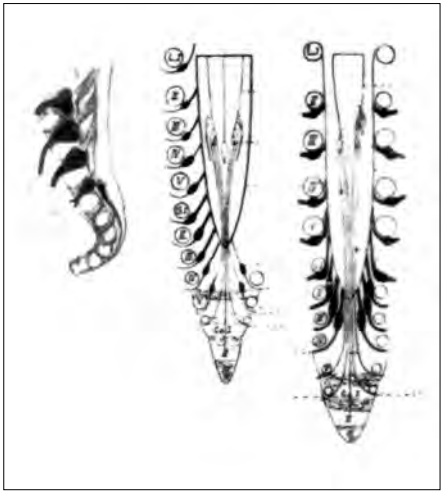

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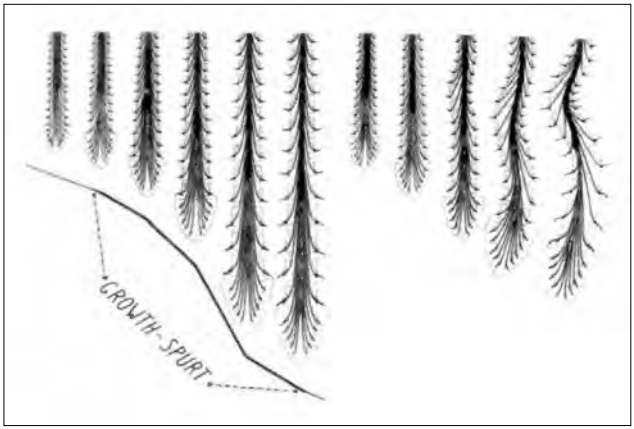
Fig. 6 a–d: Neurovertebral growth mechanism of spinal curvatures. Classic diagram by Streeter (**35**) (a) reproduced in factual length of the individual stages shows, in addition to craniocaudally directed growth of the axial organ, the retarding effect of the slower neural growth upon that of the spine with shift f embryonic kyphosis to lumbosacral lordosis (b, c). – "Withdrawal" of the sacral spinal ganglia from their intervertebral foramina (from (**9**)) (d) due to physiological, purposeful slowing down of growth of the respective nerve roots. Vertebral body L4 drawn as composed of skeletogenic cells (b, c) should indicate the two growth types participating in development of the axial organ, cellular divisional and neural extensive.



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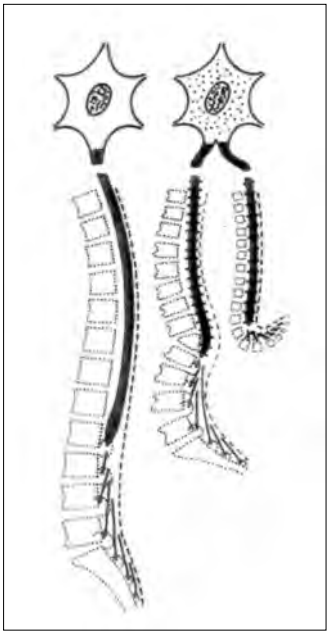

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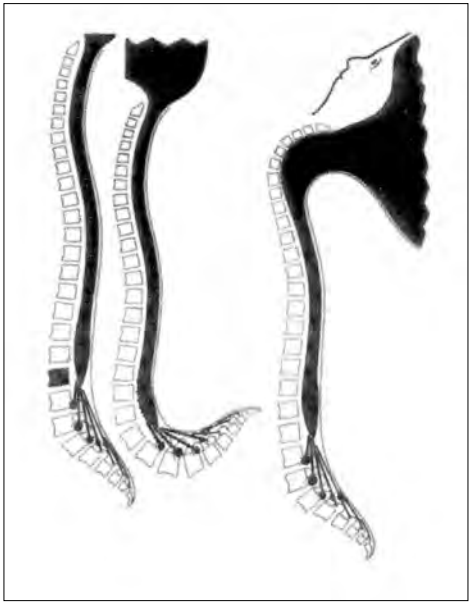

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Fig. 6 e–g: Exaggerated slowness of spinal neural growth results in pathological neuroadaptive curvatures: Kyphoscoliosis (e), cervical and/ or lumbosacral hyperlordosis in craniorhachischisis (iniencephaly), strophosomy and, above all, in a number of skeletal "dysplasias" (f, g).

Ganglio-foraminal morphogenetic interrelation is effectuated by the NPM which works both in the transversal and in the longitudinal direction. The latter circumstance is manifested in the free space left between the spinal ganglion and the roof of the intervertebral foramen (**Fig. 4, 5**). By that free space the spinal nerves are rendered slackened, they dispose of a distinct "length reserve" in respect to the vertebral envelope. The only exception to that rule are the ganglia L 4, 5 which adhere directly to the roof of their foramina so that the length reserve of those nerve roots is distinctly less than that

of all other roots. The possible bearing of that exception upon the pathomechanism and frequency of disc degeneration at the lower lumbar level is discussed elsewhere (**27, 32**) and will be briefly mentioned later in this report.

An equestrian comparison may prove useful for understanding what is advocated. Spinal nerve roots represent something like growth reins "curbing" elongation of the growing vertebral column. In man the vertebral envelope is "kept on a tight rein" whereas in the quadruped it is given much more "free rein" (**Fig. 3**). What in the horse is the bit pushing against the mouth corner with a reflectoric effect upon horse's gait (the horse modifies its gait so as to achieve slackening of the reins), this in the axial organ is the portion of the nerve root with the ganglion coursing around the pedicle with an analogous effect upon the "gait" of the growing (distally elongating) vertebral column.

Spinal curvatures related to vertebroneural growth differential

Kyphosis of the embryonic body is unanimously related to the high growth rate of the dorsally situated central nervous primordia. Slowing down of spinal neural growth (due, above all, to the shift from cellular-divisional proliferation of neuroblasts to extensive type of growth) in combination with ever faster, distally directed growth in length of the vertebral envelope results in gradual straightening of the embryonic kyphosis and installation of lumbosacral lordosis (**Fig. 6**). With slowing down of its growth the CNRC begins to exert a retarding effect upon the growing spine or, more precisely, upon the "row of vertebral arches ("Wirbelbogenreihe" of German literature) whereas the ventrally situated "row of vertebral bodies" ("Wirbelkörperreihe") escapes that effect, it grows somewhat more in length with resulting lordotization. In the quadruped with its comparatively long CNRC the growing spine is less "neurally retarded" so that lumbosacral lordotization is much less pronounced. Cervical lordosis may be attributed, however, to the same vertebroneural mechanism, thoracic kyphosis is continuation of the persisting embryonic curvature. The classic diagram by Streeter (**35**) reproduced with regard to vertebroneural developmental dynamics, i.e. in factual length of the successive stages offers a selfexplanatory insight into the vertebroneural events (**Fig. 6**).

It may be safely concluded that behind cervical hyperlordosis associated e.g. with craniorhachischisis (iniencephaly) or that involving the lumbosacral region in strophosomy or in a number of skeletal dysplasias (comp. **Fig. 1B d**) one should disclose exaggerated slowness of spinal neural growth (**Fig. 6**).

Sacral hyperlordosis leading to installation of the promontorium suggests the existence of purposefully exaggerated slowing down of growth of the sacral nerve roots. This is dramatically evident by the intraspinal site of S2–5 spinal ganglia. In the 5 cm fetus they have already left their intervertebral foramina and gradually become "crowded" at the level of S2 (**9**) (**Fig. 6d**). What has initiated the process of "withdrawal" of the ganglia is hardly anything else than purposeful slowing down of growth of sacral nerve roots. Variability of the promontorial angle thus appears to be related to the variable degree of physiological sacral neural growth slowness. Pathological degrees of that slowness result in exaggerated lumbosacral lordotization together with other neuroadaptive transformations of the spine (a striking example of platyspondylia and lumbosacral hyperlordosis reported by (**26**) is attributable to primary growth insufficiency of the spinal cord and nerve roots).

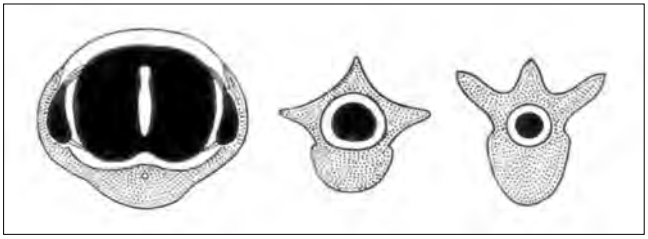
Quantitative neurovertebral developmental shift and the role of muscles

The reader may feel reluctant to credit the adolescent and adult spinal cord with such a profound influence upon the spine since it looks like "buried" within the bulky vertebral column (**Fig. 7**). Despite this, the cord does not cease to play the "leading" morphogenetic role, above all as concerns the length of the vertebral envelope. The above mentioned reluctance is due to the prevailing view concerning the axial organ as composed of bony vertebrae (together with the discs, tendons and ligaments) and of the CNRC inside, seemingly the only representative of spinal nervous tissue. Its true extent is represented, however, by the spinal nervous skeleton - periosteal, endosteal, discal, ligamentous and tendinous (its extent sec in 8, 13 a.o.) which the spine is embedded within (indicated in **Fig. 4c**). Individual vertebrae may be looked upon, without much exaggeration, as bony "casts" of correspondingly shaped cavities within the NS. This vast neural network appears to be involved, together with the CNRC, in neuroadaptive shaping of the developing vertebral column. Modern biomechanics is flooded with highly sophisticated constructions and calculations. It seems safe to conclude that within the living body these mathematico-physical operations are performed by the central nervous system, "computer of all computers" sent out into the periphery including the skeleton and, by the mechanism just suggested, the arrangement of the bony skeleton most appropriate in the given environment is accomplished under the "supervision" of the nervous system. In this system two functions are integrated, that of functional mediator between the individual and the environment and that of morphogenetic realizer of what has been and is "recommended" by the complex neural information from the environment. In this neuroadaptive way, for instance, the variable length of the cervical or lumbar spine is established (**Fig. 1–3**). The same concerns the length variability of limb bones as well (**30, 31**).

Muscles are credited with an important role in the development of the skeleton and that role seems to be unduly disregarded in the advocated concept. In the present author's opinion, however, the role of muscles is "instantaneously functional" according to the immediate needs of the individual concerning locomotion, feeding, defence a.o. Bony processes projecting from vertebrae as well as protuberances and/or crests on the neurocranium serve for muscular insertions. They represent just surface modifications of "neuroadaptively" established basic vertebral and/or neurocranial form (indicated in diagrams of the head in **Fig. 1B**).

Growth hormone and the spine

Enhanced release of growth hormone (GH) in acromegaly stimulates, among others, the bone growth. As may be noted in the specimen published in the classic article by Erdheim (**6**) the accretion of vertebrae, in spite of systemic effect of the hormones, involves predominantly the lower thoracic and lower lumbar region (**Fig. 8a**). These locally enhanced effects of systemic GH, incomprehensible from the strictly osteological point of view, are readily understandable from developmental relation of the vertebral column to the CNRC which escapes the growth stimulating effect of GH as shown years ago by Rubinstein (**30**). Any additional growth in length of the adult spine is strictly prohibited since it would result in deleterious overstretching of the CNRC. The newly formed excess of bone tissue is therefore purposefully, neuroadaptively dissipated in ventrolateral,



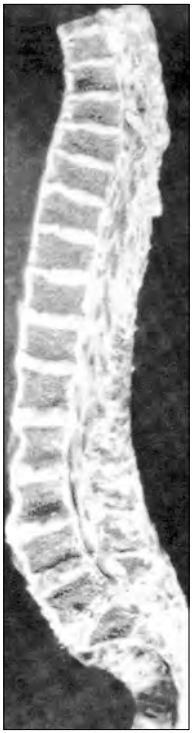
a b c

Fig. 7 a-c: Quantitative neurovertebral shift shown in crosssection of the axial organ in the embryo, newborn and adult (a–c). In the latter the spinal cord is "buried" within the bulky vertebral column. Despite this, it does not cease to play the "leading" morphogenetic role, above as concerns the length of the axial organ. Processes projecting from vertebrae and serving for muscular insertions represent just surface modifications of the neurovertebrally established basic vertebral form.

not dorsal direction since accretion towards the spinal cord is prohibited (**12**) obviously owing to its NPM. The reason why the transversal accretion of vertabrae is confined to the two above mentioned areas is enciphered in variable degree of angulation of the spinal nerve roots around the pedicles. The Th5–10 nerve roots are most sharply angulated, 90° and even less (**15, 25**). Also the L4,5 roots are more sharply bent around their pedicles than L1–3 roots (**Fig. 8b**). What this amounts to is that even by a very slight resumption of vertebral growth in length the sharply angulated nerve roots will be the first jeopardized by undue pull, viz., by reduction or loss of their length reserve (i.c. of the small free space between the spinal ganglion and the lower border of the pedicle (**Fig. 8c, 10d**)). To avoid that neurobiologically unacceptable event the basic vertebroneural mechanism is set in function, the additional bone material "spreads" in transversal direction. At the level of less angulated nerve roots such as L1–3 the regrowing vertebrae "shift" along them in length without any appreciable transversal dissipation of growing bone tissue (**Fig. 8b**).

Acromegalic and common spondylosis

It is not to be wondered at that acromegalic spondylosis involves also mainly the lower thoracic spine where the common spondylotic lipping is usually most prominent as well. Acromegalic spondylosis is associated, with massive transversal overgrowth of vertebral bodies (**Fig. 8a**). Occurrence of enhanced lower thoracic spondylotic lipping in nonacromegalic subjects speaks in favour of Bohatirchuk's (**1**) interpretation of spondylosis (and arthrosis) as sequelae of resumed activity of GH in the aged associated with declining function of sexual hormones. Naturally, this quite minimal, nonacromegalic GH effect is manifested just in marginal transversal bony overgrowth in form of spondylotic "lipping" (**Fig. 9c**).



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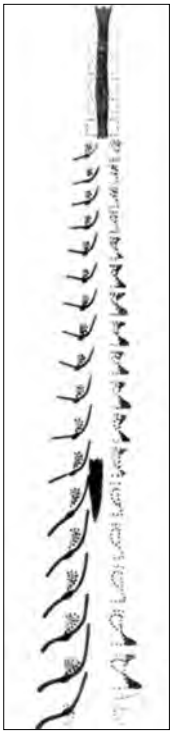

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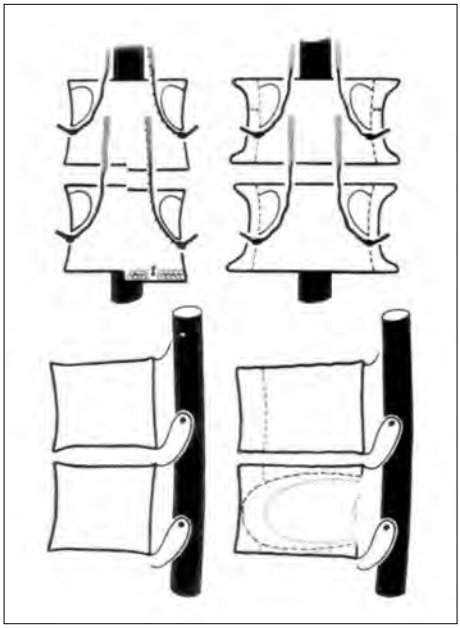


c

Fig. 8 a-c: Median section through the spine of an acromegalic subject (from Erdheim (**6**) by permission of Springer-Verlag, Heidelberg) (a). Sagittal accretion of vertebral bodies is confined to regions with most pronounced curving of spinal nerve roots around the pedicles (b). These roots are most susceptible to stretch by resumed growth of the vertebral envelope so that corresponding vertebral bodies enlarge "neuroadaptive" in strictly transversal (ventrolateral), not longitudinal direction (indicated within the outlined vertebral body (bottom right) (c).

The mysterious lower thoracic spine: Favourite site of idiopathic scoliosis and of Scheuermann's "disease"

In acromegaly the striking susceptibility of the lower thoracic spine to developmental pathology such as idiopathic scoliosis (IS) or Scheuermann's disease (SCH) is manifested in a most exaggerated form. This portion of the spine hardly differs in any osteological or biomechanical aspect from the rest of the spine. The only difference consists, however, in the length of spinal cord segments it harbours. Whereas embryonic cord segments are of uniform length, in the adolescent and adult the Th5–10 segments are by far the longest, about 20 mm (**19**) in contrast to shorter cervical and, above all, quite short lumbo-sacral segments (**Fig. 9a, b**). These differences are related to "reciprocity" of neural growth (**30**): The vast extent of the NS of the limbs is associated with short cord segments whereas the far less extensive NS of the thoracic wall originates from far longer segments. Lower

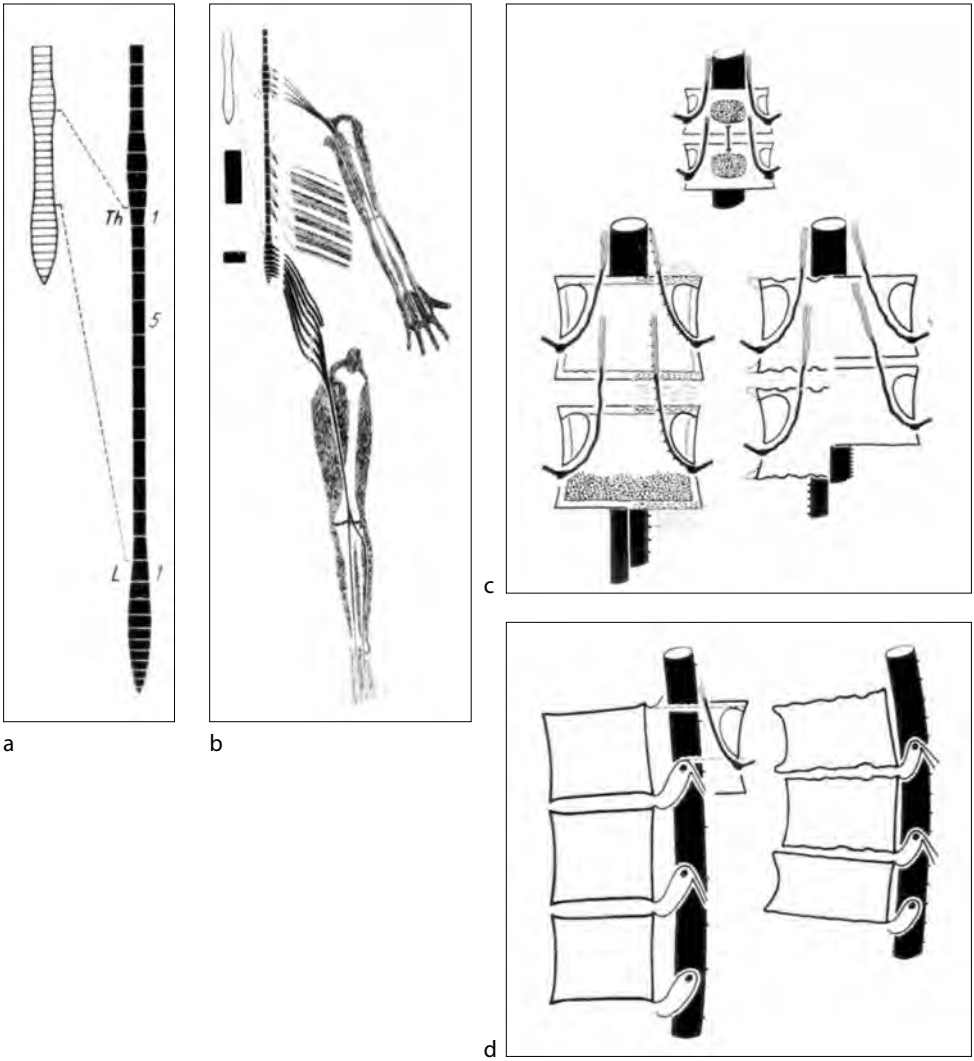
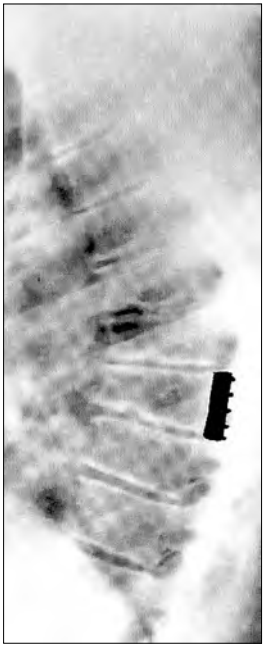


Fig. 9 a-d: Specific feature of the lower thoracic spine: It harbours the portion of the spinal cord consisting of the longest segments (one lower thoracic and one lumbosacral segment outlined in deep black in (b) (a). Different length of adult spinal cord segments, uniform in the embryo (a), is related to "reciprocity" of neural growth (b – see also human and animal head in **Fig. 1B**). Owing to the high energetic demands and vulnerability the growing Th5–10 portion of the cord is rendered highly susceptible to neurovertebral growth disproportion manifested in neuroadaptive deformities such as idiopathic scoliosis or Scheuermann's "disease" as well as in common spondylotic "lipping" (i.e. slight transverse bony "overgrowth). The biological purpose of those and other (**Fig. 6**) neuroadaptive deformities is preservation of "unloading" of the too short nervous structures.



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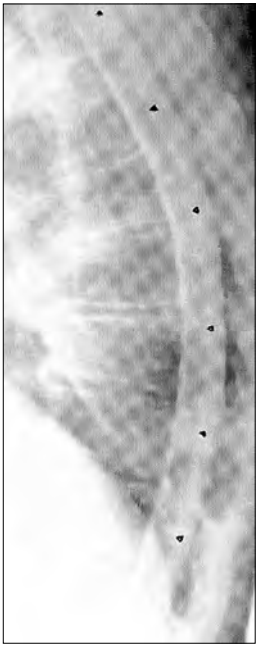

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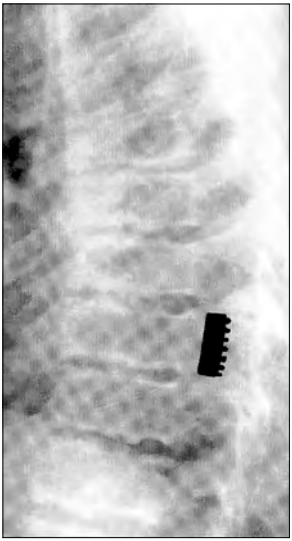

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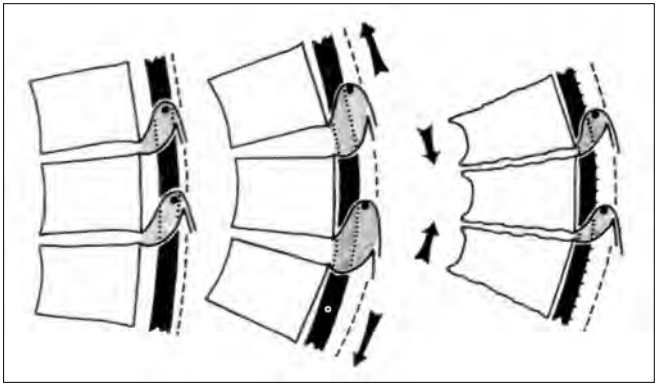
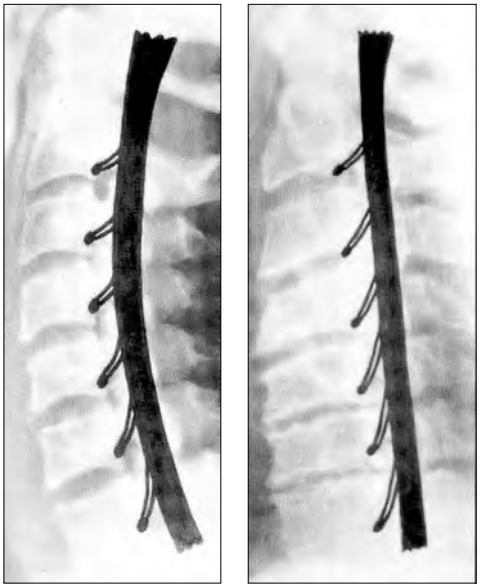


Fig. 10 a-d: "Osteological" view of Scheuennann's "disease" in lateral roentgenogram (a). Myelogram with characteristic ventral position of the spinal cord (arrowed) believed to be simply consequent to hyperkyphosis (b). It reflects, however, growth insufficiency of the cord in respect to the faster growing vertebral envelope (d). "Platyspondyly", i.e. exaggerated neuroadaptive shortness and broadness of vertebrae in spondyloepiphyseal dysplasia (comp. **Fig. 9d** bottom right) (c).

thoracic segments grow thus far more in length during development than the other segments with correspondingly higher demands of the Th5–10 portion on supply with energy and oxygen and, consequently, with higher vulnerability. Growth insufficiency of that portion of the CNRC, even a relative one due to inability to keep pace with the (distally directed) fast elongation of the spine during the growth spurts must be compensated for by shortening of the spine as though "from below" in form of IS or SCH (the latter not infrequently in combination with slight scoliosis). SCH

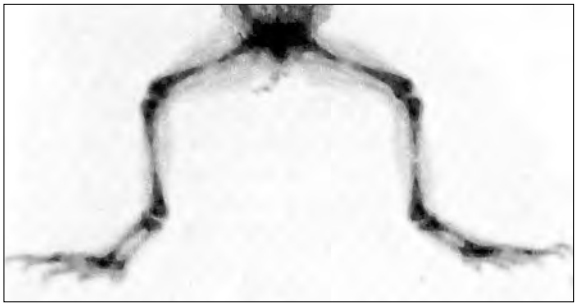


a b

Fig. 11 a-b: A "cervical model" of what is going on in acromegaly and, partly, in Scheuermann's disease: Cervical normospondyly (a) and "platyspondyly" (b) in an apparently normal, non-acromegalic subject. The abnormal quantity of vertebrogenic tissue in (b) had to spread transversally along the given length of the outlined cervical spinal cord.

shows distinct acromegalic features, viz., sagittal elongation of vertebral bodies together with a distinct "platyspondyly" (craniocaudal shortening with sagittal broadening). Irregularities of endplates of vertebral bodies reflect modifications of growth zones aimed at neuroadaptive suppression of longitudinal growth of the vertebral body at the stage of its already advanced ossification (**Fig. 9c, d, 10**). With vertebroneural growth disproportion setting in during earlier developmental stages when the less ossified spine is still fairly plastic a clearcut regular "platyspondyly" is established, i.e., as a matter of fact, exaggerated degree of what has been accomplished in the course of hominization in connection with neuroadaptive transformation of long and slender animal vertebrae into shorter and broader human ones (**Fig. 1B a, b**).

In Scheuermann's hyperkyphosis the cord takes its course along the ventral wall of the spinal canal (**Fig. 10 b**) what is held for more consequence of the skeletal deformity. Hyperkyphosis evokes the impression that the spinal canal is elongated, the cord exposed to longitudinal pull and consequently shifted ventrally (**18**). This would be true, however, if the ventral height of vertebral bodies would remain unchanged and hyperkyphosis would be due to widening of the dorsal portions of intervertebral discs. In that case the spinal canal would actually be lengthened and the cord would be dislocated ventrally. Owing to wedging of vertebral bodies, i.c. to shortening of their ventral portions, length of the spinal canal is not increased since hyperkyphosis has taken place at the expense of ventral shortening of vertebral bodies. There is thus no biomechanical reason for ventral eccentricity of the cord, the causative mechanism of which is exaggerated slowness of spinal cord growth in respect to that of the spine (**Fig. 10d**). Invariably encountered course of the cord in IS along the concavesided (shortened) wall of the spinal canal mirrors exactly the same neurovertebral growth situation.



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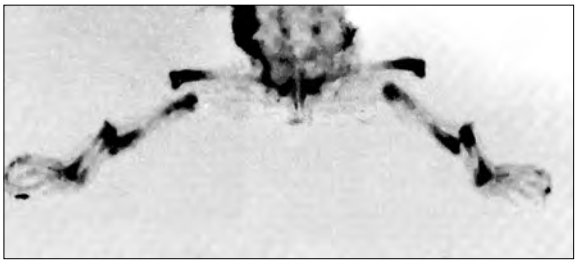

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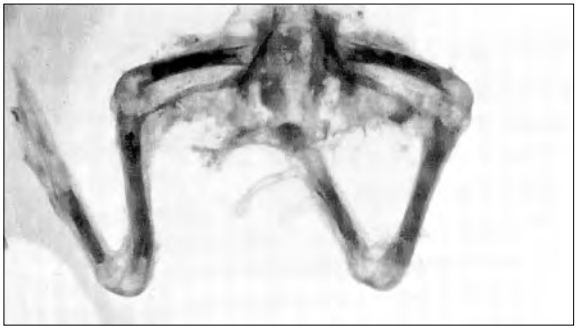
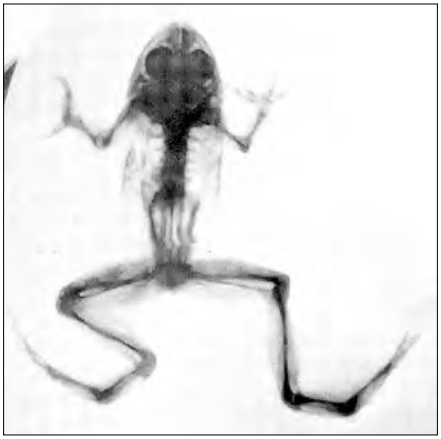


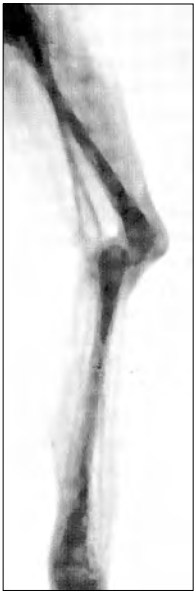
d

e

Fig. 12 a-h:
Dislocation at the knee and at the crurotarsal joint in an osteolathyric frog tadpole (a-c) and in a chick embryo treated with pilocarpin (2 mg into the yolk sac on the 5th day of incubation) (d–f). "Osteological" view (cleared according to (**21**)) (a, b), specimens cleared according to (7) in full extension show (c, e, f) that the dislocated bones, "zig-zag-ging" along the neural "axis" (above all in (f)), "hang" on the too short nervous trunks. Neutral posture in (d) with medial rotation of the rightsided limb. Spontaneous dislocation at the knee in common frog (accidental finding in an animal captured in a pond near Brno). Neutral posture (g), full extension (h) – see next page. (Cleared according to (**7**)).



g



h

Equestrian comparison of spinal nerve roots with "growth reins" may be extended further to insufficiency of spinal neural growth resulting in IS or SCH: The root reins are kept too tight, the growing spine "rears up" in a kyphotic or kyphoscoliotic manner, naturally in the course of long months and years.

In the pathomechanism of IS and SCH the double possible way how vertebroneural growth disproportion may be elicited is strikingly documented. One way is inhibition of neural growth (toxic or hypoxie in experimental teratology, infective in poliomyelitis, endogenous in dysraphic or heredodegenerative conditions), the other way consists in enhanced vertebral growth such as that underlying growth spurts or that brought about by therapeutic administration of GH (**5**). The bearing of those two ways upon osteoneural growth pathology in the limbs will be discussed in the following paragraph.

Growth hormone effects on the hip

Dislocation of joints in chick embryos and frog tadpoles is a very frequent finding in experimental teratology (**Fig. 12**). It is just another type of neuroadaptive compensation accomplished by shifting over of otherwise normal bones along the growth insufficient, too short peripheral nervous trunks (**Fig. 12c, e**) (**31**). For some unknown reason the hip joint is strictly spared in experimental animals in contrast to frequent involvement of the knee and crurotarsal joints. Moreover, roentgenograms of several tens of osteolathyric rats showed without exception dislocation of humeroscapular joints, once epiphyseolysis has been encountered (**Fig. 13a-d**). Brachial plexus has not been demonstrated

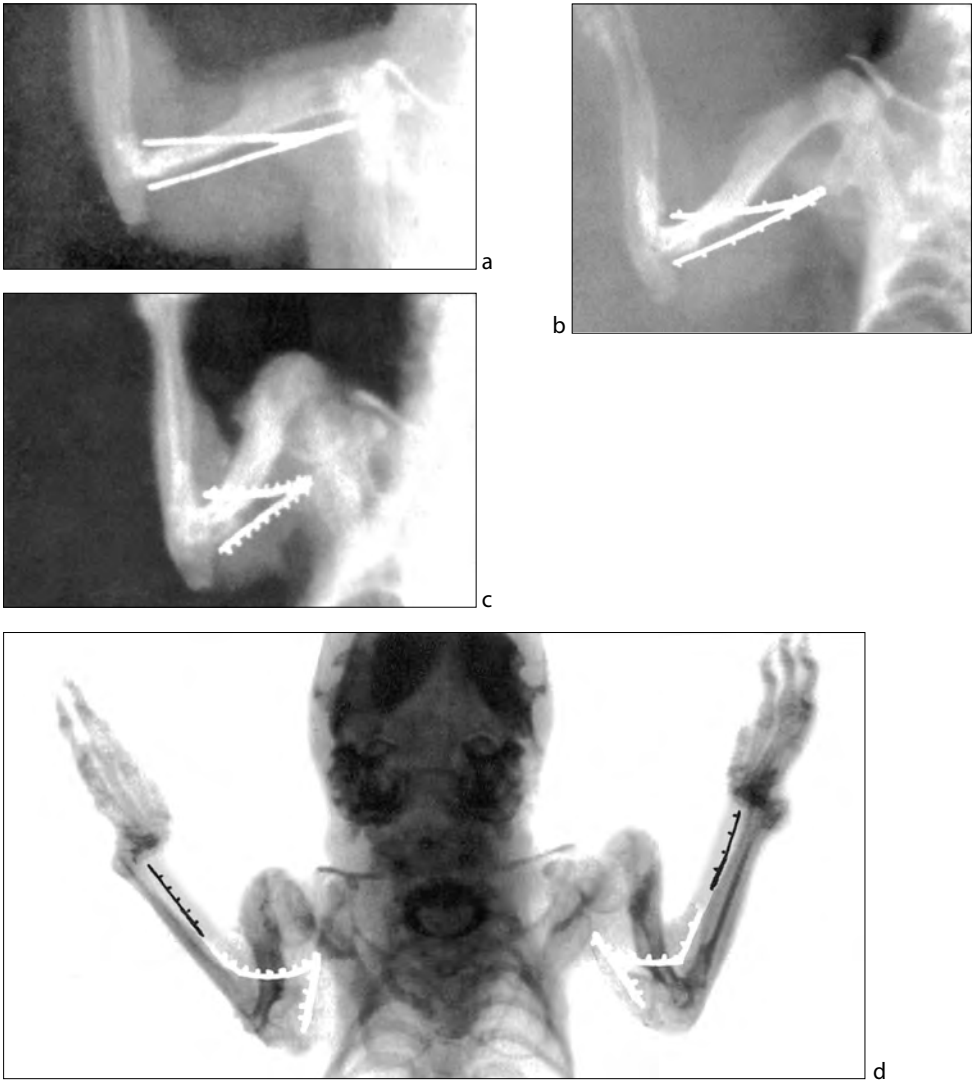
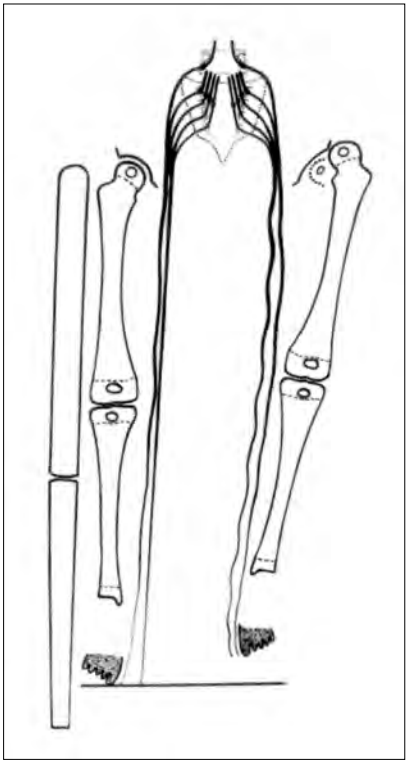


Fig. 13 a-d:
Dislocation at the shoulder joint, a constant finding in osteolathyric rats (roentgenograms, direct enlargement 1:1,5). A nervous trunk representing brachial plexus is outlined with relation to constant anatomical landmarks, viz., from the border of scapular joint facet to olecranon. Norm (a), dislocation (b), neuroadaptively slipped epiphysis (c, d). Note dislocation at the wrist as well in (d).



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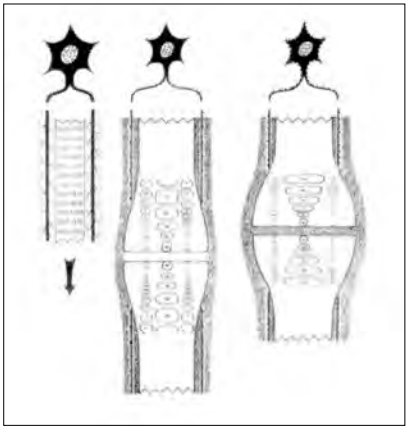


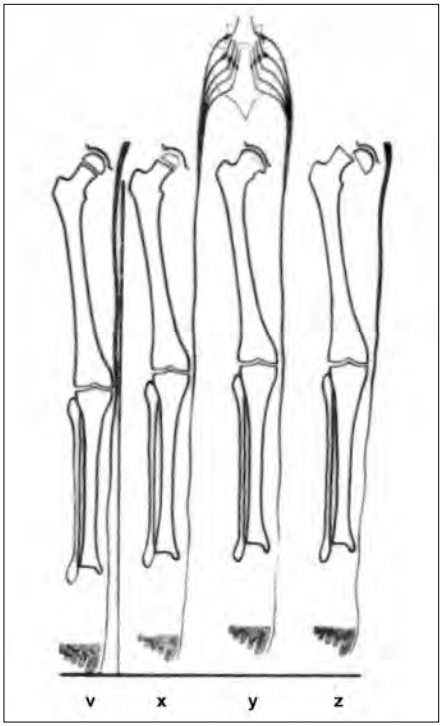
b

Fig. 14 a-b: Congenital dislocation of the hip in man interpreted as neuroadaptive response to growth insufficiency of the lumbosacral plexus. Dislocation may result in hypercompensation indicated by enhanced slackening (wavy course) of the nervous trunk (a). Bottom: Flattening of proliferating chondrocytes in the preparatory zone of enchondral ossification interpreted as due to "neuroadaptive stasis" manifested at the organ level in terminal epimetaphyseal flaring (b).

(clearing techniqueos for nerves are ineffective in mammals) but on the basis of osteoneural findings in tadpoles and bird embryos one feels justified to draw in the growth insufficient plexus as responsible for the skeletal findings including the Madelung-like deformity of the wrist (**Fig. 13d**).

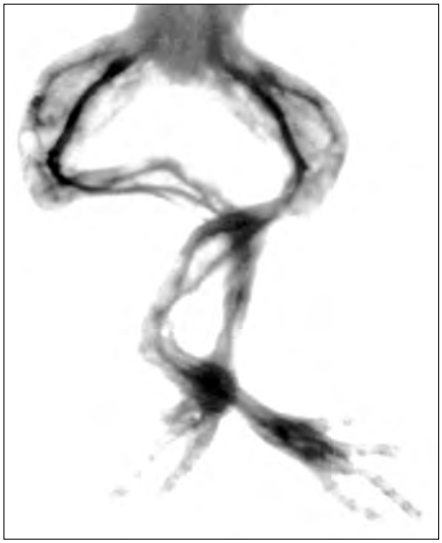
In spite of those differences of experimental findings they may serve as models of congenital dislocation of the hip in man which may be related to growth insufficiency of the massive nervous trunks of the lumbosacral plexus (**Fig. 14**). Perthes' disease or epiphyseolysis represent another types of neuroadaptive transformation of the hip during later postnatal stages when advanced ossification renders any compensation by dislocation no more feasible. Congenital coxa vara is Just another type of osteoneural growth compensation (**Fig. 15a**).

Perthes' disease and slipped capital femoral epiphysis are well known complications of growth hormone therapy in children with idiopathic growth hormone deficiency (17 a.o.). This is an expectable parallel to what has been shown in acromegalic spine, viz., vertebroneural and osteoneural growth disproportion created by enhanced stimulation of bone growth. At a time when development and ossification of the hip joint are already fairly advanced neuroadaptive compensation for an acute,



a

c



b

Fig. 15 a–c: In subjects with already advanced ossification neuroadaptive shortening of the limb is accomplished either by Perthes' necrosis (a – x,y) or slipping (a–z) of the capital femoral epiphysis (comp. **Fig. 13 c, d**). The outlined digital nervous skeleton (permeating, of course, throughout the entire limb) should illustrate the biological purpose of the deformities, viz., shortening of the limb "from below" to presearve "unloading" of the nervous trunks. Drastic stimulation of bone growth by growth hormone will have the same effect like insufficiency of neural growth. – Hind limb skeleton of hyperparathyroid frog tadpole (fed standard diet soaked with Tachystin) in neutral posture (b) and in full extension (c-cleared according to (**23**)).

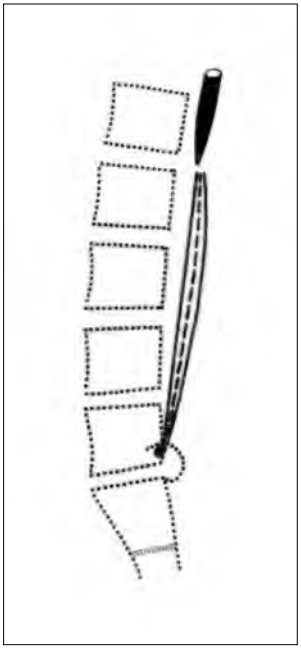
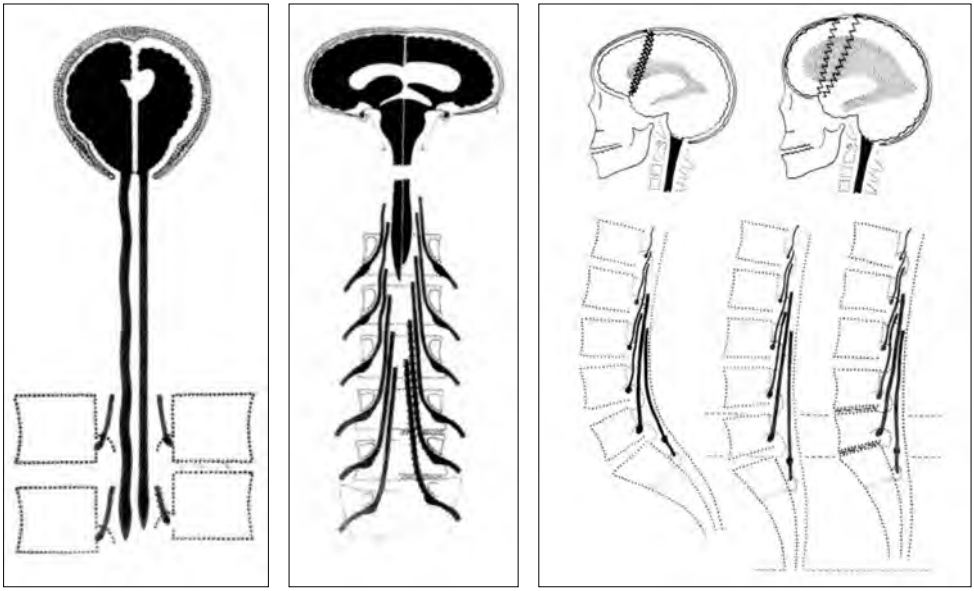


Fig. 16: Explanatory diagram to what is meant by "stretch" or "tension" of a nerve root or of a nervous trunk indicated by the straight line. Normal slackedness, "unloaded condition" is indicated by the more curved line. Diminished degree of slackedness, indicated by the less curved line and looking like a still acceptable condition of the nerve, is neurobiologically already unacceptable. Nerve root or trunk exposed to that "substretched", less slackened condition "feels" jeopardized by undue tension. It sends out warning signals to the vertebral envelope or to the limb bones, i.e. to the nervous skeleton they are embedded within.

drastic growth spurt of the femur by dislocation is no more feasible, the only possible way is shortening of the femur by necrosis or slipping of capital epiphysis (**Fig. 15a – y, z**). It might be supposed that impulses to initiation of capital necrosis are sent out from the lumbosacral plexus acutely jeopardized by stretch. There is little room for doubt left that those impulses are of vasomotoric nature not unlike in Scheuermann's "disease" where analogous necrosis of growth zones of vertebral bodies results in neuroadaptive shortening of the spine.

In slipped capital femoral epiphysis associated with renal osteodystrophy hyperparathyroidism plays the crucial role (**14, 20**). In frog tadpoles fed common diet soaked with parathyroid hormone (Tachystin) bent hind limb bones with neuroadaptive features have been encountered (**Fig. 15b, c**). The growing bones, indubitably afflicted with the induced hyperparathyroidism, had to "cram" along the straightly coursing, growth insufficient, too short "neural axis" not unlike what takes place after administration of many other "skeletal" teratogens (**31**). In view of the critical role of calcium ion in axonal outgrowth, impairment of that growth should be expected in hyperparathyroidism together with changes of bone biochemistry and texture.

What is meant by "undue tension" of a nerve/root is schematized in **Fig. 16**. Normal slackedness, "unloaded condition" is indicated by the more curved line. Diminished degree of slackedness (less curved clashed line) looking like a still acceptable condition of the nerve is, in all probability, already neurobiologically unacceptable as is naturally full mechanical stretch (straight nerve root line).



a b c

Fig. 17 a–c: Degeneration of the disc interpreted as neuroadaptive, "radiculoprotective" response of the adult spine to involutional atrophogenic shortening of the nerve roots (the counterpart, in all probability, to the analogous, well known process of the brain (a). The "degenerative" narrowing, i.e. shortening of the disc space as though "from bellow" is aimed at preservation of "unloading" of the shortened nerve roots. This "radiculoprotective" process, "neuroprotectively" at work even in the production of arthrosis in the limbs, may be paralleled with the "cerebroprotective" loosening and dehiscence of cranial sutures with erosion of the neurocranium by the expanding brain in obstructive hydrocephalus (b, c).

Osteoneural morphogenesis of the long bone

The author would like to comment upon the topic briefly alluded to in the previous communication (**31**). Together with physiological slowness of the spinal neural growth in respect to the faster growing vertebral envelope, growth of the peripheral nervous skeleton lags behind that of the limb bones. The physiological osteoneural growth differential is manifested partly in cranial eccentricity of spinal ganglia (**Fig. 4**), partly in the slight femorotibial angulation in full extension of the limb along the straightly coursing sciatic nerve and its branches (comp. **Fig. 6** in (**31**)). Owing to that differential the accumulating skeletogenic material at the growing ends of limb bones and vertebrae is dissipated "neuroadaptively" in transversal direction. This results, at the organ level, in "waisting" of vertebral bodies as well as of long bones. Their terminal epimetaphyseal flaring represents, as a matter of fact, a sort of elongated "waisting" (**Fig. 19b**). Transverse-oval shape of ossification centers at the knee as well as flattening of proliferating chondrocytes in the preparatory zone of enchondral ossification may be interpreted as concomitant manifestation of the osteoneural growth differential (**Fig. 14a, b**).

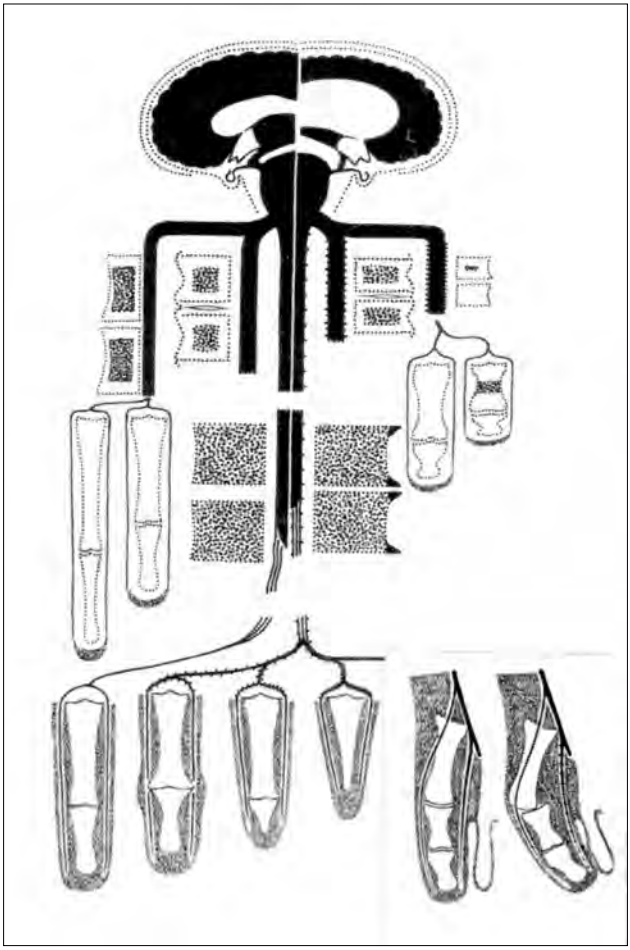
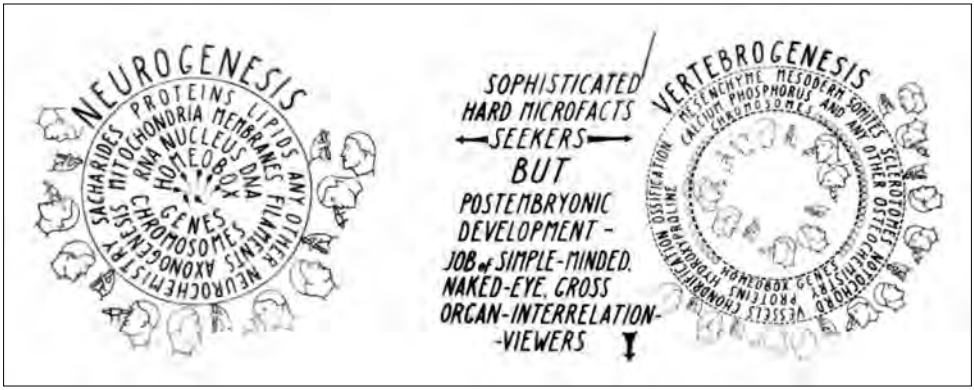


Fig. 18: Concentrated diagram of neuroadaptive transformations of the skeleton, developmental and in the adult and aged. The former is due either to insufficiency of the vulnerable neural growth or to enhanced stimulation of bone growth (upper and middle rows -utmost right hyp- and anosteogene is as response of ossification process to excessive insufficiency of neural growth), the latter to atrophogenic shortening of the spinal nerve roots and/ or peripheral nerves ("degeneration" of the disc, spondylosis, arthrosis). Bottom left neuroatrophogenic interphalangeal arthrosis, hypoplasia and aplasia of phalangae due to congenital defect of the nervous skeleton or to its atrophy in "neurogenic" osteolysis. Bottom right - atrophogenic shortening of digital nerves behind valgosity of the big toe.

"Degenerative" conditions of the skeleton interpreted as neuroadaptive response to involutional atrophogenic shortening of the adult spinal nerve roots and/ or of peripheral nerves

Severe impairment of neural growth during the developmental period suggested to be responsible for the rather drastic neuroadaptive malformations of the growing skeleton seems to have its much milder counterpart in involutional atrophogenic shortening of the spinal and peripheral nervous structures (**27, 32**). They should share with the brain the tendency to involutional atrophy. Whereas that common cerebral process leads to a distinct loss of cerebral volume, in the elongated extracerebral nervous structures atrophy should mean distinct shortening. Though taking place in the course of long years and decennimus atrophogenic neural shortening – not unlike that ensu-



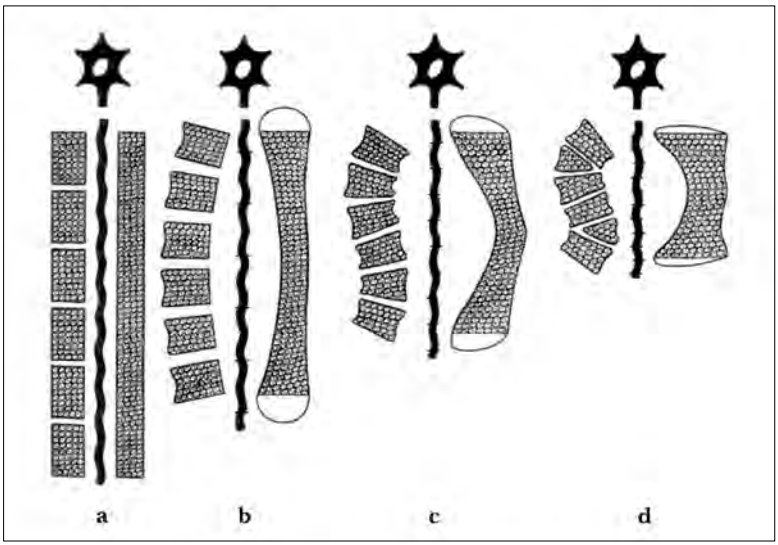


Fig. 19: Schematic drawing meant to inspire the reader with the notion that gross interrelation between the developing bony and nervous tissues cannot be understood but by naked eye synthetic view, not by any even the most detailed separate examination. Neuroadaptive behaviour of the vertebral and limb skeleton, both growing by enchondral ossification, is aimed at purposeful preservation of slackened, unloaded course of the nervous structures (indicated by exaggerated waviness).

ing from neural growth impairment during the developmental period – must be compensated for by neuroadaptive transformation even of the adult skeleton. The only plastic component capable of that transformation is the cartilage, intervertebral and articular. Its change commonly called "degenerative narrowing" means, as a matter of fact, craniocaudal shortening aimed at preservation of unloaded condition of the spinal nerve roots and/or of peripheral nerves. "Radiculoprotective"

or "peripheral neuroprotective" loosening and narrowing (shortening) of the intervertebral disc or of the joint space may be thus paralleled with the "cerebroprotective" loosening and dehiscence of cranial sutures by the effect of expanding brain in obstructive hydrocephalus (**Fig. 17a–c**). The physiologically lesser length reserve of the L4, 5 and S1 nerve roots renders them most susceptible to atrophogenic shortening with induction of disc degeneration so frequent at that level (**27, 32**).

Spondylotic or arthrotic osteophytic "lipping" means just a very slight degree of neuroadaptive transversal dissipation of bone growth when accretion in length is neuroadaptively prohibited. It is caused most probably by combination of atrophogenic neural shortening with reactivation of growth hormone associated with declining function of sexual hormones (**1**). Spondylotic or arthrotic "lipping" may be also defined as a sequel of pathologically exaggerated osteoneural growth differential the physiological degree of which is responsible for "wasting" of vertebral bodies and of long bone s (**Fig. 14a, 19** below).

Fig. 18 shows a concentrated diagram of neuroadaptive transformations of the skeleton due to the primarily inadequate or reduced length and/ or extent of the various parts of the nervous system. The self-explanatory diagram does not require any detail or comment except for the digital nervous skeleton (bottom). Defects of the phalangae, congenital or those associated with neuropathic conditions such as diabetic, tabic a.o. may be related to hypoplasia or atrophogenic reduction of the digital nervous skeleton with correspondingly decreased volume of "cavities" within that skeleton available for proliferation of skeletogenic tissues (concept of "cavities" within the nervous skeleton see (**31**)).

CONCLUSION

In the up-to-date biomedical research it is widely held that no real progress has been made until a biological mechanism is placed on a firm molecular or histobiological basis (freely quoted from (**37**)). Such approach means, however, an ever more separate investigation of individual tissues and cells including bones and nerves pursued mostly in separate institutions. In the given context, however, approach like this would be rather misleading since gross organ interrelations of nervous and bony structures is advocated. This seemingly outmoded way of analysis and documentation yields surprisingly a clue to a number of normal and pathological features of development hither to entirely enigmatic in spite of most strenuous detailed research efforts. What is put forward and what is the ambition of the author is to inspire the reader with a change of approach, from the habituated and deeply rooted notion of "neural growth passivity" to that of "neural growth activity and vulnerability".

Concerning genetics so far not mentioned by the author-non-geneticist, it is naturally closely linked with skeletal morphogenesis. There exist today a number of genes claimed to be responsible for a number of skeletal dysplasias. There is strong reason to suspect, however, that correct or incorrect coding of proteins is of basic importance for neurogenesis, probably more so than for skeletogenesis. The advocated concept of vertebral and appendicular skeletogenesis lends support to the

possibility that normal and abnormal skeletogenesis just mirrors normal or abnormal neurogenesis, viz., normal or abnormal gross neural growth.

Holmdahl (**10**) in his commentary on a severely malformed fetus with anencephaly, cleft palate, polydactyly, varosity at the knee joints and bowing of distal tibia arrived at conclusion that "the central nervous system occupies both morphogenetically and functionally a central position within the organism. It might be supposed that central nervous system can influence origin and development of all the other organs of the body" (translated from German by the author). That effect of the nervous system since ever has been and still is ascribed to its "neurotrophic" function. As concerns growth and development of non-nervous tissues and organs, however, the same parameters of the nervous system, i.e. neural growth and development should be taken into account when inquiring into the effect of the latter upon the former. Developmental defects in Holmdahl's fetus (**10**) are readily explainable as manifestations of disturbed neural growth.

Even in the utmost periphery, seemingly evident domain of histobiology, the relative two-growth-types approach appears more promising than separate investigation of cells or nerves alone (**28, 29**).

REFERENCES

1. BOHATIRCHUK, F.: Aging and ostcoarthritis. Canad.med.Ass.J., 76, 1957, pp. 106–114.
2. BRANS, H.: Über clíc Innervation der paarigen Extremität bei Selachiern, Holocephalen und Dipnoern. Jenai. Zschr.Naturwiss., 31, 1988, pp. 239–468.
3. CONLON, R.A.: Retinoic acid and pattern formation in vertebrates. Trends in Genetics, 11, 1995, pp. 314–319.
4. DONALDSON, H.H.: The nervous skeleton. Trans.Amer.neurol.Ass., 63, 1937, pp. 1–9.
5. DYMPLING, J.F., WILLNER, S.: Progression of structural scoliosis during treatment with growth hormone. Acta orthop.scand., 49, 1978, pp. 246–268.
6. ERDHEIM, J.: Uber Wirbelsaulenveranderungen bei Akromegalie. Virchows Arch. path. Anat., 281, 1931, pp. 197–296.
7. FREIHOFER, W.C., COMPAGNO, L.J.V.: Additional notes on the use of the Sihler technique of staining nerve s of small, whole specimens of fishes and other vertebrates. Copeia, 1977, No. 3, pp. 587–588.
8. GROEN, GJ., BALJET, B., DRUKKER, J.: Nerves and nerve plexuses of the human vertebral column. Amer.J.Anat., 188, 1990, pp. 282–296.
9. HOLMDAHL, D.E.: Utvecklingen av den kaudala delen av ryggmargen hos människan. (Development of the candal part of the spinal cord in man). C.Blom., Lund 191.8.
10. HOLDMAHL, D.E.: Rhachischisis. Roux' Arch.Entwicklmech.Org., 144, 1951, pp. 626–642.
11. HOLTZER, H.: An experimental analysis f the development of spinal column. I. Response of precartilage cells to size variation of spinal cord. J.exp.Zool., 121, 1952, pp. 121–149.
12. KUNTSSON, F.: Growth and differentiation of the postnatal vertebra. Acta radiol.(Stockh.), 55, 1961, pp. 401–408.
13. KOJIMA, Y., MACELA, T., ARAI, R., SHICHIKAWA, K.: Nerve supply to the posterior longitudinal ligament and the intervertebral disc of the rat vertebral column as studied by acetylcholinesterase histochemistry. I. Distribution in the lumbar region. II. Regional differences in the distribution of the nerve fibres and their origin. J.Anat., 169, 1990, pp. 237–255.

14. KREMPIEN, B., MEHLS, O., RITZ, E.: Morphological studies on pathogenesis of epiphyseal slipping in uremie children. Virchows Arch.path.Anat., 362, 1974, pp. 129–143.
15. KUBIK, S.: Zur Topographic der spinalen Nervenwurzeln. Acta anat., 63, 1966, pp. 324–345.
16. LEBEDKIN, S.I.: Changes in length of the spinal cord segments and of the axial skeleton (vertebrae) in the course of development in man and in swine. (Russian text). Izv.nantch.Inst.im.P.F.Lesgafta, XX, No I., pp. 13–102. Moskva 1936.
17. LEBL, J., CHLÁDEK, P.: Two cases of Legg-Calvé-Perthes disease during growth hormone treatment in boys with idiopathic growth hormone deficiency. Pohybové ústrojí (Locomotor System), 2, 1995, pp. 124–127.
18. LINGREN, E.: Myelographic changes in kyphosis dorsalis juvenilis. Acta radiol., 22, 1941, pp. 461–470.
19. LÜDERITZ, C.: Ueber das Rückenmarkssegment. Arch. Anat. Entwicklgesch. Anat. Abt., 1881, pp. 421–495.
20. MEHLS, O., OPPERMANN, H.C.: Renale Osteopathien. In: Handb.mediz.Radiologie. Ed. L.Diethelm, F.Heuck. Bd. V., Teil 5. Springer-Verlag, Berlin - Heidelberg-New York 1983. Pp. 181–240.
21. MILLER, C.H.: Demonstration of the cartilaginous skeleton in mammalian fetuses. Anat.Rec., 20, 1921, pp. 415–419.
22. MULLER, A.H.: Lehrbuch der Palaeozoologie. Bd. III. - Vertebraten, Teil 2 -Reptilien und Vogel. 2. Aufl. Fischer, Jena 1985.
23. NISHIKAWA, K.C.: Staining amphibian peripheral nerves with Sudan black B: Progressive vs. regressive methods. Copeia, 1987, No.2, pp. 489–491.
24. O'RAHILLY, R., BENSON, D.R.: The development of the vertebral column. In: Bradford, D.S., Hensinger, R.M. (eds.): The Pediatrie Spine. Thieme, Stuttgart-New York 1985, pp. 3–17.
25. PFITZNER, W.: Ueber Wachsthumsbeziehungen zwischen Rückenmark und Wirbelkanal. Gegenbaurs morph.Jb., 9, 1884, pp. 99–116.
26. REMAGEN, W., HIENZ, H.A., WIEDEMANN, H.-R.: Zum Problem der Frühentwicklung der Wirbelsaule. Z.Anat. Entw.-Gesch., 131, 1970, pp. 39–44.
27. ROTH, M.: Neurovertebral developmental morphodynamics and degeneration of the disc: a suggestion. In: Neurology in Europe I. Ed. Bartko D., Turčáni, P. Libbey, London 1989, pp. 632–636.
28. ROTH, M.: The properties of the nervous system and the two growth types (egg-sperm) concept of carcinogenesis. Med.Hypotheses, 37, 1992, pp. 259–267.
29. ROTH, M.: The vascular nervous skeleton: a disregarded factor of vascular pathology. Atherosclerosis, 108, 1994, pp. 1–3.
30. ROTH, M.: Macroneurotrophism in the development of the vertebrate skeleton. Anthropologie (Brno), 32, 1994, pp. 1–24.
31. ROTH, M.: Role of neural growth in the pathomechanism of skeletal dysplasias: an experimental study. Pohybové ústrojí (Locomotor System), 2, 1995, pp. 85–111.
32. ROTH, M.: Congenital vertebral block, physiological and pathological, and degeneration of the disc: Common osteo-neuroradiological interpretation. (Czech text.) Čes.Radiol., 50, 1996, pp. 98–112.
33. RUBINSTEIN, H.C.: The effect of the growth hormone upon the brain and brain weight – body weight relation. J.comp.Neurol., 64, 1936, pp. 469–496.
34. SENSENIG, E.C.: The early development of the human vertebral column. Contrib. Embryol. No.214, Vol. 33, pp. 20-41. Carnegie Inst. Of Washington 1949.
35. Streeter, G.L.: Factors involved in the formation of the filum terminale. Amer. J.Anat., 25, 1919, pp. 1–11.
36. TÖNDURY, G., THEILER, K.: Entwicklungsgeschichte und Fehlbildungen der Wirbelsaule. 2.Aufl. (Die Wirbelsaule in Forschung und Praxis, Bd. 98). Hippokrates Verlag, Stuttgart 1990.
37. WOLPERT, L.: Pattern formation in biological development. Sci.American, 239, 1974, pp. 154–165.

INFORMACE O SPOLEČNOSTI PRO POJIVOVÉ TKÁNĚ ČLS J. E. PURKYNĚ (SPT)

Vážená paní kolegyně, vážený pane kolego,

dovolujeme si Vás informovat o možnosti stát se členem **Společnosti pro pojivové tkáně** (SPT), která v roce 2004 navázala na plodnou desetiletou činnost Společnosti pro výzkum a využití pojivových tkání vedenou panem prof. MUDr. M. Adamem, DrSc. Posláním SPT je podpora rozvoje výzkumu pojivových tkání, šíření nových poznatků týkajících se všestranných analýz tkání z obecného pohledu, moderních klinických přístupů k diagnostice a léčbě. Dalším posláním SPT je usnadnění styků mezi jednotlivými odborníky navázáním spolupráce s různými vědeckými, odbornými, výrobními a farmaceutickými společnostmi.

Vědecké poznání a aplikace nejnovějších poznatků v klinické praxi nabyly v posledních letech nebývalého zrychlení, a to nejenom v zahraničí, ale i u nás. Tato skutečnost bezprostředně souvisí s kvalitativním rozvojem poznání i v nebiologických vědách a v moderních inženýrských přístupech. Stále více se prokazuje, že vše se vším souvisí – není náhodou, že nové poznatky a objevy vznikají na rozhraní oborů a různých vědních disciplín. Lidská společnost v posledních desetiletích dosáhla nové civilizační kvality – ve vědě a v jejich aplikacích zcela jistě, avšak v morálce a etice ne tak příliš. Biomedicína je v současné době rozsáhlou interdisciplinární vědou, která bez kooperace s jinými vědními obory by byla odsouzena ke stagnaci. Proto cílem SPT je nejenom integrovat odborníky v biomedicíně, ale i v technických sférách.

Prioritní snahou SPT je presentovat odborné veřejnosti a specialistům v klinické praxi nejnovější poznatky v oblasti pojivových tkání. SPT je i společenskou organizací klinických pracovníků, vědců, pedagogů, která si klade za cíl společensky sblížit nejenom pracovníky v aktivní službě, ale i kolegyně a kolegy v důchodovém věku a v neposlední řadě i studenty a mladé doktorandy z vysokých škol, universit a akademických ústavů.

SPT organizuje během každého roku alespoň dvě odborná a společenská setkání, kde vedle odborných přínosů je kladen důraz také na společenské – přátelské diskuse všech vás, kteří nechtějí stagnovat a kteří nechtějí přemýšlet o nových poznatcích izolovaně a osamoceně.

Pro uhrazení nejzákladnějších nákladů na korespondenci se členy společnosti, jejich informovanost a pořádání odborných kolokvií, symposií a společenských odborných setkání byl stanoven **roční členský příspěvek pro aktivní kolegyně a kolegy 200 Kč** a **pro studenty a důchodce 100 Kč.**
SPT vydává časopis Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii, do kterého se i vy můžete aktivně zapojit odbornými články a vašimi zkušenostmi. **Pro současné odběratele časopisu PU a další zájemce doporučujeme přihlásit se na http://www.pojivo.cz/en/newsletter/, zadat jméno a e-mailovou adresu, na kterou bude časopis posílán. Na webové doméně SPT ČLS JEP http://www.pojivo.cz/cz/pohybove-ustroji/ naleznete ve formátu PDF všechna jednotlivá čísla a dvojčísla časopisu (včetně Suplement) vydaná od roku 1997 (bezplatný přístup).**
Milí kolegové, nestůjte opodál a připojte se k české inteligenci – v oblasti pojivových tkání, ke které i Vy zcela jistě patříte. V naší krásné české zemi je třeba, aby prameny poznání byly stále živé a permanentně udržované. Poslání každého z nás není náhodné. Jsme velice zavázáni našim předkům, kteří rozvíjeli kvalitu odbornosti v naší zemi. Nepřipusťme útlum vědy u nás. Nenechme se zmanipulovat programovanou lhostejností, vyrůstající z neodbornosti, závisti a z patologického prosazování ekonomicko-mocenských zájmů.

Těšíme se na Vás a na Vaše zkušenosti – přijďte mezi nás!

Za výbor společnosti:

Prof. MUDr. Ivo Mařík, CSc. – předseda
Prof. MUDr. Josef Hyánek, DrSc. – čestný předseda
Prof. Ing. Miroslav Petrtýl, DrSc. – místopředseda
RNDr. Martin Braun, PhD – vědecký sekretář
Ing. Jana Zelenková – pokladník

Přihlášku do Společnosti pro pojivové tkáně ČLS JEP, z.s. najdete na adrese:
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INFORMATION ABOUT SOCIETY FOR CONNECTIVE TISSUES CMA J. E. PURKYNĚ (SCT)

Dear Sir/Madam, dear Colleagues,

We have great pleasure to inform you about the possibility of joining the **Society for Connective Tissues** (SCT) that was established in 2004 in order to continue the ten-year fruitful activities of the Society for Research and Use of Connective Tissue headed by Professor M. Adam, MD, DSc. The activities of the SCT are aimed at supporting the research development in the field of connective tissues, the dissemination of knowledge related to the all-purpose analyses of the tissues in general, and the application of the up-to-date approaches to the diagnostics and clinical practice. Further, the SCT is determined to facilitate contacts between the respective specialists by means of collaboration with various research, professional, production and pharmaceutical companies.

In the last few years, the scientific knowledge and the application of the latest findings in the clinical practice have accelerated on an unprecedented scale, not only abroad, but also in this country. This fact is closely connected with the qualitative development of the knowledge in the non-biological sciences and in the up-to-date engineering approaches. The fact that all things are mutually connected is becoming more and more evident. It is fairly obvious that the new knowledge and discoveries arise on the dividing line between the different fields and disciplines of science. In the last few decades, the human society has reached the new qualities of civilization. This applies, in particular, for the disciplines of science and their applications; however, this statement can hardly be used with reference to the moral and ethical aspects of the human lives. At present, the biomedical science is a wide-ranging interdisciplinary science which, in case of lack of cooperation with other scientific disciplines, would be condemned to stagnation. That is the reason why the SCT is aimed at integrating the specialists both within the biomedical science and within the engineering fields.

The priority objective of the SCT is to present the professional public and specialists involved in the clinical practice with the latest knowledge in the field of connective tissues. The SCT is also a civic society whose aim is to bring people close together by joining members of the clinical staff, researchers and teachers including the retired ex-colleagues and, last but not least, the undergraduates and PhD students from universities and academic establishments.

The SCT is planning to organize at least two professional and social meetings each year. Beside the professional contribution of these meetings, emphasis will be laid on social activities – informal

discussions of all those who do not want to stagnate and who do not want to acquire the new knowledge in solitary confinement.

The annual membership fee is 200 Czech crowns for full workers, and 100 Czech crowns for students and pensioners. This membership fee shall be used to cover the basic costs on correspondence with the members of the Society in order to inform them about organizing colloquiums, symposiums and social meetings.

The SCT is also engaged in publishing of the interdisciplinary journal entitled Locomotor System – Advances in Research, Diagnostics and Therapy. You are invited to contribute to the journal writing professional articles, exchanging experience or, simply sharing your opinions. **You can find the volumes of Locomotor System journal at http://www.pojivo.cz/cz/pohybove-ustroji/ since 1997 (free of charge). Since 2013 only electronic edition of the journal is available. That is why we recommend to all subscribers and those interested apply at http://www.pojivo.cz/en/newsletter, enter personal data, titles and e-mail address where the journal will be mailed.**

Dear Colleagues, do not stand aside (suffering from terrible lack of time) and join the professional people in the field of connective tissues to whom you undoubtedly belong. In this beautiful country, the sources of knowledge should be kept alive and maintained permanently. Our role in this process is not accidental. We are much obliged to our ancestors who had developed the qualities of proficiency in this country. Do not allow the decline of science. Do not let the programmed indifference arising from lack of professionalism, enviousness, and pathological promotion of economic and power interests manipulate us.

We are looking forward to meeting you. We will be pleased if you join us and share your experience with us.

On behalf of the committee of the Society for connective tissues:

Professor Ivo Marik, MD, PhD – chairman
Professor Josef Hyánek, MD, DSc – honorary chairman
Professor Miroslav Petrtýl, MSc, DSc – vice-chairman
Braun Martin, Dr, PhD – research secretary
Zelenková Jana, Eng – treasurer

Membership application form of the Society for Connective Tissues, Czech Medical Association J.E. Purkynje, Prague you can find on the following link:
http://www.pojivo.cz/cz/wp-content/uploads/2020/02/PrihlaskaCLS_JEP_SPT_form.pdf

Membership application form of the Orthopaedic-Prosthetic Society, Czech Medical Association J.E. Purkynje, Prague you can find on the following link:
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TÉMATIKA PŘÍSPĚVKŮ

K uveřejnění v časopise Pohybové ústrojí se přijímají rukopisy prací z oblasti pohybového ústrojí člověka, které se týkají především funkce, fyziologického i patologického stavu kosterního a svalového systému na všech úrovních poznání, diagnostických metod, ortopedických a traumatologických problémů, příslušné rehabilitace a léčebné i preventivní péče. Předmětem zájmu jsou týmové práce z oboru dětské ortopedie a osteologie, dále problémy z oboru biomechaniky, patobiomechaniky a bioreologie, biochemie a genetiky. Časopis má zájem publikovat články kvalitní, vysoké odborné úrovně, které přinášejí něco nového, jsou zajímavé z hlediska aplikací a nebyly doposud nikde uveřejněny s výjimkou publikace ve zkrácené formě.

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SUBJECT MATTER OF CONTRIBUTIONS

The journal Locomotor System will publish the papers from the field of locomotor apparatus of man which are above all concerned with the function, physiological and pathological state of the skeletal and muscular system on all levels of knowledge, diagnostic methods, orthopaedic and traumatologic problems, rehabilitation as well as the medical treatment and preventive care of skeletal diseases. The objects of interest are interdisciplinary papers on paediatric orthopaedics and osteology, further object of interest are problems of biomechanics, pathobiomechanics and biorheology, biochemistry and genetics. The journal will accept the original papers of high professional level which were not published elsewhere with exception of those which appeared in an abbreviated form.

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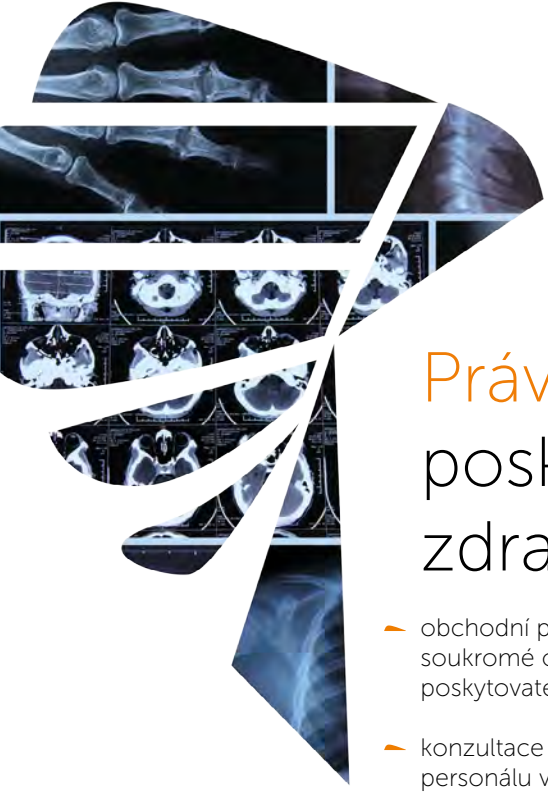

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lékařská péče v oborech ortopedie a ortopedická protetika ● zdravotní péče v ortotice a protetice ● konsilia pro zdravotnická zařízení ● výjezdová pracoviště v kraji ● zakázková činnost pro zdravotnická zařízení ● skoliotická poradna pro léčbu skolióz páteře mladistvých ● aplikace a výroba individuálních ortopedických vložek pro sport ● výroba individuálních zdravotnických prostředků – protéz končetin, ortéz, ortopedických vložek ● podologická poradna pro pacienty s problémy nohou (syndrom diabetické nohy, bolesti nohou) ● specializované centrum pro aplikaci a výrobu myoelektrických protéz horních končetin

Ortopedická protetika Praha s.r.o.

Výrobce individuálních ortopedicko-protetických pomůcek

zajišťuje:
- Lékařské vyšetření pacienta a předpis pomůcky
- Zhotovení všech individuálních ortopedických pomůcek (protézy HK a DK, končetinové a trupové ortézy, měkké bandáže, ortopedickou obuv, ortopedické vložky apod.

provozní doba:
po 7.30–17.00; **út–čt** 7.30–16.00; **pá** 7.30–15.00

Ortopedická Protetika Praha s.r.o., Kloknerova 1/1245, 148 00 Praha 4
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Metro C stanice Chodov, dále autobus č. 135 stanice Dědinova – budova MEDICENTRUM

Partner všech zdravotních pojišťoven v ČR