FORMERLY ACTA PAEDIATRICA ACADEMIAE SCIENTIARUM HUNGARICAE

# Acta Paediatrica Hungarica

VOLUME 24, NUMBER 1, 1983



Akadémiai Kiadó, Budapest
ACTA PAEDIATR. HUNG. HU ISSN 0001-6527

# ACTA PAEDIATRICA

## HUNGARICA

A Quarterly of the Hungarian Academy of Sciences

Editor

P. V. VÉGHELYI

---

*Acta Paediatrica* publishes original reports of studies in paediatrics and borderline fields.

Manuscripts and editorial correspondence should be addressed to

*ACTA PAEDIATRICA*
Bókay J. u. 53.
H-1083 Budapest
Hungary

*Subscription information*

Orders should be addressed to

KULTURA Foreign Trading Company
P. O. Box 149, Budapest
H-1389

or its representatives

*Acta Paediatrica* is published in yearly volumes of four issues by

AKADÉMIAI KIADÓ

Publishing House of the Hungarian Academy of Sciences
Alkotmány u. 21.
H-1054 Budapest

# ACTA PAEDIATRICA

## HUNGARICA

VOLUME 24



AKADÉMIAI KIADÓ, BUDAPEST

1983

CONTENTS

Vol 24

*Amador A, Rodriguez C:* Testing of two score systems for the diagnosis of malnutrition ..... 231
*Balla G, Karmazsin L:* Evolution of serum $C_3$, IgA and IgM levels of healthy mothers and their nature newborns during the early neonatal period ..... 41
*Barbacki M, Sandhage K:* Non-invasive examination of pulmonary stenosis by transcutaneous Doppler technique ..... 367
*Barta L, Czinner A, Tichy M, Bedő M:* Changes in cardiovascular factors in diabetic children during a camping holiday ..... 337
*Barta L, Molnár M, Madácsy L, Barta-Bedő M, Körner A:* The position of the diabetic child in society ..... 79
*Boda D, Németh I:* Effect of parenteral allopurinol treatment in critically ill children in need of intensive care ..... 247
*Bodánszky H, Horváth K, Horn G:* The D-xylose-test in coeliac disease ..... 17
*Book reviews* ..... 101
201
291
371
*Borbolla L, Menéndez I:* Dermatoglyphics in Saethre-Chotzen syndrome: a family study ..... 269
*Cserháti E, Gegesi Kiss A, Mezei Gy, Kelemen J, Puskás J:* Positive prick tests of immediate type in non-allergic children ..... 189
*Czeizel A, Pázsy A, Pusztai J, Nagy M:* Aetiological monitor of congenital abnormalities ..... 91
*Czinner A, Tichy M, Barta L:* Prevention of adult cardiovascular disease in obese children ..... 195
*Dobronyi I, Pásztor A, Nagy I, Paraicz E:* Cerebrovascular occlusion in childhood .. 361
*Doszpod J, Csákány MG, Török M, Gáti I:* Relationship between placental perfusion and endocrine parameters of pregnants in cases of intrauterine growth retardation ..... 355
*Endreffy E, Boda D:* Effect of drugs used in obstetrics on the constriction by oxygen of the ductus arteriosus of the rabbit fetus ..... 281
*Forrai G, Gordos G:* A new acoustic method for discrimination of monozygotic and dizygotic twins ..... 315
*Gere A, Bernolák EA, Gaál Ö, Cholnoky P, Őry I:* Fatty acid composition of human milk and milk-based formulas in Hungary ..... 53
*György I:* Prognostic value of sleep analysis in newborns with perinatal hypoxic brain injury ..... 1
*Henker J, Zugehör M, Morrenz J:* Reticulin antibodies in coeliac disease ..... 349
*Horváth K, Horn G, Bodánszky H, Tóth K, Váradi S:* Disaccharidases in coeliac disease ..... 131
*Ilyés I, Jezerniczky J, Tóth T, Csorba S:* Serum ferritin level in infants and children with anaemia and malignant disease ..... 73
*Jójárt G, Záborszky B, Szondy E, Horváth M, Hegedűs I:* Primary aortitis in childhood ..... 159
*Katona F:* An orienting diagnostic system in neonatal and infantile neurology . 299
*Kerepesi T:* Maturation of the fetal lung. I. Phosphatidic acid phosphohydrolase in the fetal and newborn rat ..... 67
*Kerepesi T, Arányi P:* Glucocorticoid receptors in circulating lymphocytes of premature infants and newborns ..... 343
*László A, Havass Z:* Serum alpha-galactosidase activity in children with Duchenne-type muscular dystrophy and in gene carriers ..... 327

*László A, Hudák J, Szabó E, Varga L:* Antinuclear factor, smooth and striated muscle antibodies in Duchenne-type muscular dystrophy ..... 331
*László A, Kaiser G:* HLA phenotypes in children with Duchenne muscular dystrophy and their gene carrier mothers ..... 323
*Lombay B:* Assessment of skeletal age in the first year of life on basis of the caput humeri ossification centres ..... 221
*Molnár S, Kajtár P:* Effect of lithium carbonate on the peripheral leukocyte count in children suffering from haematological malignancies ..... 137
*Molnár S, Kajtár P:* Effect of lithium carbonate on the bone marrow of patients treated for haematological malignancies ..... 211
*Mücke J:* Clinical diagnosis of malformation syndromes: syndromatology in paediatrics ..... 85
*Pap G, Szőke J, Pap L:* Intrauterine growth retardation: ultrasonic diagnosis .. 7
*Peja M, Madácsy L, Kassay L, Bognár M:* Metabolic relations of serum lipids and lipoproteins in diabetic children ..... 217
*Péter F, Szentistványi S:* Changes of the growth hormone level after a single small dose of somatostatin ..... 63
*Pintér AB, Schäfer J:* Renal abscess in infancy ..... 287
*Ruppert F, Adonyi M, Ertl T, Sulyok E, Zámbó K, Csaba IF, Varga F:* Thyrotropin and prolactin response to thyrotropin-releasing hormone in healthy and asphyxiated full-term neonates ..... 111
*Schuler D, Kardos G, Koós R, Polcz A, Gács G, Révész T:* Late effects of therapy in children previously treated for leukaemia or malignant tumour ..... 255
*Shahar E, Barzilay Z, Altman G, Shohet I, Cohen BE:* Elevated risk of osteoarticular complications in children with acute Brucella melitensis infection ..... 263
*Sillanpää M, Terho P, Westerén H, Pisirici H:* Accidents in schoolchildren: epidemiologic, aetiologic and prognostic considerations ..... 119
*Singh R, Abudejaja A:* Six years mortality statistics in a Lybian paediatric hospital 175
*Sulyok E, Varga F:* Renal aspects of neonatal sodium homeostasis ..... 23
*Szabolcs M, Csorba S, Hauck M:* Isolation and physicochemical properties of an adenosine-rich gluten fraction ..... 149
*Tichá R, Santavy J, Matlocha Z:* Fetal alcohol syndrome: amino acid pattern . 143
*Tóth P, Keszei K, Méhes K:* Maternal regulation of fetal growth ..... 37
*Várkonyi Á, Boda M, Szabó I:* The importance of cow's milk protein intolerance in chronic diarrhoea of children ..... 169

*Acta Paediatrica Hungarica, 24 (1), pp 1–6 (1983)*

# Prognostic value of sleep analysis in newborns with perinatal hypoxic brain injury

Ilona GYÖRGY

Department of Paediatrics, University Medical School, Debrecen, Hungary

The correlation between the findings of polygraphic sleep analysis and the late prognosis was studied in 37 full-term newborns after perinatal hypoxic-ischaemic brain injury, and in 9 healthy neonates. The relationship with a poor prognosis was significant if there was (i) a sleep cycle disturbance (decreased level of active sleep; persistence of quiet sleep-trace alternant pattern in the total cycle); (ii) immaturity in bioelectric brain maturation $\geq 4$ weeks; (iii) depression of background activity. The correlation with favourable outcome was significant if (i) the EEG was normal; (ii) sleep spindles occurred.

The following findings were unrelated to prognosis: asymmetry, paroxysmal abnormalities, and reactivity of EEG to light or sound stimulation.

Assessment of the degree of perinatal hypoxic-ischaemic brain damage may have major therapeutic and prognostic implications. The neonatal EEG can be used to identify infants liable to future neurologic dysfunction [4, 10, 11].

The purpose of the present study was to investigate the correlation between the findings of polygraphic sleep analysis and the prognosis of full-term newborns with perinatal hypoxic-ischaemic brain injury.

## SUBJECTS AND METHODS

The subjects of the present study were full-term neonates with gestational ages ranging from 38 to 42 weeks and birthweights from 2.6 to 4.2 kg (mean 3.34 kg). Thirty-seven newborns suffered from perinatal hypoxia and 9 newborns were healthy. The newborns with perinatal hypoxic brain damage were selected according to the following criteria.

1. They had neurological signs and symptoms suggestive of encephalopathy during the neonatal period.

2. In their perinatal history signs of fetal distress were documented.

Infants with intracranial haemorrhage, bacterial meningitis and CNS malformation were excluded from the study.

Newborn infants with perinatal hypoxic brain damage were subdivided into groups of moderate and serious injury. The injury was considered serious if the newborn had deep coma (lack of corneal reflex, no response to pain) for more than 48 hours. 19 newborns were in the moderate group and 18 in the serious injury group.

52 daytime sleep-polygrams were recorded in 46 infants. The first record was prepared at mean age of $8.7 \pm 5.1$ days. The examination was repeated at two months of age in six newborns. An ORION 8 channel electroencephalograph was em-

ployed, using a paper speed of 30 mm/sec, with conventional gain and filter settings [1 11]. During the polygraphic studies, 4 EEG channels were used to monitor activity from the frontocentral and parieto-occipital regions ($F_3$–$C_3$, $P_3$–$O_1$, $F_4$–$C_4$, $P_4$–$O_2$). The electrodes were placed using the 10–20 system.

In addition, the following physiological data were recorded:

1. Horizontal ocular movements;
2. muscle activity by a surface electromyograph;
3. heart rate by ECG;
4. respiratory rate by means of a thermistor.
5. The behaviour of the newborn was documented on the polygraph paper.

Polygraphic recordings were performed during the interval between two feedings in the afternoon. Each recording period lasted 90 to 120 minutes. All records were analysed visually page by page (each page epoch = 20 sec). Each epoch was classified as active sleep (AS); quiet sleep (QS); indeterminate sleep (IS) or wakefulness (W) according to the conventional criteria [1].

The maturity of AS and QS patterns was determined on the basis of the data of Parmelee et al [5], Schulte et al [9] and Werner et al [11]. The morphology of quiet sleep and the occurrence of sleep spindles were observed.

The duration of AS and QS in a total sleep cycle was measured and compared in the three groups of newborns. Abnormalities of the recordings were also identified: abnormalities in background activity, asymmetry or sharp transients.

The next step was to determine the reactivity of EEG after light (stroboscope) and sound (slow and quick hand claps) stimulation.

Finally, the duration of apnoea in the different sleep states was observed.

The results of the three groups were compared.

All infants were subjected to a routine paediatric and special developmental neurological and psychological examination every three months. At the time of writing this paper the subjects range in age from 7 to 30 months. The neonatal EEG findings and the outcome of the newborns were compared.

The chi-square test was used to assess differences between the EEG findings and the outcome in the three groups.

## Results

The outcome of the three groups of newborns is presented in Table I. The relationship between outcome and the degree of acute clinical signs and symptoms is obvious.

Bioelectric brain maturity in the AS and QS states of the investigated newborns was compared with their postmenstrual age at the time of the recordings (Table II). The EEG was considered immature if the difference between postmenstrual age at the recording and bioelectric brain maturation was four weeks or more. In the most serious cases the discrepancy was 12 weeks. In many cases a heterochronism was observed: the patterns were characteristic of two maturational levels occurring in AS and QS states within the same record. If heterochronism was found, the more immature was always the AS.

In healthy newborns the duration of active sleep was longer than that of quiet sleep in the total sleep cycle, while the proportion of AS state decreased in infants with perinatal hypoxic insult (Table III). In the three most severe cases only QS (tracé alternant pattern) was found during the sleep cycle.

TABLE I

Prognosis of the investigated control (C) and of the newborns with moderate (M) and serious (S) hypoxic brain injury

| Outcome | Subjects (n) | | |
|---|---|---|---|
| | C n=9 | M n = 19 | S n= 18 |
| Normal without therapy | 9 | 6 | — |
| Normal after habilitation | — | 12 | 11 |
| Moderate cerebral palsy with or without slight mental retardation | — | 1 | 4 |
| Severe cerebral palsy with mental retardation and epilepsy | — | — | 3 |

Statistical significance (chi-square test) among the three groups, $p < 0.001$.

TABLE II

Bioelectric brain maturation and postmenstrual age of the control (C) newborns, and of the newborns with moderate (M) and serious (S) hypoxic brain injury

| Bioelectric brain maturation and postmenstrual age at recording | Subjects | | |
|---|---|---|---|
| | C n = 9 | M n = 19 | S n = 18 |
| Equal (in QS and AS states) | 9 | 10 | 4 |
| Retardation of bioelectric brain maturation $\geq$4 weeks | — | 5 | 7 |
| Heterochronism AS/QS | — | 4/0 | 7/3 |

Heterochronism = patterns characteristic of two maturational levels occurring in AS and QS states, discrepancy $\geq$ 4 weeks
AS/QS = number of infants with immature EEG in AS/QS states
Statistical significance (chi-square test) among the three groups, $p < 0.01$.

TABLE III

Proportion of AS/QS states in the total sleep cycle in the control newborns (C), and in the newborns with moderate (M) and serious (S) hypoxic brain injury

| Duration of state | Subjects | | |
|---|---|---|---|
| | C n = 9 | M n = 19 | S n = 18 |
| AS > QS | 9 | 12 | 9 |
| AS < QS | — | 7 | 6 |
| Only QS was found | — | — | 3 |

Statistical significance (chi-square test) among the three groups, $p < 0.05$.

TABLE IV

Background activity and sharp transients in the EEG of control newborns (C) and of the newborns with moderate (M) and serious (S) hypoxic brain injury

| EEG findings | Subjects | | |
|---|---|---|---|
| | C n = 9 | M n = 19 | S n = 18 |
| Normal background activity | 8 | 15 | 10 |
| Depressed EEG | | | |
| burst suppression | — | — | 3 |
| low voltage | — | — | 2 |
| Asymmetry | 1 | 4 | 3 |
| Sharp transients | 4 | 10 | 8 |

Statistical significance (chi-square test) among the three groups of background activity: $p < 0.05$, of sharp transients: NS.

A significant difference in background activity could be observed between the three investigated groups. Burst suppression pattern or low voltage EEG was found only in the seriously asphyxiated newborns. Asymmetry and sharp transients were detected in all the three groups (Table IV).

No response to low frequency photic stimulation was obtained in the majority of newborns with and without perinatal hypoxic brain damage. A frequency of 15–25 cycles/sec elicited a reaction in half of the newborns, regardless of the fact whether or not they had a brain injury.

Auditory stimulation by slow and quick hand claps elicited a response in every subject except three infants with nonreactive low voltage EEG. In many cases a pattern similar to K-complexes appeared after the stimulation, and signs of habituation and dishabituation were also observed.

The duration of the breathing interval in the healthy newborns was always less than 3 sec, also during active sleep. In the group of moderate asphyxia, 9 out of 19 infants, and in the group with serious asphyxia, 15 of 19 newborns had apnoeas longer than 3 sec during AS states.

The examinations were repeated in three infants from the moderate, and in three from the serious group. In the newborns with moderate hypoxic brain injury the seizure pattern persisted even at two months of age. At present these children are 7, 18, and 30 months old, respectively, and they have no symptoms of epilepsy. Of the three infants from the serious group who exhibited only a tracé alternant pattern in the total sleep cycle during the neonatal period, in two cases the abnormality was unchanged at the age of two and a half months. The third infant had

TABLE V

Correlation between EEG and prognosis

| | |
|---|---|
| Findings associated with favourable prognosis: | |
| normal EEG | $0.05 > p < 0.1$ |
| occurrence of sleep spindles | $p < 0.05$ |
| Findings associated with unfavourable prognosis: | |
| depressed background activity | $p < 0.05$ |
| QS > AS in the sleep cycle | $p < 0.05$ |
| immaturity $\geq$ 4 weeks in EEG | $p < 0.01$ |
| apnoea longer than 3 sec | $p < 0.05$ |
| TA predominance during the total sleep cycles | $p < 0.001$ |
| Findings failing to predict prognosis: | |
| asymmetry | |
| sharp transients | |
| non-reactivity to light or sound stimulation (except total lack of reactivity and lability of EEG) | |

developed AS by this time but in quiet sleep the tracé alternant could still be observed. One of the infants with disorganization of the sleep cycle at four months of age fell asleep during the examination. During sleep high voltage slow patterns predominated but bursts reminiscent of tracé alternant (TA) were periodically visible in the record. The EEG findings and their correlation with the prognosis can be summarized as in Table V.

## DISCUSSION

The present study has shown that neonatal sleep analysis is a good prognostic indicator after perinatal hypoxic insults. Our prospective examinations corroborated the data in the literature in that the depression of background EEG had a high prognostic value, whereas an asymmetry and paroxysmal EEG abnormalities did not predict the outcome [4, 7, 10, 11].

We found that the disturbances of the sleep cycle also correlated with the prognosis. When the background activity was depressed, the sleep cycles were always disturbed.

In contrast with the experience of Watanabe et al (10), we found that the duration of quiet sleep increased after perinatal hypoxic brain injury. This finding corresponds to the observations in adult patients with traumatic brain injury [6] and to some experimental findings [8].

The persistence of the QS state (tracé alternant pattern) during the total sleep cycle seems to be an unfavourable prognostic sign. The retardation in biolectric brain maturation after neonatal hypoxic brain damage agree well with the findings of Karch et al. [3]. They interpreted

the immature bioelectric brain activity occurring in patients with perinatal hypoxia as an unspecific response to functional and structural changes in the CNS. As to respiration, Haidmayer and Kurz [2] found considerably prolonged apnoea periods in high risk infants. Our experience was the same. The long apnoea of newborns with hypoxic brain injury appeared always during active sleep.

## References


1. Anders TF, Emde R, Parmelee A: A manual of standardized terminology, techniques and criteria for scoring of states of sleep and wakefulness in newborn infants. UCLA Brain Information Service NINDS Neurological Information Network, Los Angeles 1971
2. Haidmayer RH, Kurz R: Respirationsanalysen beim schlafenden Säugling. Wien Med Wochenschr 129: 372, 1979
3. Karch D, Kastl E, Sprock I, Bernuth H: Perinatal hypoxia and bioelectric brain maturation of the newborn infant. Neuropaediatrie 8: 253, 1977
4. Monod N, Rajot N, Guidasci S: The neonatal EEG: statistical studies and prognostic value in full-term and preterm babies. Electroenceph. clin. Neurophysiol. 32: 529 (1972)
5. Parmelee AH Jr, Schulte FJ, Akiyama Y, Wenner W, Schultz MA, Stern E: Maturation of EEG activity during sleep in premature infants. Electroencephalogr Clin Neurophysiol 24: 319, 1968
6. Ron S, Agom D, Hary D, Cohen M: Time related changes in the distribution of sleep stages in brain injured patients. Electroencephalogr Clin Neurophysiol 48: 432, 1980
7. Rose AL, Lombroso CT: Neonatal seizure states. A study of clinical, pathological and EEG features in 135 full-term babies with a long term follow-up. Pediatrics 45: 404, 1970
8. Saino K, Putkonen PTS: Sleep-waking cycle after cerebral ischemia. Electroencephalogr Clin Neurophysiol 39: 663, 1975
9. Schulte FJ, Michaelis R, Nolte R, Albert G, Parl U, Lasson U: Brain and behavioural maturation in newborn infants of diabetic mothers. Part I. Nerve conduction and EEG patterns. Neuropaediatrie 1: 24, 1969
10. Watanabe K, Miyazaki S, Hara K, Hakamada S: Behavioral state cycle, background EEG-s and prognosis of newborns with perinatal hypoxia. Electroencephalogr Clin Neurophysiol 49: 618, 1980
11. Werner SS, Stockard JE, Bickford RG: Atlas of Neonatal Encephalography. Raven Press, New York 1977


*Received July 27, 1981*

I György MD
Pf 32
H-4012 Debrecen, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 7—15 (1983)*

# Intrauterine growth retardation: ultrasonic diagnosis

G Pap, J Szőke, L Pap

County Hospital, Nyíregyháza, and Institute for Telecommunication Electronics, Technical University, Budapest

In 3258 pregnant mothers with ascertained gestational length, 3736 biparietal and transverse thoracic diameters were measured by a rapid screen ultrasound device. The data were processed by computer and the possibilities of detection and typing of intrauterine fetal retardation were examined. Serial measurements performed during pregnancy satisfactorily detected type I or the proportional type. The asymmetrical form, type II, can be distinguished by the Neyman-Pearson method. The decision curves applicable for each gestational week have been computed and are described. They can also be used for determination of the degree of intrauterine wasting.

Unsatisfactory development of the fetus has become a central problem of both obstetrics and paediatrics. Increased attention paid to "small for dates" is justified by their increased perinatal and infant mortality rates, their high incidence of malformations and their elevated risk for late, principally cerebral, complications [2, 9, 17]. Prevention and therapy of intrauterine growth retardation (IUR) have not yet been fully solved but early detection and the choice of the optimum time for delivery may help to achieve good results before irreversible changes have occurred.

The introduction of ultrasound (US) has revolutionized the diagnostics of intrauterine development of the fetus. The best known approach is measuring the biparietal diameter of the skull (Bip) and by weekly measurements performed in a sufficient number of cases a standard curve can be established. Comparison of the actual measurement with this curve allows the conclusion whether development of the fetus is normal or retarded [2, 3, 5, 8, 11, 13, 14, 15]. Two main types of retardation have been recognized [9, 12, 17], different in both aetiology and consequences [1, 9, 17]. Therefore, distinction of the two types is imperative (see Table I). If the growth rate of Bip declines from the second trimenon but the decline is gradual, the proportional type can be assumed. If the onset of the retardation in Bip increase falls to the third trimenon and skull development stops, this points to an asymmetrical retardation [9, 10, 13, 18].

In many cases of the disproportionate type malnutrition hardly or not at all affects skull development,

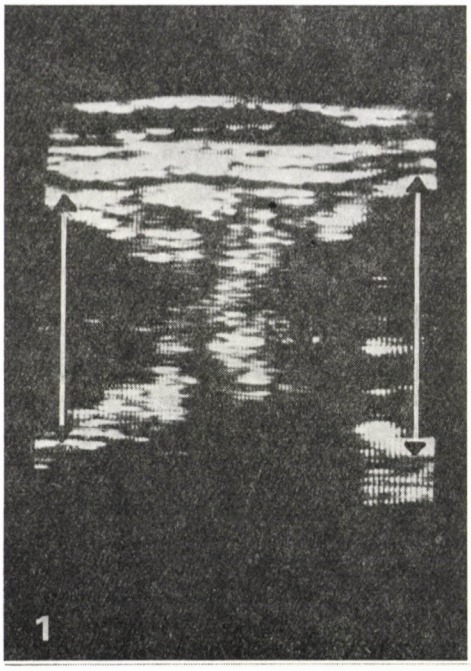
TABLE I

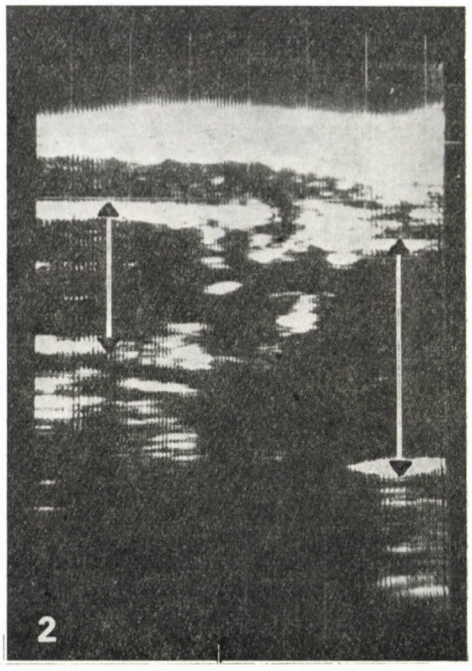
The main characteristics of IUR types
Either type occurred in 9.9% of all neonates in our material
(literature data: 8—12%)

| | Type I Symmetrical | Type II Asymmetrical |
|---|---|---|
| Incidence within the retarded | 14% in our series (literature: 10—30%) | 86% in our series (literature: 70—90%) |
| Causes | physique, inheritance, social factors, chronic diseases, tobacco, etc. | placental insufficiency (gestosis, nephritis, hypertension, heart defect, postponed labour, diabetes, etc.) |
| Period of onset | from the beginning of the 2nd trimenon, during the period of cell proliferation. | during the 3rd trimenon, the period of cell hypertrophy |
| Consequences | Small, proportionate organs containing a reduced number of cells; persistence beyond the neonatal period. Good Apgar values and adaptation. High incidence of malformations and enzymopathies. | Normal number of cells of reduced size. Length and skull size hardly affected, wasting in other organs, especially in adipose tissue, disproportionate body. Intrauterine asphyxia, low Apgar values, pulmonary oedema and haemorrhage, hypoglycaemia, high perinatal and neonatal mortality and morbidity, late neurological sequelae. |

the fetus appears to economize with the brain tissue, while other, less vital organs may cease to develop or, in extreme cases, may even lose weight [9, 17, 18]. It seems therefore logical that in addition to measuring the Bip, exact and synchronous measurements of other organs by ultrasound are necessary for a better approach of actual fetal development and distinction between the two main types of intrauterine retardation. Better estimates of the actual weight have been achieved [5, 7, 11, 16], by adding some other measurements to the previously used Bip. Most workers use quotients for the diagnosis of asymmetric intrauterine retardation; Bip/abdominal diameter [15], Bip/abdominal circumference [9], Bip/thorax area [18], Bip/transverse thorax diameter (Thq) [6], etc. A quotient exceeding a certain value can be regarded as an indicator of asymmetric retardation. E.g. during the 40th gestational week fetuses showing the proportionate type have a Bip/Thq value between 0.93 and 1.05 while a value above 1.05 points to disproportionate growth retardation (Figure 2).

In this study we have attempted to improve early detection and distinction of IUR by computer analysis of our serial data obtained in a large number of pregnancies.



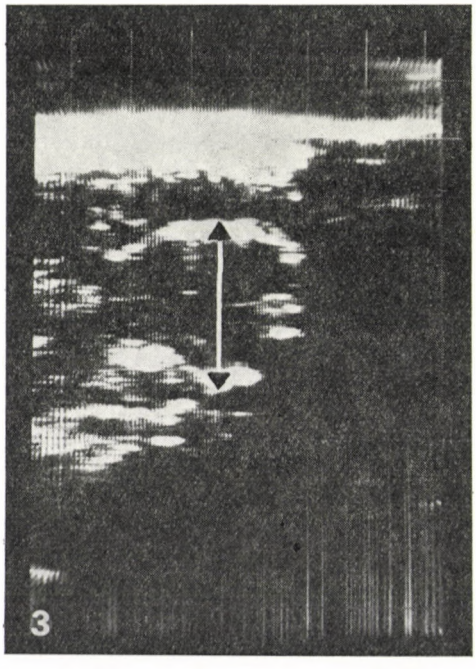




FIG. 1. Fetus of 34 weeks. Skull (right) and thorax (left), longitudinal sections. Bip: 88 mm, Thq: 84 mm. Physiological proportional development

FIG. 2. Fetus of 33 weeks. Skull (right) and thorax (left), longitudinal sections. Bip: 83 mm, Thq: 56 mm. Severe asymmetrical IUR

FIG. 3. Fetus of 33 weeks. Transverse section of thorax. Thq: 56 mm. Severe asymmetrical IUR

## Material and Method

A total of 3736 US measurements were performed by the rapid screen device Vidoson 635-S from the 25th week of gestation. All consecutive patients fulfilling certain criteria and attending from 1 January, 1975, to 31 December, 1979, were involved in the study. In addition to measuring Bip, Thq was measured in the plane between the dome of the diaphragm and the apex of the heart using the method of Hansmann [5, 8] (Figures 1, 2 and 3). Data obtained in 3258 mothers who had had a regular bleeding cycle, the exact date of the last menstruation of whom was known, who had single pregnancy and gave birth to a live child were also included in the study. Retardation was diagnosed in all infants having a birth weight below the 10th percentile, as generally accepted [9, 13, 18]. This group was then subdivided on the basis of the ponderal index (PI)

$$PI = \frac{\text{body weight in g}}{(\text{body length in cm})^3} \times 100.$$

All neonates born during or before the 36th gestational week and having a PI value attaining or exceeding 2.0 and all infants born during or after the 37th week and having a PI value equal to or higher than 2.2 were regarded as belonging to the asymmetrical, disproportionate type of intrauterine growth retardation [4]. Since we have shown that the predictive value of Bip on weight can markedly be increased by measuring also Thq [11], we have attempted to find relationships between Bip and Thq values obtained at various gestational ages and the weight and proportions of the subsequently born infant.

## Results

In the histograms of Bip-Thq values plotted against gestational age the areas of infants without retardation, of infants affected by symmetrical or asymmetrical retardation showed considerable overlapping. This is the result of the statistical character of biological events and in our case it means that even theoretically there is no method of decision perfectly discriminating the three types on the basis of measurements performed before birth since some retarded infants exhibit the same parameters as normal infants do.

In agreement with other workers [9, 13, 15, 18] we believe that serial US measurements are best for the early detection of type I, the symmetrical form of retardation. If the menstruation history is exactly known, Bip and Thq values corresponding to the same earlier gestational week indicate a proportionate retardation [5, 6, 11]. If the calculated term is uncertain, calculation of the weekly rates may be helpful, flattening of the Bip growth rate normally occurs during the 32nd or 33rd week of gestation (Fig. 4).

Histograms were composed from the Bip-Thq values obtained in non-retarded respectively asymmetrically retarded fetuses during the 32—42 weeks of gestation. Fig. 5. illustrates the results obtained for the 40th gestational week. It can be seen and be proved mathematically that the Bip/Thq value does not optimally discriminate the two groups because the lines constructed by connecting the points representing identical proportions (Lines A, B and C) cross the scatter areas of both non-retarded and asymmetrically retarded infants

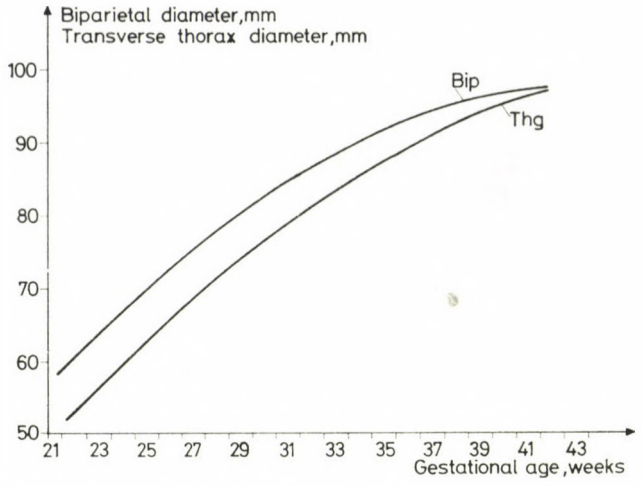



FIG. 4. Mean growth curve for Bip and Thq from the 22nd gestational week

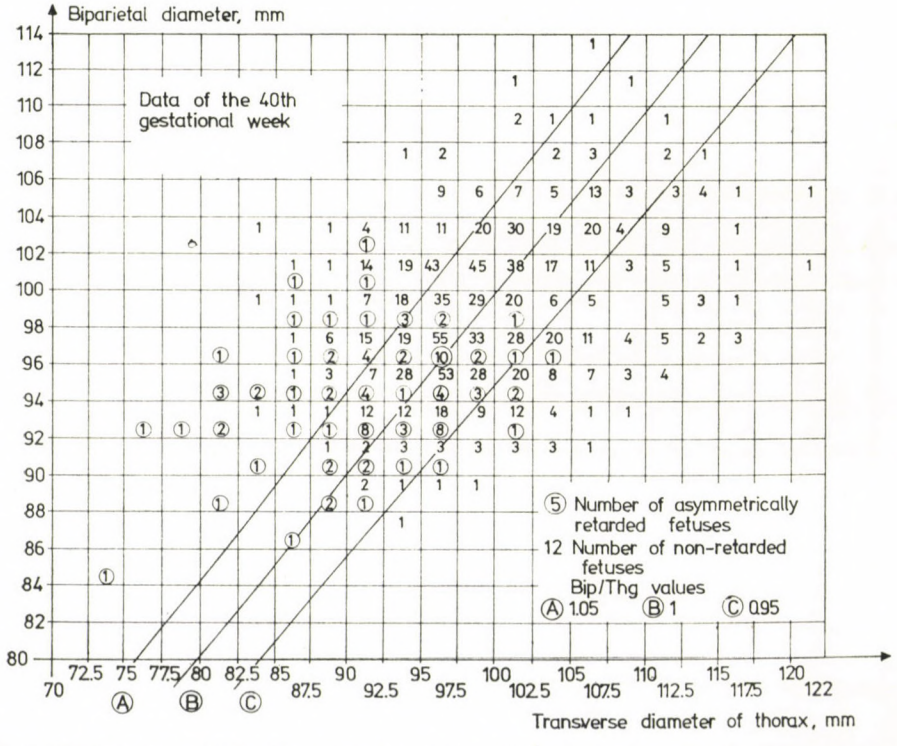



FIG. 5. Histograms of Bip-Thq measurements obtained in non-retarded and asymmetrically retarded fetuses in the 40th gestational week. A, B, C: lines representing identical Bip/Thq values

without separating them satisfactorily.

Optimum separation can be achieved by application of the mathematical method of Neyman-Pearson. By this method various optimal decision curves can be constructed fulfilling requirements arbitrarily fixed in advance; these curves separate the two groups, leaving the retarded values on the left and the normal ones on the right of the curve. Of course, the curves cannot perfectly separate the groups for the aforementioned reasons; quite obviously, any of them can be characterised by two values of error, the ratio of undetected asymmetrically retarded neonates to all cases showing this abnormality and the number of normal infants falsely classified as asymmetrically retarded ones to the total number of non-retarded neonates. The principal difference between the various decision curves consists in the capacity of detecting a certain percentage of asymmetrically retarded fetuses minimalizing at the same time the proportion of normal fetuses falsely diagnosed as retarded ones. Quite evidently, if we arbitrarily increase the percentage of retarded fetuses detected by the discrimination curve, the proportion of the spurious retarded cases will also increase; these latter cases have then to undergo

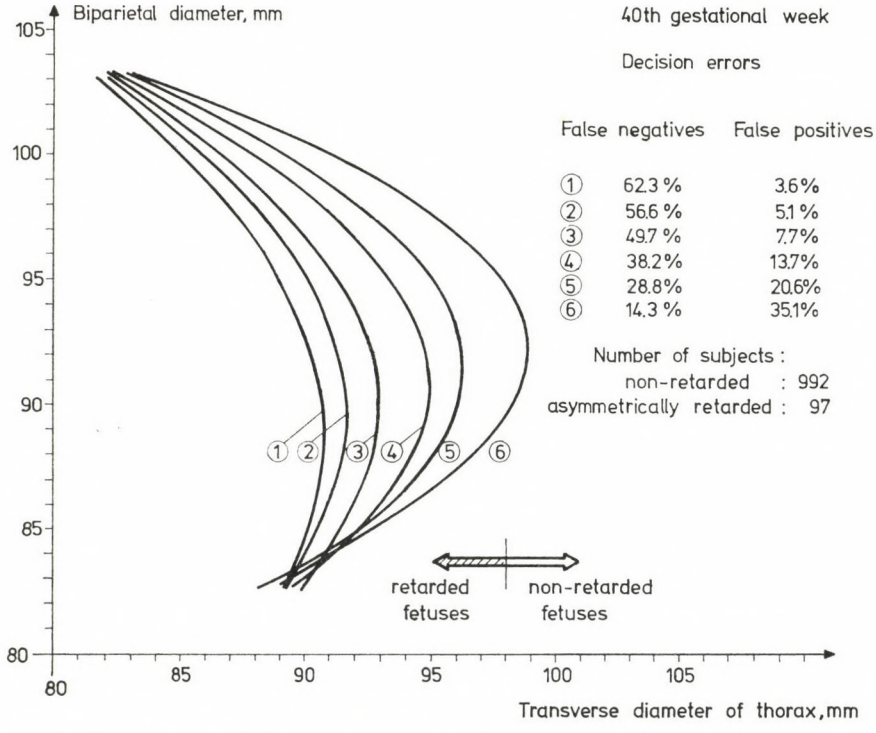



FIG. 6. Decision curves with various percentual error values for discrimination of non-retarded and asymmetrically retarded fetuses in the 40th gestational week

superfluous examination. It is just the clinician's task to decide how much additional work is tolerable as the price of better detection. Fig. 6 shows the various decision curves constructed for the 40th gestational week and the percentual risks for error are also indicated. The clinically acceptable risks have to be established according to facilities and other factors. It has however, to be stressed, that the differences between the various curves only influence decisions in ambiguous situations since values very far away from any curve, i.e. representing cases with extremely severe intrauterine malnutrition can be evaluated beyond doubt.

## Discussion

Our weekly sets of decision curves are helpful in the early diagnosis of our suspicion for asymmetric retardation. A 50 respectively 80% safety for detection of type II malnutrition was fixed, this is related to an acceptably low risk of error of a false diagnosis of growth retardation among normal fetuses (Figs. 7 and 8). Since this type of retardation does not occur before the third trimenon and no sufficient number of data for the period before the 32nd gestational week are available, no curves were constructed for the period preceding the 32th week. In addition, such

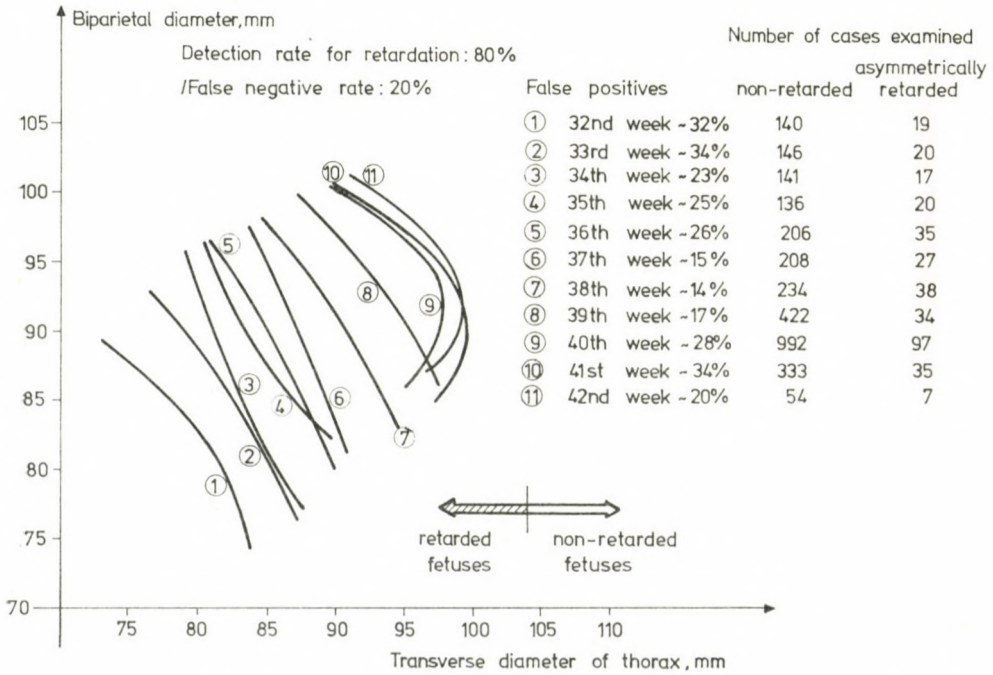



Fig. 7. Decision curves with a fixed 50% safety for detection of asymmetrical retardation and with different percentual error values in misclassifying normal fetuses, from the 32nd to the 42nd gestational week

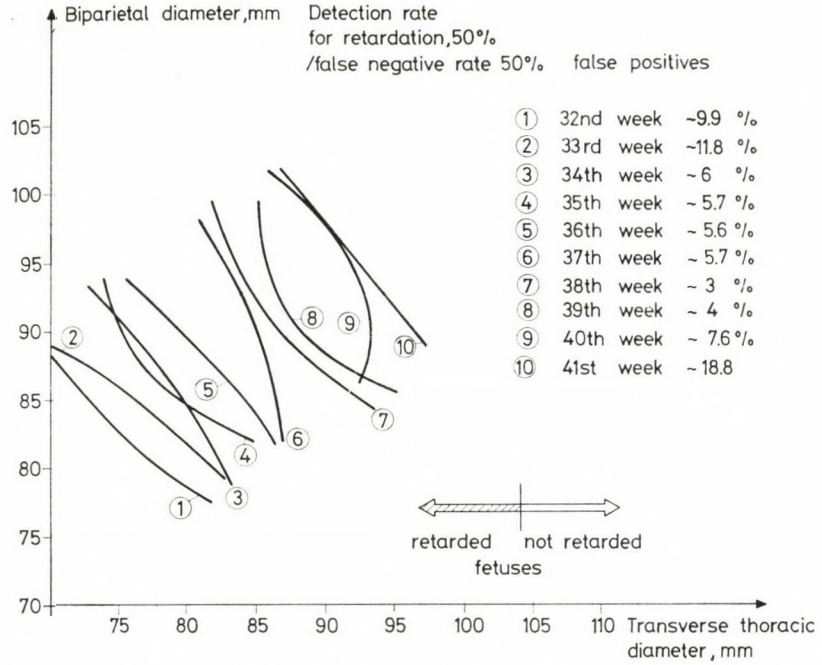



FIG. 8. Decision curves with a fixed 80% safety for detection of asymmetrical retardation and with different percentual error values in misclassifying normal fetuses, from the 32nd to the 42nd gestational week

curves would be rather impracticable considering the low viability of neonates born before this time. An exact menstrual history is also important but the decision curve of the week corresponding to the Bip value can be used in cases with uncertain menstrual history; in fact, in certain cases a single measurement may be sufficient for validation of the diagnosis of severe intrauterine retardation of the asymmetrical type. The validity can be further strengthened by serial measurements.

Our mathematical approach underlines the principle that a single examination or finding cannot alone lead to the diagnosis. No strict line can be drawn between the retarded and non-retarded during pregnancy and after birth. Let us mention that the critical values of the weight percentile (e.g. the 10th) or the ponderal index are also fully arbitrary. Careful observation, serial hormone determinations, loading tests, amnioscopy, etc., are all indispensable in the diagnosis of intrauterine malnutrition, transitory and mild cases included. Ultrasound is only one of these methods.

## REFERENCES

1. Campbell S: Fetal growth. Clin Obstet Gynecol 1: 41, 1974
2. Campbell S, Dewhurst CJ: Diagnosis of the small-for-dates fetus by serial ultrasonic cephalometry. Lancet 2: 1002, 1971

3. Campbell S, Newmann GB: Growth of fetal biparietal diameter during normal pregnancy. J Obstet Gynaec Br Cwlth 78: 513, 1971
4. Fekete M, Járai I: Fetal growth and its measurement. In: Perinatal Medicine (Kerpel-Fronius E, Véghelyi P, Rosta J eds) Akadémiai Kiadó, Budapest 1978. p 71
5. Hansmann M: Kritische Bewertung der Leistungsfähigkeit der Ultraschalldiagnostik in der Geburtshilfe heute. Gynaekologe 7: 1, 1974
6. Hansmann M, Voigt M, Lang N: Ultraschallmessdaten als Parameter zur Erkennung einer intrauterinen Wachstumsretardierung. Arch Gynaecol 214: 194, 1973
7. Issel EP, Prenzlau P: Eine neue Methode zur Berechnung des fetalen Gewichtes mittels Röntgenstrahlen. Zentralbl Gynaecol 96: 417, 1974
8. Kratochwil A: The state of ultrasound diagnosis in perinatal medicine. J Perinat Med 3: (2) 75, 1975
9. Kurjak A, Latin V, Polak J: Ultrasonic recognition of two types of growth retardation by measurement of four fetal dimensions. J Perinat Med 6: 102, 1978
10. Levi S, Smets P: Intrauterine fetal growth studied by ultrasonic biparietal measurements. Acta Obstet Gynecol Scand 52: 193, 1973
11. Pap G, Pap L: Ultrasonic estimation of gestational age and fetal weight. Acta Paediatr Acad Sci Hung 20: 119, 1979
12. Rosso P, Winnick M: Intrauterine growth retardation. A new systematic approach based on the clinical and biochemical characteristics of this condition. J Perinat Med 2: 147, 1974
13. Sabbagha RE: Intrauterine growth retardation antenatal diagnosis by ultrasound. Obstet Gynecol 52: 252, 1978
14. Szemesi I: Über die Ultraschall-Diagnostik in der Geburtshilfe und Frauenheilkunde. Acta Chir Acad Sci Hung 15: 239 1974
15. Tarró S: Ultraschallzeichen der intrauterinen Stoffwechselstörungen. Zentralbl Gynecol 101: 41, 1979
16. Thompson HE, Holmes JH, Gottesfeld KR, Taylor ES: Fetal development as determined by ultrasonic pulse echo techniques. Am. I Obstet Gynecol 92: 44, 1965
17. Urrusti J, Yoshida P, Velasco L, Frenk S, Rosado A, Sosa A, Morales M, Yoshida T, Metcoff J: Human fetal growth retardation: I. Clinical features of sample with intrauterine growth retardation. Pediatrics 50: 547, 1972
18. Wladimiroff MD, Bloesma CA, Wallenburg HCS: Ultrasonic assessment of fetal head and body sizes in relation to normal and retarded fetal growth. Am J Obstet Gynecol 131: 857, 1978

*Received 3 April 1982*

G Pap MD
Megyei Kórház
H-4400 Nyíregyháza, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 17—22 (1983)*

# The D-xylose test in coeliac disease

Hedvig BODÁNSZKY, K HORVÁTH, Gabriella HORN

Second Department of Paediatrics, Semmelweis University Medical School, Budapest

The results of more than 500 D-xylose loading tests are described. In almost half of the cases proven or suspected to be coeliac disease, the blood xylose level was low. In 69 patients the result was compared to that of small bowel biopsy. Abnormal levels were found in 98% of total or subtotal villous atrophy. It is therefore suggested to apply the test for screening in severe cases.

Since with increasing age the absorption of xylose improves, this is to be considered when evaluating the test.

At the time of gluten readministration the D-xylose test suggests the presence of histological changes well before their clinical manifestation. Therefore the result of the D-xylose test serves as an indication for small bowel biopsy. An abnormal D-xylose test after introduction of the gluten-free diet points to its deficiency.

During the past two decades several methods have been worked out for diagnosing the malabsorption syndromes. Small intestinal biopsy is the most helpful of these. By now it has become a routine examination in most children's hospitals and it is generally accepted as the only reliable test in the diagnosis of coeliac disease [1].

In spite of all its advantages, intestinal biopsy cannot be carried out as an initial test, therefore it was necessary to find a way to prove its necessity. The D-xylose test serves this purpose.

D-xylose is a carbohydrate made up of 5 carbon atoms, which does not exist in the body. It is non-toxic and penetrates the intestinal wall by active absorption [3, 5], mainly in the upper small intestine, but if this area is damaged, in other areas as well. In case of impaired enterocyte function, the absorption of the D-xylose is reduced, therefore it can be used as a screening test in diseases involving villous damage in the small intestine [9].

In the last 6 years we have carried out more than 500 D-xylose tests. The present study reports on the results.

## MATERIAL AND METHODS

Between 1974 and 1980, 553 D-xylose tests were done in 321 children who were examined for malabsorption. The patients ranged in age from 2 months to 14 years. In 69 children the test was done before biopsy and the results were compared to the degree of villous damage.

Histological grouping was done after Oehlert [12]. The test was applied in children suffering from coeliac disease both during a gluten-free diet and during the administration of gluten.

The D-xylose test and blood level determination was done according to Rolles et al [14]. Children under 30 kg were given 5.0 g, and over 30 kg, 15.0 g/m² body surface D-xylose after 8 hours fasting, making an effort to administer the full dose in a short time.

In the case of increased intestinal motility with a temperature the examination was postponed.

In 186 cases blood samples were taken also before the test. The fasting blood level was $\bar{x}$ 2.4 $\pm$ 1.2 mg/dl. Later, blood sampling before the test was omitted but the limit was modified to 1.65 mmol/l (25 mg/dl). This was possible as the test did not serve diagnostic purposes but was applied for screening and to examine the conditions of absorption.

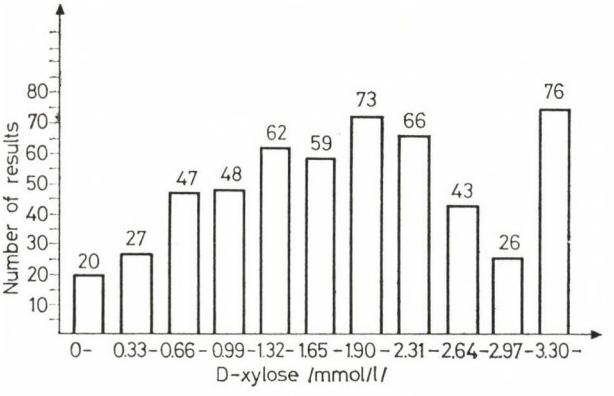



FIG. 1

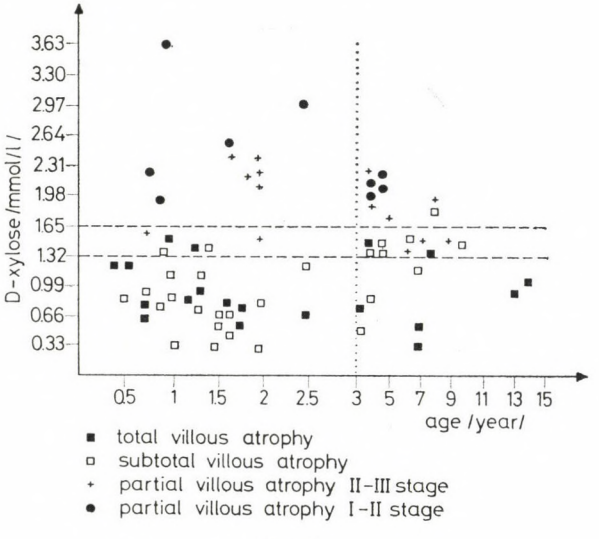



FIG. 2

TABLE I

Abnormal D-xylose test and clinical diagnosis

| Diagnosis | Number of cases | Per cent |
|---|---|---|
| Coeliac disease | 69 | 34 |
| Coeliac disease suspects | 30 | 15 |
| Malabsorption syndrome | 83 | 41 |
| Herpetiform dermatitis | 4 | 2 |
| Giardiasis | 2 | 1 |
| Intestinal lymphangiectasis | 2 | 1 |
| Others | 12 | 6 |

TABLE II

Result of small bowel biopsy and D-xylose level

| Degree of villous damage | No. of cases | Below 1.65 mmol/l | Per cent |
|---|---|---|---|
| Partial villous atrophy I—II | 9 | 0 | 0 |
| Partial villous atrophy II—III | 15 | 5 | 33 |
| Subtotal villous atrophy | 25 | 24 | 96 |
| Total villous atrophy | 20 | 20 | 100 |

## RESULTS

The results and distribution of 553 D-xylose tests are shown in Fig. 1. The result was abnormal in 204 cases (37%). The clinical diagnosis in these cases is seen in Table I; 48% of the abnormal values were noted in children with proven or suspected coeliac disease but the percentage was high in cases of chronic enteritis, cow milk protein allergy and other conditions with malabsorption (40.6%).

Table II shows the D-xylose test results connected with intestinal biopsy. Biopsy revealed in 20 patients a total and in 25 patients a subtotal villous atrophy. Among these 45 cases there was only a single one whose D-xylose value was within normal limits; so the test was diagnostic in 98% of the severe cases.

One-third of the II and III stage cases of partial villous atrophy showed abnormal values; these were never lower than 1.32 mmol/l (20 mg/dl).

The results are classified by age in Fig. 2. The examination was carried out mostly in children under 3 years of age (44 cases) where in cases of subtotal atrophy the average D-xylose level was 0.84 mmol/l (12.8 mg/dl). Over 3 years this value was 1.44 mmol/l (21.4 mg/dl). In the younger children, 13% of the results and in the older children, 46% of the results fell between 1.32 and 1.65

mmol/l (20—25 mg/dl). This proves that in the case of comparable villous damage, the absorption of D-xylose is better in older children:

## Discussion

The D-xylose test has been employed in the diagnostics of coeliac disease for almost 3 decades. First, the urine excretion was measured. Then Rolles et al. [14] suggested the easier and more reliable method of measuring the D-xylose level in blood. The values vary in the different studies for different reasons; for instance, some authors do not use Somogyi's protein agglutination. A misleading factor can be the administration of other actively absorbing substances just before the test.

There is no standard D-xylose dosage; it is important that the patient with coeliac disease should receive 10—20 g of gluten daily prior to the test. Elimination of the gluten for a few days affects the result [14]. It is necessary therefore to ensure the normal daily gluten intake in these cases before the examination.

Since D-xylose is actively absorbed from the intestine, normal enterocyte function is a prerequisite of the presence of D-xylose in blood. In diseases with villous damage (coeliac disease, cow milk protein allergy, Duhring syndrome, viral enteritis, etc.) the epithelial cells are affected. The absorption is diminished also by protozoa, bacteria or fungi in the small intestine. Utilization of D-xylose by intraluminal bacteria and the absorption-reducing effect of alien flora have been reported [6, 7]. Among the patients with low D-xylose level, there were many for whose malabsorption or severe atrophy the ascending small intestinal flora was responsible.

The low D-xylose level, especially if it is repeatedly low, is an indication for duodenal juice analysis or intestinal biopsy.

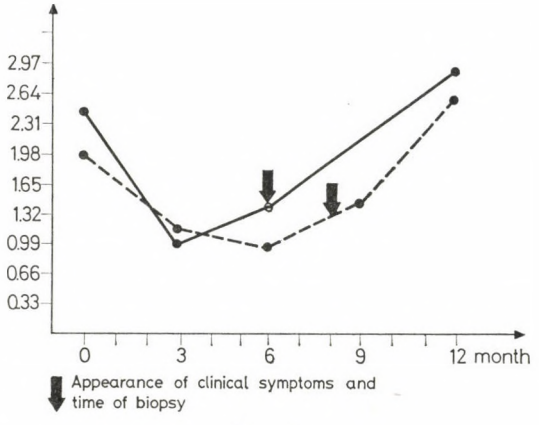



Fig. 3

Out of the 192 patients reported in 6 papers [2, 9, 10, 13, 14, 16] the result was abnormal in 180 cases. Our results were similar. The only patient whose D-xylose level was abnormal was an 8 year old boy with subtotal villous atrophy. The patients of Ose and Rolles who had levels over 1.32 mmol/l (20 mg/dl) were 5 and 6 years old respectively [13, 14].

The clinical symptoms of coeliac disease are known to improve with age and often only a retardation of height and weight indicates the presence of malabsorption. This is explained by the compensating function of the ileum [8].

In our patients over 3 years the D-xylose level showed higher values even with comparable villous damage. In these cases, if the value is 1.65—1.98 mmol/l, the test should be repeated, and if the same result is obtained, duodenal juice analysis or biopsy is indicated to elucidate the cause of malabsorption.

During the follow-up period the test should be repeated every 3 months especially when gluten is again added to the diet or in the case of complaints.

In our experience, the D-xylose level points to intestinal damage well before its clinical manifestation. This is demonstrated in 2 patients (Fig. 3.)

In the cases of proven coeliac disease the change of the D-xylose level was seen at different points of time. This could be due to the varying individual sensitivity and the different amount of ingested gluten.

According to the European Paediatric Gastroenterologists' Association, a relapse may occur even as late as 2 years after gluten readministration [11]. On a gluten-free diet the D-xylose test becomes normal before clinical symptoms would appear. If this is not the case then the diet should be controlled and the eventual presence of an abnormal small intestinal flora has to be excluded.

## References


1. Berg NO, Borulf S, Jakobson J, Lindberg T: How to approach the child suspected of malabsorption. Acta Pediatr Scand 67: 403, 1978
2. Buts JP, Morin CL, Roy CC: One-hour blood xylose test: a reliable index of small bowel function. J Pediatr 92: 729, 1978
3. Caspary WF: On the mechanism of D-xylose absorption from the intestine. Gastroenterology 63: 531, 1972
4. Christie DL: Use of the one-hour blood xylose test as an indicator of small bowel mucosal disease. J Pediatr 92: 725, 1978
5. Csáky TZ, Lassen VV: Active intestinal transport of D-xylose. Biochym Biophys Acta 82: 215, 1964
6. Goldstein F, Criden LE, Jenner ER: Bacterial utilization of D-xylose. Gastroenterology 48: 818, 1965
7. Goldstein F, Karacadag S, Wirst CW: Intraluminal small-intestinal utilization of D-xylose by bacteria. Gastroenterology 59: 380, 1970
8. Katz AJ, Falchuk ZM: Current concepts in gluten sensitive enteropathy (celiac sprue). Pediatr Clin North Am 22: 767, 1975
9. Kósnai I, Tichy M, Bucsky P: The 1-hour D-xylose test in the diagnosis of villous atrophy. Acta Paediatr Acad Sci Hung 19: 221, 1978
10. Lamabadusuriya SP, Packer S, Harries JT: Limitations of xylose tolerance test as a screening procedure in childhood. Arch Dis Child 50: 34, 1975
11. McNeish AS, Harms HK, Rey J: The diagnosis of coeliac disease. A commentary on the current practices of

members of ESPGAN. Arch Dis Child 54: 783, 1979
12. Oehlert W: Pathologie des Magen-Darm-Traktes. Schattauer Verlag, Stuttgart—New York 1978, p 326
13. Ose L, Fluge G: Usefulness of the xylose test for coeliac disease. Arch Dis Child 51: 400, 1976
14. Rolles CJ, Kendall MJ, Nutter S, Anderson CM: One hour blood xylose screening test for coeliac disease in infants and young children. Lancet 2: 1043, 1973
15. Rolles CJ, Kendall MJ, Nutter S, Anderson CM: Confirming persistence of gluten intolerance in children diagnosed as having coeliac disease in infancy. Arch Dis Child 50: 748, 1975
16. Schaad U, Gaze H, Hadorn B: Value of 1-hour blood xylose test in diagnosis of childhood coeliac disease. Arch Dis Child 53: 420, 1978

*Received 11 April 1982*

H Bodánszky MD
Tűzoltó u 7
H-1094 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 23—35 (1983)*

# Renal aspects of neonatal sodium homeostasis

E Sulyok, F Varga

Department of Obstetrics and Gynaecology, University Medical School, Pécs, Hungary

Current knowledge on renal sodium handling during the neonatal period is reviewed with particular reference to its clinical implications.

It has been demonstrated that fractional sodium excretion is inversely proportional to the maturity of the neonate. The high rate of urinary sodium excretion in the low-birth-weight premature infants results in sodium depletion, hyponatraemia and hypoosmolality; evidence has been provided to indicate that it may contribute to the development of late metabolic acidosis, failure to gain weight and impaired function of the central nervous system.

When challenged by salt loading, a significantly more marked natriuretic response could be seen in preterm than in full-term neonates. Acute sodium overdose may cause iatrogenic hypernatraemia and neonatal intracranial haemorrhage. Long-term high sodium intake may induce salt and water retention, peripheral oedema, increased intracranial pressure, congestive heart failure, reopening of the ductus arteriosus and hypertension in adult life.

Alterations in salt balance even in the very low-birth weight premature infant result in adaptive changes in the function of the renin--angiotensin-aldosterone system, renal prostaglandin E and $F_{2\alpha}$ production and plasma prolactin level.

When drug therapy known to affect renal sodium handling such as indomethacin, furosemide, dopamine, aminophylline and glucocorticoid is prescribed in the perinatal period, neonatal salt and water balance should carefully be monitored.

In the newborn period there are limitations of the homeostatic function of the kidney [17]. Full-term newborn infants are, however, able to maintain the volume and composition of body fluids within a narrow range unless they are challenged by nutritional or environmental stress, disturbances of the adaptation to extrauterine life or drug therapy compromising renal function.

In low-birth weight premature infants the physiologic limitations of the renal control of salt and water balance are exaggerated and may manifest clinically even under conditions appropriate for their care.

This paper discusses some of the clinical implications of current knowledge on the limitation of renal sodium handling and its control by the endocrine system during the neonatal period.

## *Renal sodium excretion under basal conditions*

Recent studies have shown that in the first week of life urinary sodium

excretion and, in particular, fractional sodium excretion is elevated and inversely proportional to the maturity of the neonate [2, 7, 10, 39, 43, 46]. Premature infants of less than 35-weeks gestation have an obligatory sodium loss which was believed to be a physiologic measure resulting from the isotonic contraction of body fluid compartments and the disposal of intra- and extracellular fluid solute through the kidney [10, 33, 39].

Furthermore, it is also to be considered that depending on fluid intake, sodium and water movement occurs out of the intracellular space to maintain circulating blood volume and tissue perfusion [13]. Intracellular sodium and water therefore serves as a reservoir to avoid clinical dehydration caused by the 7 to 11% reduction of total body water due to either inadequate intake or renal and non-renal loss of fluid and electrolyte [33].

When the concomitant fall in plasma sodium level has been demonstrated, it became evident that the redistribution of body fluid compartments does not account for the high rate of urinary sodium excretion but should rather be due to the inability of the immature kidney to reabsorb sodium [45]. Further studies indicated that the increased urinary sodium loss in preterm infants resulted from the deficient proximal and distal tubular reabsorption of sodium [50] and renal sodium conservation has been found to improve significantly with advancing gestational [17, 39,

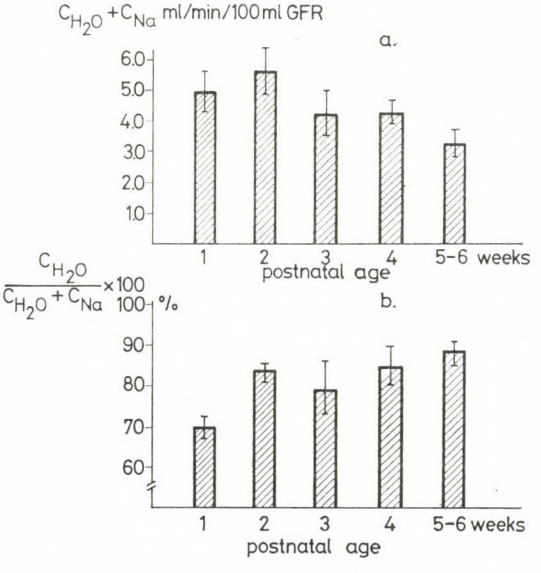



FIG. 1. Postnatal changes in distal tubular sodium delivery (a) and distal tubular sodium reabsorption (b) in premature infants during the first six weeks of life

43] and postnatal age [2, 5, 26, 31, 39, 45].

It has also been shown that proximal and distal tubular sodium reabsorption does not develop together, the progress is more rapid with distal than proximal reabsorption of sodium [49] (Fig. 1).

*Renal sodium excretion in response to salt loading*

Administering orally a dose of 0.12 g/kg NaCl to premature and full-term neonates during the first week of life, Aperia et al. observed a significantly higher natriuretic response in premature infants of 29—35 weeks gestation than in full-term neonates [1, 2]. The renal capacity to excrete sodium in preterm infants, however, was found to be still much lower than in children of 8—14 years of age. When the natriuretic response to salt challenge was followed postnatally until term they could demonstrate its marked reduction to a value characteristic of full-term neonates [1].

It has also been documented that the postnatal development of the natriuretic response to salt challenge can be accelerated by dietary manipulation. Infants receiving a high-salt diet prior to the salt load had a greater capacity to excrete sodium than those on a diet low in sodium [4].

It is of clinical interest that sodium is better tolerated when it is given as $NaHCO_3$ than in the form of NaCl as demonstrated by the higher urinary sodium excretion after $NaHCO_3$ load than after NaCl load [3].

*Renal sodium excretion and acid-base balance*

Recent studies from our laboratory provided evidence that acid-base regulation and renal sodium handling are closely related in the neonatal period. The limited capacity of the immature kidney to excrete $H^+$ is associated with an obligatory sodium loss. The maturation of renal acidifying processes with increasing gestational and postnatal age results in a progressive increase in renal $Na^+—H^+$ exchange and in a steady decline in sodium excretion [31, 46] (Fig. 2).

Furthermore, metabolic acidosis has been shown to enhance renal sodium excretion and the acidosis-induced urinary sodium loss has been found to follow a developmental pattern; the lower the birth weight and the younger the age of the neonate, the less pronounced was the sodium excretory response [47] (Fig. 3).

Renal salt wasting, in turn, has been shown to contribute to the development of late metabolic acidosis as indicated by

a) a significantly negative correlation between the renal threshold for bicarbonate reabsorption and urinary sodium excretion [48] (Fig. 4);

b) the similar trend and time course of late metabolic acidosis and late hyponatraemia due to the low rate of renal sodium reabsorption in exchange for $H^+$ [45]; and

c) metabolic acidosis in premature infants was less severe when supplemental NaCl was given to prevent

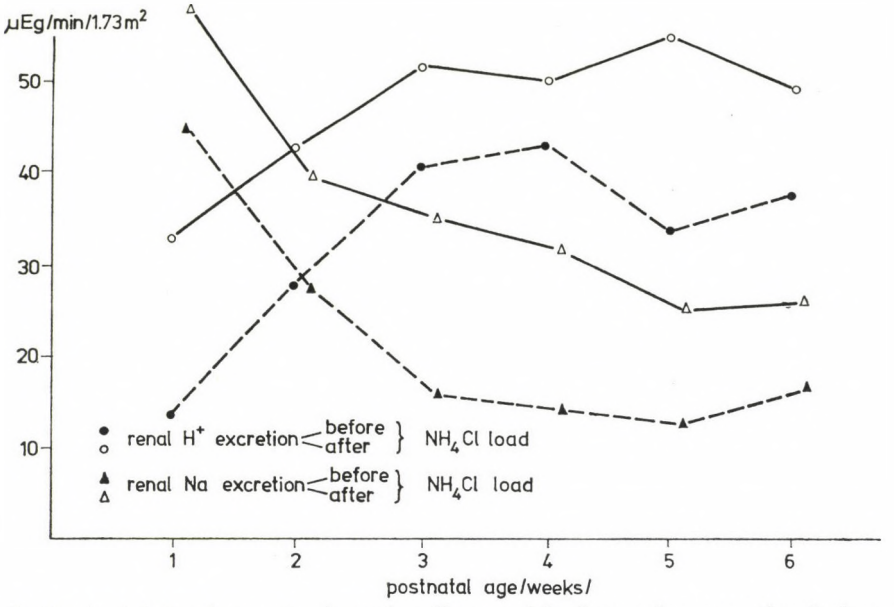



FIG. 2. Postnatal development of renal sodium and hydrogen ion excretion before and after 2.8 mEq/kg $NH_4Cl$ load in premature infants during the first six weeks of life

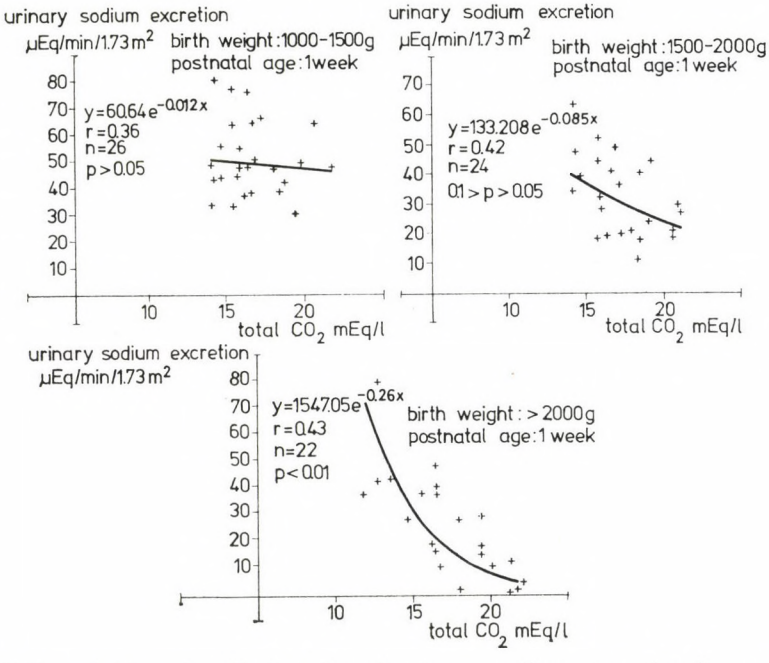



FIG. 3. Birth weight and acidosis-induced urinary sodium excretion in one-week-old newborn infants

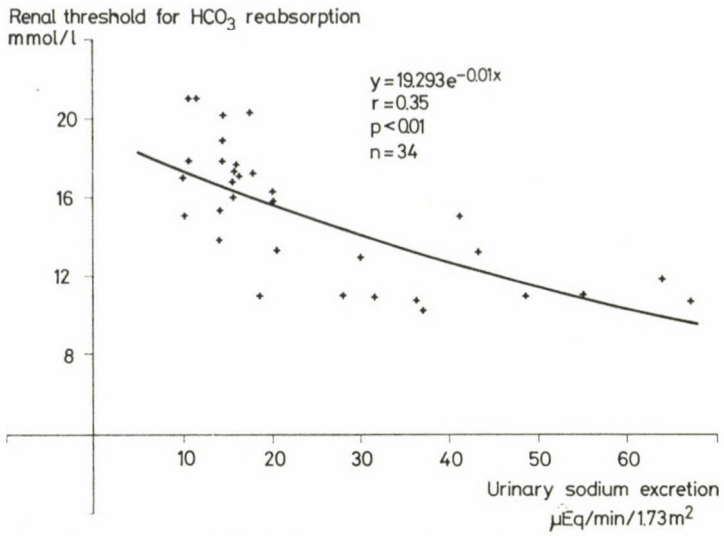



FIG. 4. Relationship between renal bicarbonate threshold and urinary sodium loss in 1—6 week-old premature infants

sodium depletion and late hyponatraemia [53].

*Clinical consequences of excessive inadequate sodium intake*

Excessive use of $NaHCO_3$ for the correction of severe metabolic acidosis associated with perinatal asphyxia and respiratory distress syndrome has been reported to cause iatrogenic hypernatraemia which is thought to be implicated in the aetiology of neonatal intracranial haemorrhage. It causes a rapid fluid shift from the intracellular compartment, cell dehydration, brain shrinkage and tearing of the cerebral capillaries [21, 28, 44].

In addition to the hazard of acute sodium overdosage, long-term high sodium intake exceeding the daily requirement is also harmful. Low-birth weight infants fed high sodium formulas have been found to retain salt and water [27, 30] as manifested by a delayed onset peripheral oedema, symptoms consistent with increased intracranial pressure and congestive heart failure.

When body fluid expansion takes place, reopening of the ductus arteriosus may also appear further to complicate the postnatal course of premature infants whose fluid and electrolyte balance has already been compromised [8].

It is of further concern that a high dietary sodium intake early in life may increase the risk of hypertension in adult ife [14].

When low-birth weight infants are fed breast milk or a formula low in sodium, the renal salt wasting results in a negative sodium balance and hyponatraemia. The lower the birth weight and the younger the gestational age of preterm infants are the more

severe hyponatraemia can be anticipated [15, 19, 26, 32, 41, 45]. The clinical significance of late hyponatraemia may be summarized as follows.

1. The marked fall of the plasma sodium level may in itself be regarded to indicate the extreme limitation of the homeostatic mechanisms controlling salt and water balance. Pathologic processes and therapeutic interventions which are known to compromise salt and water metabolism may therefore be critical by leading to an abrupt deterioration of the infant's condition.

2. Hyponatraemic premature infants are mostly asymptomatic, although neurological symptoms such as irritability, convulsions and apnoea may appear.

3. Sodium makes the major contribution to plasma osmolality. As a result, the fall of plasma sodium is accompanied by a parallel decline in plasma osmolality [34].

4. Osmotic equilibrium between the extra and intracellular compartments in infants presenting with hyponatraemia is attained as follows. Either water moves into the cells resulting in expansion of the intracellular fluid compartment or else a reduction in osmotically active cellular solute occurs. Since antipyrine and bromide space studies did not reveal any differences in the distribution of body water between low birth weight infants with various plasma sodium levels [41], it seems that the hyponatraemic infant's cells fail to maintain the normal intracellular solute composition [22]. This assumption is consistent with the observation that the rate of growth and weight gain is lower in hyponatraemic infants than in those without hyponatraemia [11].

Moreover, hyponatraemia lasting for several weeks in this critical period of brain development may have a deleterious influence on the vulnerable central nervous system. Profound alterations in the osmolality of cell fluid with or without impairment of cellular metabolism are likely to cause permanent brain injury. Well-controlled follow-up studies are needed to define the effect of late hyponatraemia on the development and later performance of the central nervous system.

*Endocrine control of sodium balance*

In a series of recent studies on the control of neonatal sodium homeostasis we have shown that in low-birth-weight premature infants renal salt wasting, the subsequent negative sodium balance and the fall in plasma sodium level induce a marked elevation of the activity of the renin-angiotensin-aldosterone system (RAAS) [51]. In response to the highly activated RAAS, rapid improvement occurs in the aldosterone-mediated distal tubular sodium reabsorption. RAAS is therefore thought to contribute substantially to the reestablishment of positive sodium balance [49]. When supplemental NaCl was given to prevent sodium depletion and hyponatraemia, the postnatal increase in the activity of RAAS was also prevented and plasma

renin activity, plasma aldosterone concentration and urinary aldosterone excretion remained within the range characteristic of healthy full-term infants of the same postnatal age [53] (Fig. 5).

The high activity of RAAS in preterm infants fed low sodium formulas was associated with a rapid increase of urinary PGE excretion during the first three weeks of life [52] (Fig. 6) and plasma PGE and

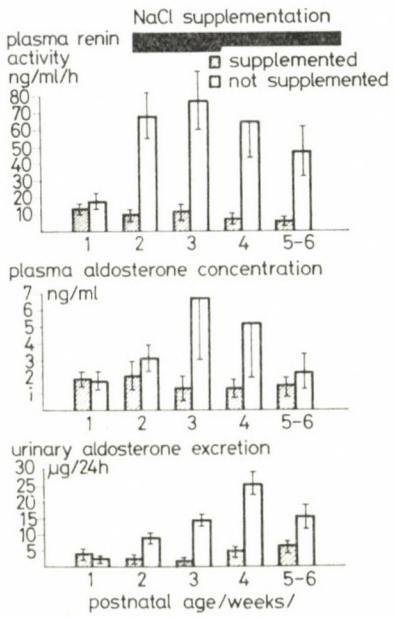



FIG. 5. Postnatal development of plasma renin activity, plasma aldosterone concentration and urinary aldosterone excretion in premature infants with and without NaCl supplementation during the first six weeks of life

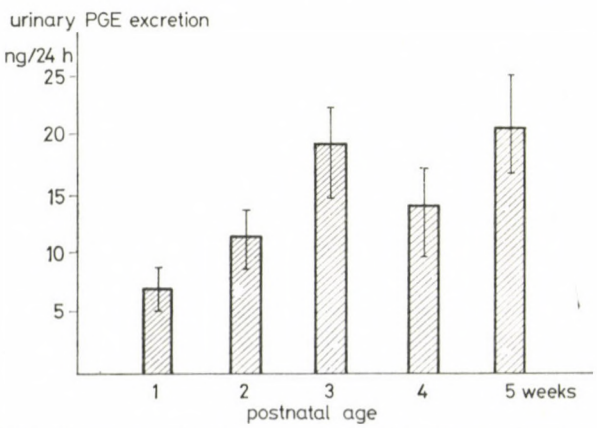



FIG. 6. Postnatal development of urinary prostaglandin E excretion in premature infants during the first 5 weeks of life

$PGF_2$ levels were also found to be higher in infants without supplementation than in those supplemented with NaCl [19] (Figs. 7—8).

The increased rate of renal PG production and the elevated level of plasma PGs in face of the high activity of RAAS might be of great importance in maintaining normal systolic blood pressure, decreasing renal vascular resistance and increasing renal blood flow in premature infants.

Interestingly, prolactin has also been found to be more elevated in preterm infants fed a low sodium diet than in those with NaCl supplementation [54] (Fig. 9). Prolactin is a stress hormone with salt-retaining properties. The higher plasma prolactin level in sodium depleted infants can therefore be regarded as reflecting either its regulatory role to enhance renal sodium reabsorption or its aspecific reaction to sodium depletion as a stress.

In view of the limitation of renal sodium handling, the untoward clinical consequences of inadequate or

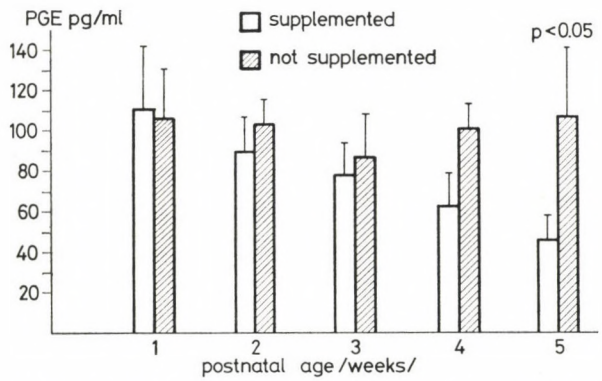



FIG. 7. Postnatal course of plasma prostaglandin E level in premature infants with and without NaCl supplementation during the first five weeks of life

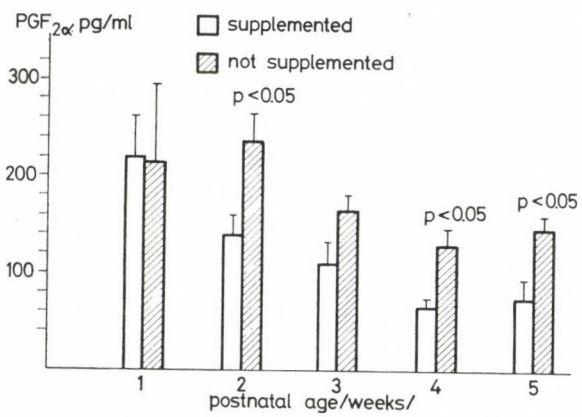



FIG. 8. Postnatal course of plasma prostaglandin $F_{2\alpha}$ level in premature infants with and without NaCl supplementation during the first five weeks of life

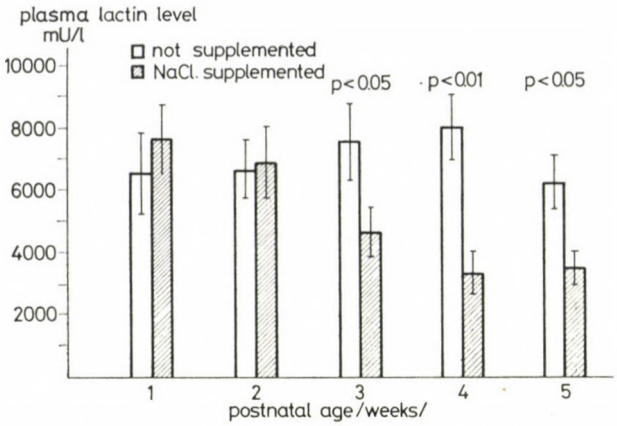



FIG. 9. Postnatal course of plasma prolactin level in premature infants with and without NaCl supplementation during the first five weeks of life

excessive sodium intake and the profound endocrine reactions induced by the alterations of sodium balance it is necessary to establish the daily sodium requirement of premature infants of various gestational and postnatal ages. Appropriate supplementation should be done according to the individual needs determined by close monitoring of sodium and water balances and hormone parameters.

### *Drug therapy and renal sodium excretion*

*Indomethacin*, a potent PG synthetase inhibitor given either antenatally to the mother to prevent preterm delivery [58] or postnatally to the premature infant to induce closure of the patent ductus arteriosus [23, 25, 42, 43] has been shown to cause a transient diminution in neonatal renal function.

A significant reduction in urinary flow rate, glomerular filtration rate and free water clearance occurs with a concomitant decrease in fractional excretion of sodium, chloride and potassium in premature infants on indomethacin. These changes were found to be accompanied by some fall of the plasma sodium concentration and plasma osmolality. It is to be noted that the depressed renal functions return to normal only one to two weeks after stopping indomethacin administration [9, 12]. Studies performed in animals and adults provided inconclusive results as to the influence of indomethacin on renal function [38]. Whereas the drug reduced significantly renal sodium excretion in sodium depleted normal subjects, it caused no alteration in sodium excretion when sodium was repleted or in subjects on normal sodium [16, 37].

*Furosemide* is a diuretic frequently used in low-birth-weight infants to treat fluid overload and congestive heart failure resulting from patent ductus arteriosus with left-to-right shunt.

Pharmacologic studies revealed that furosemide given intravenously in a dose of 1 mg/kg to premature infants reached its peak action within one hour and the duration of action lasted for six hours. Administration of furosemide produced a significant increase in urine volume, sodium excretion, fractional sodium excretion and potassium excretion [40]. In newborn piglets the natriuretic response expressed as fractional sodium excretion was not influenced by postnatal age and averaged a high value of about 20% [36].

Recently *dopamine* has been introduced successfully to manage sick neonates with severe cardiopulmonary distress such as persistence of fetal circulation syndrome [20], perinatal asphyxia [24] and shock resulting from septicaemia [56]. Tulassay et al. investigating the renal effect of dopamine in premature infants could demonstrate that parallel to the rise in blood pressure there was a significant increase in glomerular filtration rate, urine flow, actual sodium excretion and fractional sodium excretion [55].

In view of the widespread use of *aminophylline* to prevent idiopathic apnoea of prematurity it is of importance to consider that marked salt and water diuresis with or without hyponatraemia and dehydration has been observed in low-birth-weight premature infants while on aminophylline therapy [35].

Recent studies [42, 6] raised the possibility that *antenatal glucocorticoid* administration to accelerate fetal lung maturation might have a significant influence on the development on renal sodium handling.

The activity of Na—K—ATP-ase, the enzymatic equivalent of active sodium transport [29], has been found to be lower in each segment of the immature nephron than in the corresponding segments of the mature nephron [42]. The low level of Na—K—ATP-ase activity in preterm infants may therefore account for the limited rate of active sodium reabsorption. When low doses of glucocorticoid were given in the immature tubules Na—K—ATP-ase activity increased to almost adult levels [6]. It is reasonable to assume that antenatal glucocorticoid administration may induce elevated transport enzyme activity, improved tubular sodium reabsorption and a lower rate of urinary sodium loss in low-birth-weight premature infants.

On the basis of these clinical and experimental evidences we suggest that when the above drugs are prescribed for premature infants or for the mothers, their profound influence on neonatal renal function should be considered. Careful monitoring of renal salt and water excretion and appropriate estimation of fluid and electrolyte requirements are essential during such therapy to avoid fluid and electrolyte imbalance.

## References

1. Aperia A, Broberger O, Thodenius K, Zetterström R: Renal response to an oral sodium load in newborn full term

infants. Acta Paediatr Scand 61: 670, 1972
2. Aperia A, Broberger O, Thodenius K, Zetterström R: Developmental study of the renal response to an oral salt load in preterm infants. Acta Paediatr Scand 63: 517, 1974
3. Aperia A, Broberger O, Herin P, Thodenius K, Zetterström R: A comparative study of the response to an oral NaCl and $NaHCO_3$ load in newborn preterm and full-term infants. Pediatr Res 11: 1109, 1977
4. Aperia A, Broberger O, Herin P, Thodenius K, Zetterström R: Renal sodium excretory capacity in infants under different dietary conditions. Acta Paediatr Scand 68: 351, 1979
5. Aperia A, Broberger O, Elinder G, Herin P, Zetterström R: Postnatal development of renal function in preterm and full-term infants. Acta Paediatr Scand 70: 183, 1981
6. Aperia A, Larson L, Zetterström R: Hormonal induction of Na—K—ATPase in developing proximal tubular cells. Am J Physiol 10: F356, 1981
7. Arant BS: Developmental patterns of renal functional maturation compared in the human neonate. J Pediatr 92: 705, 1978
8. Bell EP, Warburton D, Sonestreet BS, Oh W: Randomized trial comparing high and low-volume maintenance fluid administration in low-birth-weight infants. Pediatr Res 13: 489, 1979
9. Betkerur MV, Yeh TF, Miller K, Glasser RJ, Pildes RS: Indomethacin and its effect on renal function and urinary kallikrein excretion in premature infants with patent ductus arteriosus. Pediatrics 68: 99, 1981
10. Butterfield J, Lubchenco LO, Bergstedt J, O'Brien D: Patterns in electrolyte and nitrogen balance in the newborn premature infant. Pediatrics 26: 777, 1960
11. Chance GW, Radde IC, Willis DM, Roy RN, Park E, Ackerman I: Postnatal growth of infants of less than 1.3 kg birth weight: Effects of metabolic acidosis, of caloric intake, and of calcium, sodium, and phosphate supplementation. J Pediatr 91: 787, 1977
12. Cifuentes RF, Olley PM, Balfe JW, Radde IC, Soldin SJ: Indomethacin and renal function in premature infants with persistent patent ductus arteriosus. J Pediatr 95: 583, 1979
13. Coulter DM, Avery ME: Paradoxical reduction in tissue hydration with weight gain in neonatal rabbit pups. Pediatr Res 14: 1122, 1980
14. Dahl LK: Salt in processed baby foods. Am J Clin Nutr 21: 787, 1968
15. Day GM, Radde IC, Balfe JW, Chance GW: Electrolyte abnormalities in very low birth weight infants. Pediatr Res 10: 522, 1976
16. Donker AJ, Arisz L, Brentjens JR, Van Derhem GK, Hollemans HJ: The effect of indomethacin on kidney function and plasma renin activity in man. Nephron 17: 288, 1976
17. Edelmann CM, Spitzer A: The maturing kidney. A modern view of well-balanced infants with imbalanced nephrons. J Pediatr 75: 509, 1969
18. Engelke SC, Shah BL, Vasan U, Rayer JR: Sodium balance in very low-birth-weight infants J Pediatr 93: 837, 1978
19. Ertl T, Sulyok E, Német M, Tényi I, Csaba IF, Varga F: The effect of NaCl supplementation on the postnatal development of plasma prostaglandin E and $F_{2\alpha}$ levels in premature infants. J Pediatr 101: 761, 1982
20. Fiddler GI, Chatrath R, Williams GJ, Walker DR, Scott O: Dopamine infusion for the treatment of myocardial dysfunction associated with persistent transitional circulation. Arch Dis Child 55: 194, 1980
21. Finberg L, Luttrell O, Redd H: Pathogenesis of lesions in the nervous system in hypernatremic states. II. Experimental studies of gross anatomic changes and alterations of chemical composition of the tissues. Pediatrics 23: 46, 1959
22. Flear CTG: Hyponatremia. Lancet 2: 164, 1974
23. Friedman WF, Hirshklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE: Pharmacological closure of patent ductus arteriosus in the premature infant. N Engl J Med 295: 526, 1976
24. Gregory GA: Resuscitation of the newborn. Anesthesiology 43: 225, 1975
25. Heymann MA, Rudolph AM, Silverman NH: Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N Engl J Med 295: 530, 1976
26. Honour JW, Valman HB, Shackleton CHL: Aldosterone and sodium homeostasis in preterm infants. Acta Paediatr Scand 66: 103, 1977
27. Hornych H, Amiel-Tison C: Retention hydrosaline chez les enfants de faible poids de naissance. Arch Fr Pediatr 34: 206, 1977
28. Horváth M, Mestyán I, Mestyán J: Iatrogenic hyperosmolality in critically in low-birth-weight infants. Acta Paediatr Acad Sci Hung 16: 231, 1975

29. Jörgenssen PL: Sodium and potassium ion pump in kidney tubules. Physiol Rev 60: 864, 1980
30. Kagan BM, Stanincova V, Felix NS, Hodgman J, Kalman D: Body composition of premature infants: relation to nutrition. Am J Clin Nutr 25: 1153, 1972
31. Kerpel-Fronius E, Heim T, Sulyok E: The development of the renal acidifying processes and their relation to acidosis in low-birth-weight infants. Biol Neonate 15: 156, 1970
32. Kumar SP, Sacks LM: Hyponatraemia in very low-birth-weight infants and human milk feedings. J Pediatr 93: 123, 1978
33. MacLaurin JC: Changes in body water distribution during the first two weeks of life. Arch Dis Child 41: 286, 1966
34. Mestyán I, Horváth M, Mestyán J: Plasma osmolality in the early and late neonatal period with particular reference to low birth weight infants. Biol Neonate 28: 303, 1976
35. Nobel PA, Light GS: Theophylline-induced diuresis in the neonate. J Pediatr 90: 825, 1977
36. Noordewier B, Bailie MD, Hook JB: Effect of furosemide on renal function of the newborn piglet. Pediatr Pharmacol 1: 113, 1980
37. Oliver JA, Pinto J, Sciacca RR, Cannon PJ: Increased renal secretion of norepinephrine and prostaglandin $E_2$ during sodium depletion in the dog. J Clin Invest 66: 748, 1980
38. Osborn JL, Hook JB, Bailie MD: Effect of saralasin and indomethacin on renal function in developing kidney. Am J Physiol 238: R438, 1980
39. Ross B, Cowett RM, Oh W: Renal functions of low birth weight infants during the first two months of life. Pediatr Res 11: 1162, 1977
40. Ross BS, Pollak A, Oh W: The pharmacologic effects of furosemide therapy in the low-birthweight infants. J Pediatr 92: 149, 1978
41. Roy RN, Chance GW, Radde IC, Hill DE, Willis DM, Sheepers J: Late hyponatremia in very low birthweight infants (< 1.3 kilograms). Pediatr Res 10: 526, 1976
42. Schmidt U, Horster M: Na—K-activated ATP-ase activity maturation in rabbit nephron segments dissected in vitro. Am J Physiol 233: F55, 1977
43. Siegel SR, Oh W: Renal function as a marker of human fetal maturation Acta Paediatr Scand 65: 481, 1976
44. Simmons MA, Adcock EW, Bard H, Battaglia FC: Hypernatraemia and intracranial hemorrhage in neonates. N Engl J Med 291: 6, 1974
45. Sulyok E: The relationship between electrolyte and acid-base balance in the premature infant during early postnatal life. Biol Neonate 17: 227, 1971
46. Sulyok E, Heim T, Soltész G, Jászai V: The influence of maturity on renal control of acidosis in newborn infants Biol Neonate 21: 418, 1972
47. Sulyok E, Varga F, Kerekes L: Relationship of metabolic acidosis to urinary sodium excretion in the newborn infant. Acta Paediatr Acad Sci Hung 19: 285, 1978
48. Sulyok E, Varga F: Relationship of renal threshold for bicarbonate reabsorption to urinary sodium excretion in premature infants. Acta Paediatr Acad Sci Hung 19: 281, 1978
49. Sulyok E, Varga F, Győry E, Jobst K, Csaba I F: Postnatal development of renal sodium handling in premature infants. J Pediatr 95: 787, 1979
50. Sulyok E, Varga F, Győry E, Jobst K, Csaba I F: On the mechanism of renal sodium handling in newborn infants. Biol Neonate 37: 75, 1980
51. Sulyok E, Németh M, Tényi I, Csaba I F, Győry E, Ertl T, Varga F: Postnatal development of renin-angiotensin-aldosterone system (RAAS) in relation to electrolyte balance in premature infants. Pediatr Res 13: 817, 1979
52. Sulyok E, Ertl T, Csaba I F, Varga F: Postnatal changes in urinary prostaglandin E excretion in premature infants. Biol Neonate 37: 192, 1980
53. Sulyok E, Német M, Tényi I, Csaba I F, Varga L, Varga F: Relationship between the postnatal development of the renin-angiotensin-aldosterone system and the electrolyte and acid-base status in the sodium chloride supplemented premature infant. The First International Workshop on Developmental Renal Physiology. New York 1980
54. Sulyok E, Ertl T, Csaba I F, Varga L, Varga F: The effect of NaCl supplementation on the postnatal development of plasma prolactin level in premature infants. Biol Neonate, to be published
55. Tulassay T, Seri I, Machay T, Kiszel J, Csömör S: Effect of dopamine on the renal function in sick premature infants. Int J Pediatr Nephrol, to be published
56. Wille L, Obladen M: Neonatal Intensive Care. Springer-Verlag, Berlin, Heidelberg, New York, p 208, 1981

57. Winick M: Malnutrition and brain development J Pediatr 74: 667, 1969
58. Zuckerman H, Reiss U, Rubinstein I: Inhibition of human premature labour by indomethacin. Obstet Gynecol 44: 787, 1974

*Received 7 May 1982*

E Sulyok MD
P.O.B. 178
7601 Pécs, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 37—40 (1983)*

# Maternal regulation of fetal growth

P Tóth, K Keszei and K Méhes

Departments of Paediatrics of the Hospitals in Sopron, Mosonmagyaróvár and Győr, Hungary

The birth weight of the mothers, sibs, maternal aunts and their children were compared with those of 400 full-term, appropriate-for-gestational age, 181 true premature, 200 small-for-gestational age, and 261 large-for-gestational age neonates. Except for true prematures, a close correlation was found between the weight of the newborns and their mothers and maternal relatives in each case. The findings support the Ounsted theory that the rate of fetal growth is influenced by a familial component with maternal transmission. This regulation does not operate in true prematurity where the effect of environmental and pathological factors seems to prevail over the familial and genetic features.

In the last two decades many efforts have been made to identify the factors responsible for the great variation in mean birth weight both between and within ethnic groups. It has been shown that the socio-economic situation, maternal nutrition, smoking habits, height of the parents, parity and high altitude may all influence the rate of fetal growth. Familial low birth weight has also long been known but the data on genetic factors are still rather speculative [5]. Considering the theory of Ounsted and Ounsted [2, 3] that through maternal regulatory genes the mother's own intrauterine experience affects her reproductive performance, we have made an attempt to compare the birth weight of neonates with those of their mothers, sibs, maternal aunts and cousins.

## Material and Methods

In the neonatal units of three hospitals in County Győr-Sopron, West-Hungary, birth weight, length, head circumference and gestational age of a total of 2149 consecutive newborn infants were determined. Gestational age was calculated from the day of the last normal menstruation period. If this was not possible or a remarkable discrepancy between calculated week of pregnancy and somatic or neurological maturity was noted, the baby was excluded from the study.

The mothers of the infants were personally interviewed and their age, height, prepregnancy weight, profession, qualification, social status, and smoking habit were registered. Inquiries were made also about their previous diseases, spontaneous and artificial abortions, and labours. Special care was taken to find out the birth weight of the mothers themselves, that of their other children, of their sisters, and of the children of the latter.

At final evaluation only those families

were considered in which the mother could give reliable information on her own birth weight. Thus, the family data of 1042 neonates were involved in the study, who could be grouped according to gestational age and birth weight as follows.

1. Full-term appropriate-for-gestational age (AGA) newborns with a gestational age from 37 to 42 weeks, and with a birth weight between the 10th and 90th percentile values of the Hungarian standard. 400 neonates fulfilled these requirements.

2. True premature neonates with a gestational age under 37 weeks, whose birth weight fell between the 10th and 90th percentile curves of the local chart. This group included 181 infants.

3. Small-for-gestational age (SGA) newborns, whose birth weight was under the 10th percentile, irrespective of their gestational age. 200 babies were regarded as SGA.

4. Large-for-gestational age (LGA) infants, whose birth weight was above the 90th percentile, irrespective of their gestational age. 261 neonates belonged to this group.

Student's $t$ test, correlation coefficients, and regressions were used to evaluate the data.

## Results

The analysis of the effect of some maternal and environmental factors on fetal growth confirmed the well established facts that the weight of

Table I

Age, height and prepregnancy weight of the mothers of infants of the four groups examined (mean ± S. D.)

| | Age (year) | Height (cm) | Prepregnancy weight (kg) |
|---|---|---|---|
| Full-term AGA | 23.9±4.3 | 163±5.7 | 59.7±8.9 |
| SGA | 24.2±4.7 | 159±6.6[c] | 55.8±10.4[c] |
| True prematures | 24.5±5.0 | 161±6.6[b] | 57.5±9.8[a] |
| LGA | 25.6±4.4[c] | 165±5.9[c] | 66.4±11.1[c] |

Significance of the difference from the mean of the full-term AGA mothers:
[a] = $p < 0.01$
[b] = $p < 0.005$
[c] = $p < 0.001$

Table II

Birth weight of neonates, their mothers, sibs, maternal aunts and their children in the four groups examined (mean ± S. D.)

| | True prematures | | SGA | | Full-term AGA | | LGA | |
|---|---|---|---|---|---|---|---|---|
| | N | Birth weight | N | Birth weight | N | Birth weight | N | Birth weight |
| Index neonates | 181 | 2.16±0.55 | 200 | 2.43±0.29 | 400 | 3.29±0.30 | 261 | 4.17±0.27 |
| Mothers | 181 | 3.02±0.63 | 200 | 2.75±0.48 | 400 | 3.30±0.74 | 261 | 3.68±0.58 |
| Sibs | 137 | 3.04±0.41 | 114 | 2.54±0.47 | 457 | 3.23±0.38 | 215 | 3.79±0.37 |
| Maternal aunts | 90 | 3.24±0.54 | 83 | 2.65±0.56 | 214 | 3.28±0.41 | 113 | 3.80±0.49 |
| Children of maternal aunts | 87 | 3.10±0.44 | 84 | 2.73±0.46 | 145 | 3.24±0.33 | 80 | 3.80±0.41 |

the neonate was positively correlated to height, weight, qualification and standard of life of the mother, while previous abortions, smoking and diseases during the pregnancy predisposed to lower birth weight. Thus, these factors are not dealt with in detail, only age, height and prepregnancy weight of the mothers are shown in Table I.

Average birth weight of the neonates and those of the mothers and maternal relatives is summarized in Table II.

As shown by the figures, a fairly small variation in birth weight was observed when full-term AGA infants were compared with their mothers, sibs, maternal aunts and cousins. The differences between the various family members examined were not significant statistically, on the other hand, when calculating correlation coefficients ($r$), a significantly close correlation was demonstrated in each case.

Similar tendencies were verified in the case of both SGA and LGA infants. The birth weight of SGA children correlated well to the birth weight of their mothers ($r = 0.312$; $p < 0.001$), and even the sibs, aunts and their children were born with a weight of remarkably less than 3.00 kg. The mothers and other family members of LGA infants were also heavy newborns, and there was a close correlation between probands and mothers ($r = 0.326$; $p < 0.001$), and between probands and sibs ($r = 0.511$; $p < 0.001$), respectively. At the same time, the true prematures proved to be significantly lighter than their mothers whose birth weight was considerably higher than that of the SGA mothers ($p < 0.005$). This was valid also for sibs, aunts and the children of aunts, whose mean birth weight nearly reached that of the full-term AGA infants and their relatives.

## Discussion

Small and light women have generally smaller babies than those who are tall and heavy [6]. Ounsted and Scott [4] showed, however, that this generalization is not applicable throughout the whole spectrum. In their survey the proportion of heavy women in the SGA group did not differ from the full-term AGA group, whereas in the LGA group it was six times greater. In our material the mothers of LGA infants were remarkably heavier and moderately taller than the mothers of full-term AGA babies, while the mothers of SGA neonates proved to be significantly smaller and lighter. Since the majority of the infants of these three groups was born after the 37th week of gestation, this roughly means that maternal stature essentially affected the birth weight of near-term and term babies. At the same time, the measures of the mothers of true prematures differed only slightly from those of the full-term eutrophic group. This suggests that maternal height and weight have a less significant influence on the termination of preg-

nancy before the 37th week of gestation.

When examining the familial variation of fetal growth rate, our findings in the SGA, full-term AGA and LGA groups do offer support to the Ounsted theory. A strong familial tendency of intrauterine growth retardation was seen in the maternal relatives of SGA babies, and a predisposition to large birth weight was verified among the relatives of LGA infants. This familial component of growth variation is certainly operative on the female side. The male side was not investigated in this study, but its influence was excluded in the survey of Johnstone and Inglis [1]. The question whether the maternal transmission of the tendency to overgrowth or growth retardation is of merely genetic origin or it can be attributed to microsocial factors such as dietary habits as a result of shared learning experience in the family, cannot be answered.

Whatever the mechanism, the maternal regulation probably does not operate in the case of true prematurity. It seems most likely that the too early termination of a pregnancy is caused rather by various diseases, known and/or as yet unidentified biological and environmental factors than by maternal regulatory and genetic effects. As already mentioned, maternal stature, being itself a genetically controlled property, has a limited influence on premature birth.

In conclusion, normal or pathological fetal growth certainly depends on several endogenous and exogenous factors, the overlapping of which should be taken in account in the different types of birth weight variations. Our findings suggest that one of the essential differences between SGA and true premature infants is that maternal regulation plays a major role in intrauterine growth retardation but is insignificant in prematurity. This underlines again that statistics seeking the causes leading to low birth weight should always consider the gestational age of the neonate.

## References

1. Johnstone F, Inglis L: Familial trends in low birth weight. Br Med J 3: 659, 1974
2. Ounsted M, Ounsted C: Rate of intrauterine growth. Nature 220: 599, 1968
3. Ounsted M, Ounsted C: On fetal growth rate, its variations and their consequences. Clinics in Developmental Medicine No. 46, S. I. M. P. Heinemann, London 1973
4. Ounsted M, Scott A: Associations between maternal weight, height, weight-for-height, weight gain and birth weight. In: Maternal nutrition in pregnancy—Eating for two? ed. Dobbing J, Academic Press, New York 1981, p. 113
5. Roberts DF: Genetics of growth. Br Med Bull 37: 239, 1981
6. Thomson AM: Physiological determinants of birth weight. In: Proc. 2nd European Congress of Perinatal Medicine, London, Karger S, Basel 1970 p. 147

*Received 22 April 1982*

P Tóth MD
Városi Kórház
H-9400 Sopron, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 41—51 (1983)*

# Evolution of serum $C_3$, IgG, IgA and IgM levels of healthy mothers and their mature newborns during the early neonatal period

G Balla, L Karmazsin

Department of Paediatrics, University Medical School, Debrecen

Susceptibility to infections is most pronounced during the perinatal period. The main characteristic feature of the clinical course is a proneness to generalisation; this can be attributed to immaturity of the immune system.

In addition to a series of laboratory parameters, quick and exact determinations of immunoglobulins and complement fractions repeatedly performed within a short time may be useful in confirming a suspected infection and in following the course of the disease.

In order to establish the normal basal levels and the dynamics of changes 30 mothers, all healthy, having no abnormality during pregnancy or shortly after delivery, and their healthy mature neonates were examined for IgG, IgA, IgM and $C_3$ serum levels. These basal values are useful in judging the parameters under pathological conditions.

During the perinatal period of life the fetus leaves his isolated environment and enters in, and adapts himself to, an open world carrying stimuli markedly increased both in quality and quantity. No order of importance can be established among the organ systems participating in this adaptation. Among them, the immune system faces extremely augmented tasks from the first second after birth: the organism changes its stimulus-free environment for a world full of antigens and it has to defend its integrity under the new conditions. It can do this only if its ontogenetic development has been undisturbed in the intrauterine environment. Maturation of the defence mechanism does not stop at birth; on the contrary it deepens and markedly speeds up after birth. Studies on the immune system in perinatal life not only elucidate the controlling mechanisms but also lead to a better understanding of the newborn's immunity and defence against infections.

Separate analysis of cellular and humoral immunity is not justified as the distinction between them has methodological rather than theoretical reasons. There is much controversy concerning perinatal immunology owing to the great number of methods and in pathological conditions their interpretation is even more difficult. The aspecific cellular immune functions like microphage activity, chemotaxis, phagocytosis and killing have been elucidated in most details [4, 16]. In newborn babies especially in those exposed to stress

situations, bactericidal activity is decreased mostly due to defects in the hexosemonophosphate shunt and the late oxidation system [36, 37]. In addition, the endogenous anti-oxidant system is less effective, leading to enhanced auto-oxidation and a further impairment of the newborns' defence mechanism [5, 39].

Neonatal proneness to viral and bacterial infections has been ascribed to the impaired function of the lymphoid cell population; some workers found, however, normal lyphocyte competence in newborn babies [13]. Among the lymphocytes there is a higher incidence of 0-cells void of surface markers [7, 18]. The response to various antigens and mitogens is also impaired, pointing to a decreased cellular immunity. In cases with high serum IgM levels the lymphocyte response to C on A is weak [14]. The B-lymphocytes induced in cord blood by PMW, a T-cell dependent activator, and one-week old neonates do not produce immunoglobulins in spite of a normal mitotic index, while T-cell dependent inductors are capable of enhancing IgM production in cells from the same blood samples [3]. The depressed immunoglobulin secretion has been attributed to increased suppressor activity originating from a lymphocyte population binding the monoclonal antibody OKT 8. these cells can be found both among E-rosette forming and non-forming cells, they are also present in the $T_{gamma}$ and $T_{non\text{-}gamma}$ fractions alike [10, 12, 26, 33]. The supernatant of umbilical cord T-cells also shows a suppressive property against PWM stimulation [25].

An inhibitory effect of monocytes has not yet been fully proved but it is certainly a negative factor in IgG and IgM synthesis of newborns. In cell interaction studies primary B-cell immaturity has been demonstrated [11, 24]. Similarly, responses to T-cell mitogens, the NK cell effect and the MLC phenomenon all show a lower activity in newborns than in adults [1, 21, 40]. In the neonate the mitogenic response to Gram-negative bacteria is weaker than to Gram-positive ones [34].

Immaturity of cellular immunity is accompanied or followed by incomplete competence of the humoural system. The course of maturation of the various serum protein fractions is variable. A careful follow-up of the immunoglobulin levels is not only important for establishing the normal value and its limits but indispensable in the diagnosis of pathological conditions; in fact, it bears therapeutic consequences. At birth, only the IgG levels are equal to adult values; they fall to a minimum by the third month even in healthy infants. This is due to the well-known gap between transplacentar transfer and initiation of endogenous synthesis of IgG [8, 9, 38].

Recent work has shown that the transfer through the placenta is promoted by an active process showing increasing activity during pregnancy. This is the reason why the IgG concentration is low in immature babies.

In some mature newborns levels twice higher than the maternal value can be demonstrated. There is a linear correlation between gestational age and placentar transfer of IgG [30]. The placenta is impermeable for IgA and IgM [2].

IgG, IgM and IgA concentrations in the duodenal juice are constant from the second week to the nineteenth year of life [20]. The mammary secretion of neonates contains 0.03 times less IgA than the milk of their mother [40]. Newborns undergoing surgery for gastrointestinal anomalies and fed parenterally have markedly higher IgM and IgA and lower IgG levels than normal babies [31]. The maturation curves of $C_3$, $C_4$ and immunoglobulins obtained by nephelometry closely correspond to earlier findings [17]. Among the components of the complement system $C_{1q}$, $C_3$, $C_4$, $C_5$ and the total haemolytic complement ($CH_{50}$) have a reduced level during the neonatal period. Some other humoural factors such as properdin and interferon are also deficient [6, 32]. Alpha-fetoprotein, which has an immunosuppressive effect, exhibits a level increasing with the degree of immaturity [22, 27].

During the perinatal period even the mature organism has difficulties in surmounting viral and bacterial infections. Sepsis is often diagnosed late, although prevention and early diagnosis are the best weapons against sepsis. Birth and the subsequent few days are the most vulnerable period in this respect. Studies of the IgG, IgA, IgM and $C_3$ levels, the dynamics of their changes and interactions between these parameters during that period are thus justified.

The basis of our investigations were estimations of the $C_3$, IgG, IgA and IgM levels in maternal blood, in cord blood and blood taken from the newborn 72 hours after birth.

## Material and Methods

Thirty mother-infant pairs were selected for the study. Pregnancy was uneventful and uncomplicated in all mothers, the history revealed no infection or drug effect. Delivery was uncomplicated, all newborn babies were mature and healthy. Blood for blood chemistry was taken by vein puncture during delivery, from the cord by the dropping method after dissection of the umbilical cord, and from a peripheral vein of the newborn infants 72 hours after birth. One ml blood was necessary for the determinations. All newborn babies were exclusively breast-fed. No infection was detected during the neonatal period, neither maternal nor neonatal.

Of the babies 16 were boys and 14 were girls. The mean duration of gestation was 38.7 weeks with a range from 37 to 41 weeks. Mean birthweight was 3150 g, the highest value was 3850 g, the lowest 2400 g (Table I). The mentioned determinations were performed in all three samples of each mother-infant pair. The measurements were carried out by rate nephelometry in the Beckman Immunochemistry System (ICS, Beckman Instruments, Inc., Fullerton, CA 92634). All dilutions and the solution for nephelometry were prepared by the use of a Beckman dilutor and dispenser.

All antisera, calibration mixtures, buffers and solutions were special Beckman kits; all the prescriptions of the makers

TABLE I

Number and data of mothers and newborn infants

| n | Male/female | Gestational age week | Birth weight gram |
|---|---|---|---|
| 30 | 16/14 | 38.5±1.5 | 3150±480 |

were strictly observed. The mean duration of one measurement was 1 minute. The levels were expressed in gram/liter units.

The maternal and newborn values were then compared; comparison was also made between the cord blood value and the 72 hour value in each case. The individual percentual changes or differences were calculated as follows

$$\Delta c\% = \frac{c_2 - c_1}{c_1} \times 100$$

where $c_1$ is the initial maternal resp. cord-blood concentration and $c_2$ the cord-blood resp. 72-hour concentration of the protein.

Statistical analysis comprised calculation of the means ($\bar{x}$) with scatter (s); the linear regression equation was constructed ($y = ax + b$), the correlation coeffient (r) was calculated. The levels of statistical significance were estimated by Student's *t*-test.

## RESULTS

Marked differences were found in the $C_3$ level of the maternal and infant blood samples; the mean cord-blood level was 50% of the maternal level (cord-blood value, 0.88 g/l), it sharply increased by the third day of life (mean, 1.24 g/l) (Fig. 1).

The percentual average increase was 42%, however even the 72 hour value was significantly lower than the adult, maternal level (Table II). The IgG concentration of the cord-blood was higher than the maternal level but the difference was not significant statistically. It showed no change over the three days. Pair analysis of the maternal versus infant values revealed, however, deeper re

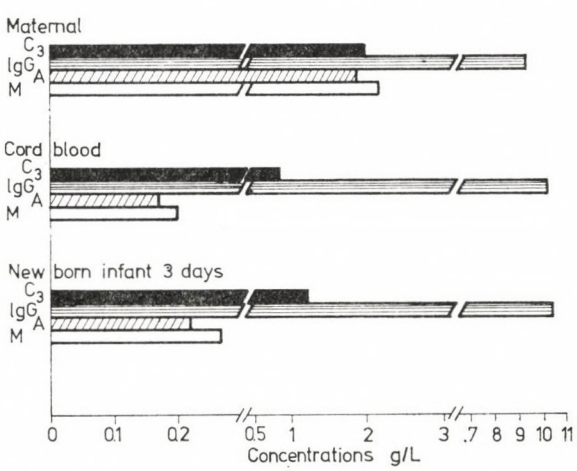



FIG. 1. Serum $C_3$, IgG, IgA and IgM in mothers, in cord-blood and in neonatal blood samples taken 72 hours after birth

TABLE II

Serum concentrations, g/L

| | $C_3$ | | IgG | IgA | IgM |
|---|---|---|---|---|---|
| Maternal | 2.04±0.45* | ++ | 9.32±2.31 | 1.91±0.82 | 2.23±0.87 |
| Cord-blood | 0.88±0.30 | ++ ++ | 10.26±2.14 | 0.17±0.06 + | 0.201±0.12 + |
| Newborn infant 3 days | 1.25±0.35 | ++ | 10.39±2.76 | 0.22±0.09 | 0.22±0.08 |

* Values are (x ± SD) g/L

+ $p < 0.05$
++ $p < 0.001$

lationships which will be discussed in detail later.

The mean value of maternal IgA was nearly 2 g/l. There was no correlation between the maternal level and the cord-blood value.

After 72 hours the mean neonatal value was slightly but statistically

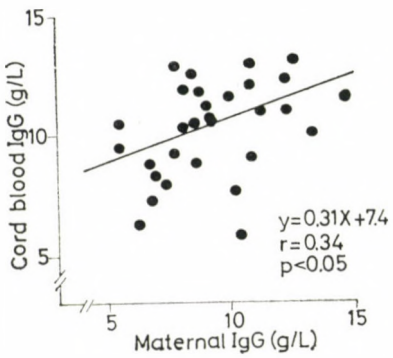



FIG. 2. Correlation between maternal and cord-blood IgG concentrations

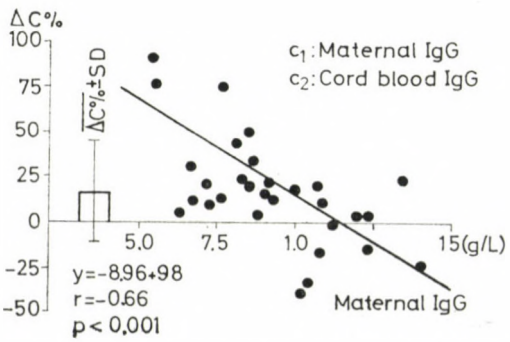



FIG. 3. Percentual difference between the cord-blood IgG level and the maternal IgG level plotted against the absolute value of the maternal IgG level

significantly increased. A value exceeding 0.1 g/l represents a markedly high level in healthy neonates of this age.

IgM showed a similar behaviour, a significant increase was seen by the third day of life. Here, a value higher than 0.2 g/l can be taken as a markedly increased level.

The following correlations were found.

There was a positive correlation between the maternal IgG level and the corresponding cord-blood value (Fig. 2). The infant's values were generally higher than the corresponding maternal value, the correlation was significant statistically.

A negative correlation was found between the percentual mother-infant difference and the maternal level (Fig. 3). In the infants of mothers with a low level the cord-blood value was about double while there was no increase or even a slight decrease occurred whenever the maternal IgG level was above the average. This correlation was significant statistically. The mean IgG level of the cord-blood samples and those taken 72 hours

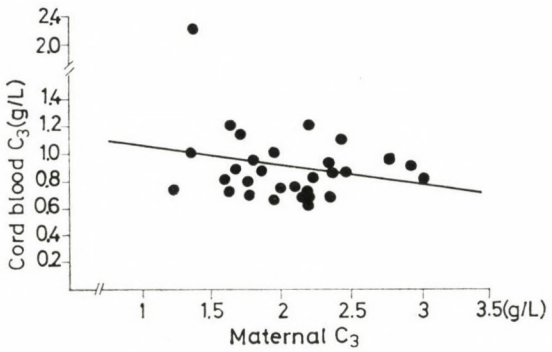



FIG. 4. Correlation between maternal and cord-blood $C_3$ levels

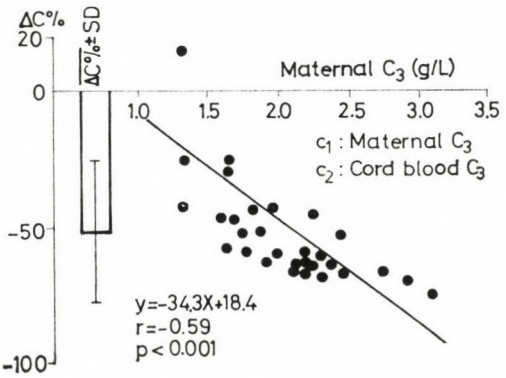



FIG. 5. Percentual difference between the cord-blood $C_3$ level and the maternal $C_3$ level plotted against the absolute value of the maternal $C_3$ level

after birth did not differ significantly.

In spite of considerable variations in the maternal $C_3$ level the cord-blood concentration showed a narrow scatter (Fig. 4). With a low maternal value the percentual deviation of the newborn value was small, i.e. a

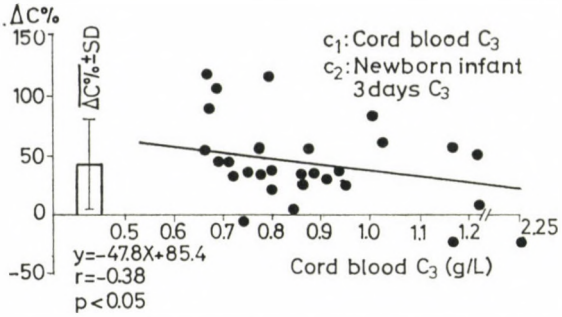



FIG. 6. Percentual increase in $C_3$ concentration in the same newborn during the first three days plotted against the absolute cord-blood value

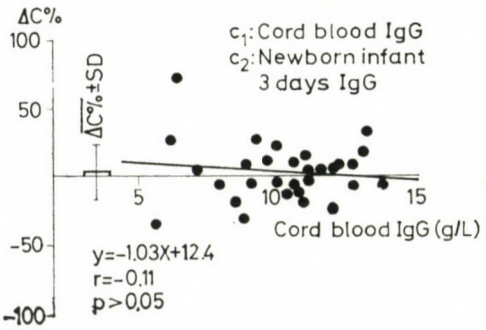



FIG. 7. Percentual increase in IgG concentration in the same newborn during the first three days plotted against the absolute cord-blood value

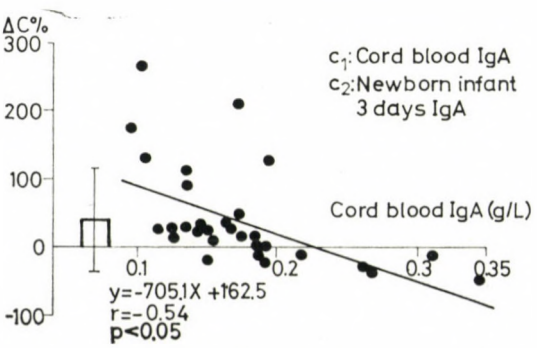



FIG. 8. Percentual changes in IgA in the same newborn during the first three days, plotted against the absolute cord-blood value

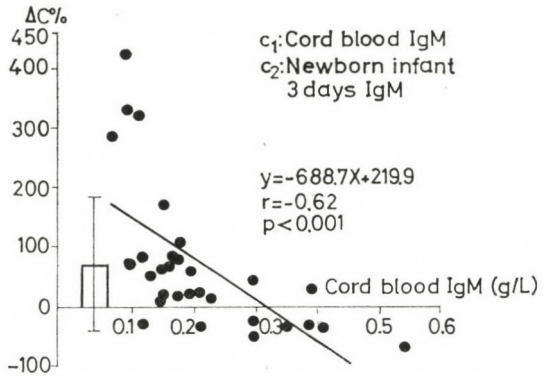



FIG. 9. Percentual changes in IgM concentration in the same newborn during the first three days plotted against the absolute cord-blood value

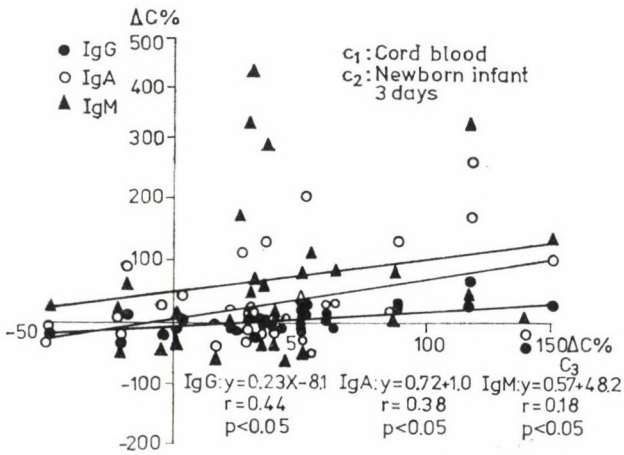



FIG. 10. Percentual changes in IgG, IgA and IgM concentrations plotted against percentual changes in $C_3$ concentration during the first three days of life

relative stability of the newborn level is secured (Fig. 5). The lower the cord-blood value the larger the increase by the end of the third day of life (Fig. 6). This correlation was also significant statistically.

Generally, the immunoglobulin levels increased within the first 72 hours of life, the increase was, however, different for the individual Ig classes. The IgG hardly changed (Fig. 7). The percentual increase of IgA was steeper in cases with an initially low IgA level (Fig. 8), and a similar trend was found with IgM (Fig. 9). Both correlations were significant.

A positive, significant correlation could be established between the percentual increase of $C_3$ and that of IgG and IgA. A similar trend between the increments of $C_3$ and of IgM was

seen but the degree of correlation did not attain statistical significance (Fig. 10).

The higher the maternal $C_3$ level, the higher were the IgG and the IgM levels in the same mother. High IgG levels were linked with high IgA and IgM in the same mother. A positive correlation was found for $C_3$—IgG and IgG—IgM in newborns at 72 hours of age. No other statistically significant relationship was observed, and the sex of the newborn had no effect on any parameter.

## Discussion

In Hungary, 19% of the perinatal mortality was due to infection during the early seventies [19]. Since then, the situation has not changed significantly. Therefore, rapid and exact methods are necessary for the early detection of infection. Among others, leucocyte count, blood smear, erythrocyte sedimentation rate, C-reactive protein, haptoglobin, antithrombin III are of use, and determination of immunoglobulins and complement components and bacteriological cultures are of outstanding importance [28, 29, 35].

Most newborns infected during the perinatal period show a marked increase in IgM and IgA with a concomitant decrease in IgG [23]. In animal experiments, low activity of the complement system may lead to fatal bacterial infection. A follow-up of the $C_3$ level is of primary importance since it is a central link of both the classical and the alternative pathways. A low or absent value may critically affect the mechanisms of defence [15].

The method used for the determination of IgG, IgM and IgA and $C_3$ is rapid and reproducible. They are not only ancillary aids but elementary tools in screening and detection of neonatal infection.

Our data help in establishing the normal mean values and limits of these parameters in newborn babies. In addition, interesting relationships have been detected. The active transport responsible for the materno-fetal transport of IgG works more efficiently in the presence of a low maternal level. This secures an invariably high level in the mature infant. This in turn does not change during the first three days provided no infection or other pathological conditions occur.

Similarly, a slightly low but rather uniform level of $C_3$ is found in the cord-blood in spite of considerable variations of the maternal level. In other words, the newborn's level is rather independent of that of the mother. During the first 72 hours intensive synthesis occurs, especially if the initial value was lower than average.

IgM shows the steepest increase during the first 72 hours of life. This points again to the fact that the primary immune response is perfectuated by IgM production. In the newborn, all environmental antigens elicit a primary immune response. For similar reasons, the course of

IgA changes during the first days of life is only natural.

A common anabolic capacity may be the cause of certain correlations between the course of changes in various immunoglobulin levels; a steeper increase in $C_3$ is accompanied by a more marked increase in IgA and IgG. This development can be hindered by any derangement in the newborn's metabolism. In normal populations, a positive correlation exists between $C_3$ and immunoglobulin levels.

Serial determination of these parameters during the newborn period of life may be of great help in the early diagnosis and classification according to severity of infection. It may also be useful in evaluation of substition therapy carried out by administration of blood, plasma, immunoglobulins, leucocyte or platelet and complement preparations.

## References


1. Abedin M, Kirkpatrick CH: Immunosuppressive activity of cord-blood leukocytes. Pediatrics 66: 405, 1980
2. Allansmith M, McCleelan BH, Butterworth M: The development of immunglobulin levels in man. J Pediatr 72: 276, 1968
3. Andersson U, Bird AG, Britton S, Palacios R: Humoral and cellular immunity in humans studied at the cell level from birth to two years of age. Immunol Rev 57: 5, 1981
4. Babior BM, Kipnes RS, Curnutte JF: Biological defense mechanism. The production by leukocytes of superoxide, a potential bactericidal agent. J Clin Invest 52: 741, 1973
5. Balla G, Makay A, Szabó L, Karmazsin L: Superoxyd-Dismutase-Aktivität der polymorphonuklearen Leukozyten der Neugeborenen. Acta Paediatr Acad Sci Hung 22: 201, 1981
6. Bryson YJ, Winter HS, Gard SE, Fischer TJ: Deficiency of immune interferon production by leukocytes of normal newborns. Cell Immunol 55: 191, 1980
7. Christiansen JS, Osther K, Peitersen B, Bach-Mortensen N: B, T and Null lymphocytes in newborn infants and their mothers. Acta Paediatr Scand 65: 425, 1976
8. Csorba S, Kávai M, Jezerniczky J: Immune globulins in maternal, cord, and infant blood. Acta Paediatr Acad Sci Hung 10: 53, 1969
9. Csorba S, Kávai M, Karmazsin L: Untersuchungen über die Immuneiweiß-Stoffe (IgG-, IgA-, IgM-Globulin) bei reif- und frühgeborenen Säuglingen in den Monaten nach der Geburt. Acta Paediatr Acad Sci Hung 8: 405, 1967
10. Durandy A, Fisher A, Griscelli C: Active suppression of B lymphocyte maturation by two different newborn T lymphocyte subsets. J Immunol 123: 2644, 1979
11. Fergusson AC, Cheung SSC: Modulation of immunglobulin M and G synthesis by monocytes and T lymphocytes in the newborn infant. J Pediatr 98: 385, 1981
12. Gupta S, Good RA: Subpopulations of human T lymphocytes. III. Distribution and quantitation in peripheral blood cord-blood, tonsils, bone marrow, thymus, lymph nodes, and spleen. Cell Immunol 36: 263, 1978
13. Handzel ZT, Levin S, Dolphin Z: Immune competence of newborn lymphocytes. Pediatrics 65: 491, 1980
14. Haneberg B, Bertnes E, Ulstein M: Mitogen-induced multiplication of lymphocytes from newborn infants. Eur J Pediatr 134: 23, 1980
15. Hosea SW, Brown EJ, Frank MM: The critical role of complement in experimental pneumococcal sepsis. J Infect Dis 142: 903, 1980
16. Johnston RB, Jr, Keele B, Jr, Misra H, Lehmeyer JE, Webb LS, Baehner RL, Rajagopaian KR: The role of superoxide anion generation in phagocytic bactericidal activity. J Clin Invest 55: 1357, 1975
17. Jolliff, CR, Cost KM, Stivrins PC, Grossman PP, Nolte CR, Franco SM, Fijan KJ, Fletcher LL, Shriner HC: Reference intervals for serum IgG, IgA, IgM, $C_3$ and $C_4$ ad determined by rate nephelometry. Clin Chem 28: 126, 1982
18. Karmazsin L, Makay A, Balla Gy: Lymphocyte subpopulations and devel-

opment of immune functions in the newborn baby. Acta Paediatr Acad Sci Hung 19: 303, 1978
19. Korányi G: Neonatal infections. In: Perinatal Medicine eds. Kerpel-Fronius E, Véghelyi PV, Rosta J, Akadémiai Kiadó, Budapest 1978, p. 1069
20. Lebenthal E, Clark BA, Kim O: Immunglobulin concentrations in duodenal fluid of infants and children. Amer J Dis Child 134: 834, 1980
21. Leino A, Hirvonen T, Soppi E: Ontogeny of phytohemagglutinin and concanavalin A responses in the human fetus: effect of thymosin. Clin Immunol Immunopath 17: 547, 1980
22. Lester EP, Miller JB, Yachnin S: Human alpha-feto protein as a modulator of human lymphocyte transformation. Correlation of biological potency with electrophoretic varients. Proc Natl Acad Sci USA 12: 4645, 1976
23. McMurray DN, Rey H: Immunological sequelae of intrauterine infection. Clin Exp Immunol 44: 389, 1981
24. Miyagawa Y, Sugita K, Komiyama A, Akabane T: Delayed in vitro immunglobulin production by cord lymphocytes. Pediatrics 65: 497, 1980
25. Miyawaki T, Moriya N, Nagaoki T, Kubo M, Yokoi T, Taniguchi N: Mode of action of humoral suppressor factor derived from pokeweed mitogen-stimulated cord T cells on adult B cell differentiation. J Immunol 126: 282, 1981
26. Moriya N, Nagaoki T, Okuda N, Taniguchi N: Suppression of adult B cell differentiation in pokeweed mitogen-stimulated cultures by Fc(IgG) receptor-negative T cells from cord-blood. J Immunol 123: 1795, 1979
27. Murgita RA, Tarnasi TB, Jr: Suppression of the immune response by alpha-fetoprotein. J Exp Med 141: 269, 1975
28. Philip AGS: Detection of neonatal sepsis of late onset. JAMA 247: 489, 1982
29. Philip AGS, Hewitt JR: Early diagnosis of neonatal sepsis. Pediatrics 65: 1036, 1980
30. Pitcher-Wilmott RW, Hindocha P, Wood CBS: The placental transfer of IgG subclasses in human pregnancy. Clin Exp Immunol 41: 303, 1980
31. Puri P, Reen DJ, Browne O, Guiney EJ: Immune status of the neonate maintained on total parenteral nutrition. Arch Dis Childh 56: 283, 1981
32. Roach B, Kim Y, Jerome E, Michael AF: Influence of age and sex on serum complement components in children. Amer J Dis Child 135: 918, 1981
33. Rodriguez MA, Bankhurst AD, Ceuppens, JL, Williams RC, Jr: Characterisation of the suppressor cell activity in human cord-blood lymphocytes. J Clin Invest 68: 1577, 1981
34. Rubin HR, Sorensen RU, Palmar SH: Lymphocyte responses of human neonates to bacterial antigens. Cell Immunol 57: 307, 1981
35. Sabel KG, Wadswoth C: C-reactive protein (CRP) in early diagnosis of neonatal septicemia. Acta Paediatr Scand 68: 825, 1979
36. Shigeoka AO, Charette RP, Wyman ML, Hill HR: Defective oxidative metabolic responses of neutrophils from stressed neonates. J Pediatr 98: 392, 1981
37. Shigeoka AO, Santos JI, Hill HR: Functional analysis of neutrophil granulocytes from healthy, infected and stressed neonates. J Pediatr 95: 454, 1979
38. Sterzl J, Silvestrein A: Developmental aspects of immunity. Development of immunglobulins and other serum proteins. Advanc Immunol 5: 337, 1967
39. Strauss RG, Snyder EL: Neutrophils from human infants exhibit decreased viability. Pediatr Res 15: 794, 1981
40. Toivanen P, Uksila J, Leino A, Lassila O, Hirvonen T, Ruuskanen O: Development of mitogen responding T cells and natural killer cells in the human fetus. Immunol Rev 57: 89, 1981
41. Yap PL, McKiernan J, Mistle CL, McCelland DBL: The development of mammary secretory immunity in the human newborn. Acta Paediatr Scand 70: 459, 1981

*Received 15 June 1982*

G. Balla MD
Pf. 32
H–4012 Debrecen, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 53—61 (1983)*

# Fatty acid composition of human milk and milk-based formulas in Hungary

Anna GERE,* Erzsébet A BERNOLÁK,* Ö GAÁL,* P CHOLNOKY,** I ŐRY***

*Institute of Nutrition, Budapest; **District Hospital, Szombathely; and ***Hungarian Ministry of Health, Budapest

Fatty acid composition of breast milk from 250 Hungarian women being 1, 3 and 6 months post partum was studied. It was shown that the fatty acid composition of mature breast milk does not vary greatly with the length of lactation. Data from women with different education levels and places of residence were found similar, suggesting similarities in the dietary habits of Hungarian women. Fatty acid levels in human milk did not show significant seasonal variation. The content of linoleic acid (expressed as g/l and percent of total energy) was calculated in relation to the length of lactation.

Fatty acid composition of Hungarian milk-based formulas (Robebi A, Robebi B and Linolac) was also studied and compared to the mean composition of milk from 250 mothers. The results indicated differences in the contents of most saturated and unsaturated fatty acids and confirmed the finding that even the most carefully adapted formulas cannot substitute human milk.

In recent years the importance of breast feeding as a basis for healthy child growth and development has become increasingly recognized. There has been a resurgence of interest in breast feeding, which has led to the initiation of research on the composition of human milk and the establishment of several nationally supported projects on the subject.

The content of nutrients in breast milk shows considerable variations The following factors are known to influence human milk composition [1, 6, 8, 9, 11—14, 16, 17, 20, 21];

- stage of lactation,
- stage of breast emptying,
- time of the day,
- premature birth,
- nutritional circumstances of the mother, i.e. the mother's intake of food, vitamins, alcohol, drugs and contaminants.

Hall [12] studied the composition of mature milk in relation to the suckled breast, the time of the day, the course of the feed and the length of lactation. She found that while the amount of lipid of milk obtained from either breast rose significantly during the feed as well as throughout the day, the protein and lactose content and pH remained constant. Forsum and Lönnerdal [6] also reported a rise in the fat content during emptying of the breast while the concentrations of water-soluble components practically did not change.

Several reports [8, 17, 18] indicated that milk from mothers with preterm

infants contained significantly more protein, sodium and chloride and less lactose than milk from women delivering at term. Energy value, potassium, calcium, phosporus and magnesium contents one generally similar for both groups.

Gibson and Kneebone [7] analysed milk samples obtained early and later in lactation. In comparison with mature milk, human colostrum was characterized by a lower percentage of saturated fatty acids, a higher concentration of monounsaturates and a lower level of linoleic and linolenic acids. This agrees with the findings of Droese et al. [4] who studied the lipid content and fatty acid composition of human colostrum, transitional and mature milk. Their results also showed that the amount of lipid increases during lactation, which is attributed to maturation of the milk and is not influenced by the maternal diet.

Much work has been done to investigate the effects of diet [1, 11–14, 16, 21]. The contents of several nutrients such as fat, fatty acids, proteins, vitamins can be altered by the maternal diet. In 1965 a study presented by Kramer et al. [16] demonstrated that an increase in the sunflower oil content of the diet results in a rise in the concentration of linoleic acid of breast milk. Usually, the increase of a fatty acid in the diet is reflected within hours in a higher percentage of the same fatty acid in milk and after the return to the usual diet a reverse change can be observed [12, 21].

Human milk composition is considerably affected by the above factors, i.e. data on the composition of breast milk are often difficult to compare when different methods of collection are applied. The importance of proper sampling has been emphasized in several reports [1, 6, 14] and adequate sampling techniques have also been suggested. Analysis of pooled 24 hour collections appears to be ideal. Since this may be difficult to carry out in practice, another useful sampling protocol is that the entire contents from one breast should be obtained with an electric pump at a specific time in the day, at a fixed interval after the previous feed.

Since breast feeding of infants is not always possible, efforts have been made to produce a special range of breast milk substitutes designed to meet all the food requirements of infants. It has become strikingly evident that even the most sophisticated and carefully adapted formulas can never replicate human milk [2, 5, 13]. In addition to differences in nutrient composition, human milk has anti-infective properties implying that it is a "live" fluid in a way that cannot be mimicked in an artificial formula. As regards the nature of fats, besides their composition the position of the fatty acids within the triglyceride molecule is of great importance. Even in the case of a similar fatty acid composition the fat of human milk is more efficiently digested and absorbed, which is attributed to structural differences within the triglycerides [10].

The purpose of this work was to examine the fatty acid composition of milk from Hungarian mothers in relation to the length of lactation, as part of the WHO Collaborative Study on Volume and Composition of Breast Milk, and to compare the results obtained to the fatty acid composition of Hungarian commercial milk-based formulas.

*Collection of human milk samples*

Collection of milk samples was carried out according to the protocol developed by the organizers and researchers of the countries taking part in the WHO Collaborative Study on Volume and Composition of Breast Milk.

Volunteer healthy mothers with healthy infants were chosen as milk donors. Samples were taken under standard conditions at noon, 4 hours after the previous feed. Milk samples for analysis were collected by health visitors as follows. The nipple and the area surrounding it were cleaned using an appropriately diluted detergent solution (baby shampoo provided by the International Atomic Energy Agency), rinsed with distilled water and then patted dry with clean tissue paper. The contents from one or both breasts were expressed until no secretion was left, with a mechanic pump connected to a special milk collection vessel (provided by WHO and IAEA). The samples were immediately placed into cooling containers and conveyed to our laboratory where they were stored below —20°C until analysed.

*Analysis of milk samples*

Milk samples were creamed by centrifugation. Milk lipids were converted into methyl esters according to Szőke et al [21]. Fatty acid composition was determined by gas chromatography (GLC). GLC analyses were performed by a Carlo Erba Fractovap model 2400 T using a 2 m × 4 mm glass column packed with 10% EGSSX by 80/100 mesh Gas Chrom Q, at 180°C. Peaks were identified by comparison with known standards.

## Results and Discussion

The average fatty acid compositions of milk samples from three groups of mothers (those with university education, those who did not complete secondary school, and those from villages) were calculated separately, in relation to the length of lactation. The values obtained are listed in Tables I, II and III. It can be concluded that only minor differences occurred in the proportion of fatty acids from mothers belonging to different groups; this was probably due to similarities in the diets consumed. Comparison of the data from women being 1, 3 and 6 months post partum also showed similarities, suggesting that the fatty acid composition of human milk does not vary greatly with the length of lactation. This agrees with the results of other authors [5, 12, 13] who also found that the fatty acid composition of

mature breast milk remains unchanged during lactation.

Considering that the fatty acid composition of milk samples from 9 groups of mothers appeared to be similar, a mean composition was calculated using data from all samples collected. The results are presented in

TABLE I

Fatty acid composition of milk from mothers being 1 month post partum

| | Fatty acids in percent of total fatty acids (mean ± SD) | | |
|---|---|---|---|
| | Mothers with university education (from Budapest) n = 26 | Mothers with primary education (from Budapest) n = 29 | Mothers from villages n = 29 |
| $C_{12:0}$ | 1.7±0.8 | 1.9±1.3 | 1.6±1.0 |
| $C_{14:0}$ | 4.0±1.4 | 4.4±1.7 | 4.9±2.1 |
| $C_{16:0}$ | 28.2±2.0 | 26.0±4.5 | 26.1±3.4 |
| $C_{16:1}$ | 2.6±0.8 | 2.6±0.8 | 3.1±1.1 |
| $C_{18:0}$ | 10.4±1.3 | 9.2±1.9 | 9.5±1.4 |
| $C_{18:1}$ | 43.2±9.3 | 44.7±4.8 | 44.3±4.7 |
| $C_{18:2}$ | 9,0±1.6 | 9.8±5.0 | 9.5±2.8 |
| Other | 0.9±0.4 | 1.4±0.7 | 1.0±0.5 |
| $\Sigma$ saturates | 44.3 | 41.5 | 42.1 |
| $\Sigma$ monounsaturates | 45.4 | 47.3 | 47.4 |
| $\Sigma$ polyunsaturates | 9.0 | 9.8 | 9.5 |

TABLE II

Fatty acid composition of milk from mothers being 3 months post partum

| | Fatty acids in percent of total fatty acids (mean ± SD) | | |
|---|---|---|---|
| | Mothers with university education (from Budapest) n = 26 | Mothers with primary education (from Budapest) n = 29 | Mothers from villages n = 27 |
| $C_{12:0}$ | 2.6±0.6 | 2.2±0.9 | 2.6±1.8 |
| $C_{14:0}$ | 3.9±2.1 | 4.9±2.6 | 4.8±1.9 |
| $C_{16:0}$ | 25.6±3.5 | 25.3±2.8 | 26.8±2.6 |
| $C_{16:1}$ | 2.3±0.7 | 2.5±0.6 | 2.0±0.5 |
| $C_{18:0}$ | 9.7±1.7 | 9.7±1.3 | 9.6±1.7 |
| $C_{18:1}$ | 44.0±4.8 | 43.5±3.9 | 42.7±3.1 |
| $C_{18:2}$ | 10.6±2.0 | 10.7±3.3 | 10.6±3.3 |
| Other | 1.3±0.8 | 1.2±0.9 | 0.7±0.3 |
| $\Sigma$ saturates | 41.8 | 42.1 | 43.8 |
| $\Sigma$ monounsaturates | 46.3 | 46.0 | 44.9 |
| $\Sigma$ polyunsaturates | 10.6 | 10.7 | 10.6 |

TABLE III

Fatty acid composition of milk from mothers being 6 months post partum

| | Fatty acids in percent of total fatty acids (mean ± SD) | | |
|---|---|---|---|
| | Mothers with university education (from Budapest) n = 25 | Mothers with primary education (from Budapest) n = 34 | Mothers from villages n = 25 |
| $C_{12:0}$ | 2.4±1.7 | 2.3±1.5 | 2.2±1.9 |
| $C_{14:0}$ | 5.5±2.2 | 5.8±2.0 | 5.0±2.2 |
| $C_{16:0}$ | 26.5±3.5 | 26.1±3.1 | 25.3±2.2 |
| $C_{16:1}$ | 2.4±0.9 | 2.9±0.9 | 2.5±0.5 |
| $C_{18:0}$ | 9.8±1.7 | 10.1±2.7 | 10.1±1.4 |
| $C_{18:1}$ | 41.8±3.4 | 42.5±3.3 | 44.1±2.9 |
| $C_{18:2}$ | 10.9±3.1 | 9.8±3.6 | 10.2±2.6 |
| Other | 0.7±0.6 | 0.5±0.3 | 0.6±0.3 |
| $\Sigma$ saturates | 44.2 | 44.3 | 42.6 |
| $\Sigma$ monounsaturates | 44.2 | 45.4 | 46.6 |
| $\Sigma$ polyunsaturates | 10.9 | 9.8 | 10.2 |

TABLE IV

Mean fatty acid composition of milk from 250 mothers

| | Fatty acids in percent of total fatty acids (mean ± SD) |
|---|---|
| $C_{12:0}$ | 2.1±0.6 |
| $C_{14:0}$ | 4.9±0.8 |
| $C_{16:0}$ | 26.2±0.8 |
| $C_{16:1}$ | 2.6±0.3 |
| $C_{18:0}$ | 9.8±0.4 |
| $C_{18:1}$ | 43.4±1.1 |
| $C_{18:2}$ | 10.1±0.7* |
| Other | 0.9±0.2 |
| $\Sigma$ saturates | 43.0 |
| $\Sigma$ monounsaturates | 46.0 |
| $\Sigma$ polyunsaturates | 10.1 |

* Highest value: 23.5
Lowest value: 5.3

Table IV. In comparison with other reports on the fatty acid composition of human milk [5, 7, 12, 14] the percentages of lauric and miristic acid of Hungarian breast milk are slightly lower, while the level of linoleic acid is somewhat higher. These differences may be caused by variations in the maternal diet in different countries and by different sampling techniques.

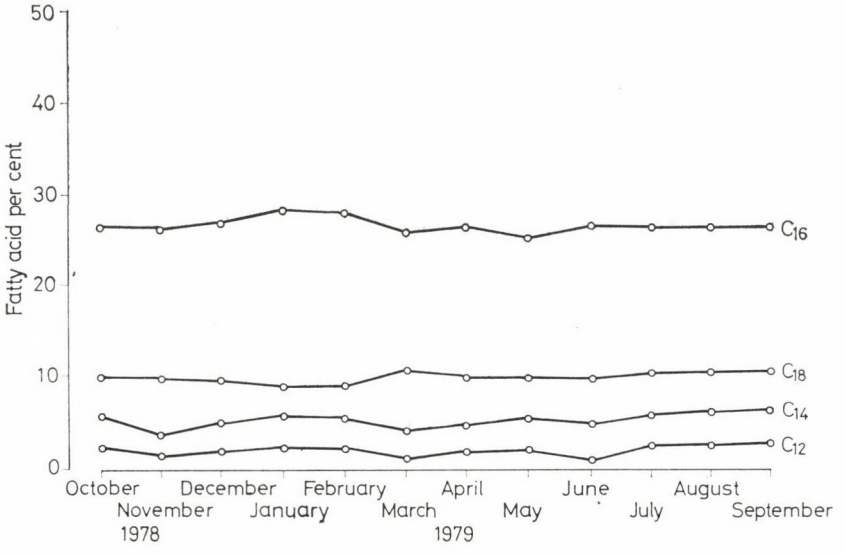



FIG. 1. Monthly variations of saturated fatty acids of human milk

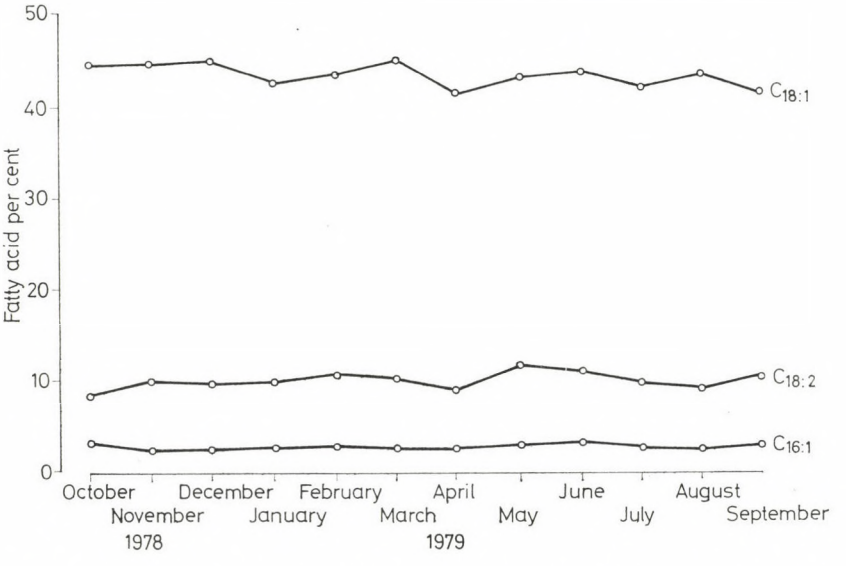



FIG. 2. Monthly variations of unsaturated fatty acids of human milk

TABLE V

Linoleic acid content of milk from 250 mothers

| Length of lactation | Concentration of linoleic acid (g/l) mean ± SD | Linoleic acid in percent of total energy mean ± SD |
|---|---|---|
| 1 month (n = 84) | 3.42±1.81 | 4.96±2.10 |
| 3 months (n = 82) | 3.38±1.46 | 4.66±2.05 |
| 6 months (n = 84) | 3.99±1.67 | 4.76±2.12 |

It has been shown that the diet is the most important factor influencing the fatty acid composition of breast milk [5, 12–14, 16, 21]. We found that education and place of residence do not significantly affect the dietary habits of Hungarian women. As the diets consumed may change according to seasons, monthly variations of the level of each fatty acid were also investigated. From Fig. 1 and 2 it is equally clear that practically no change could be observed, i.e. seasonal variation of the diet does not concern fatty acid composition.

The level of linoleic acid, which is the main essential fatty acid of breast milk, was determined in each of the 250 samples. Mean concentrations and energy values were calculated in relation to the length of lactation, as shown in Table V. According to recommendations of the Joint FAO/WHO Food Standards Programme [15] infant foods must contain a minimum of 0.3 g/100 kcal (about 1.9 g/l) of linoleic acid. Crawford et al. [3] indicate a linoleic acid requirement of at least 1% of the total energy. From Table V it is clear that all mean values were significantly higher than the above limits. Examination of the individual data indicated that out of the 250 samples 18 showed a linoleic acid concentration below 1.9 g/l and all the energy values markedly exceeded 1%. The total volume of milk produced by mothers during a 24 hour period was also measured. On the basis of the values obtained and data listed in Table V, the daily excess linoleic acid requirement of lactating women was found to amount to 2.1—2.3 g.

When breast feeding cannot be carried out, milk formulas are applied the composition of which is more or less like that of human milk. We compared the fatty acid composition of commercial milk-based formulas produced in Hungary (Robebi A, Robebi B and Linolac) and cow's milk to that of breast milk from the 250 women. As regards the saturates/unsaturates ratio, in Robebi A (0.68) and Robebi B (1.04) it was similar to the ratio in human milk (0.77). Linolac and cow's milk with high concentrations of saturated fatty acids showed different ratios (1.84 and 1.60

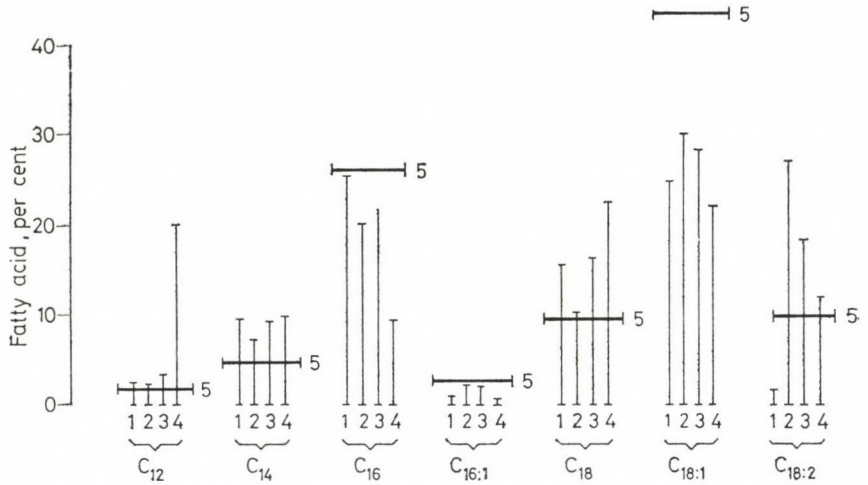



FIG. 3. Levels of fatty acids in cow's milk and milk-based formulas as compared to breast milk: 1. cow's milk; 2. Robebi A; 3. Robebi B; 4. Linolac; 5. human milk

respectively). The level of each fatty acid is shown in Fig. 3. In milk-based formulas cow's milk fat is combined with vegetable oils in order to increase the degree of unsaturation and to improve absorption. The fat content of human milk and of the formulas was found nearly the same, about 3.5%, but as Fig. 3 indicates, none of the formulas has a fatty acid composition similar to that of human milk. The high concentration of lauric acid in Linolac is attributed to its special vegetable oil content. The most important unsaturated fatty acids in both human milk and the formulas are oleic and linoleic acid. In breast milk the level of oleic acid is about 40% and that of linoleic acid is 10% while the formulas contain significantly less oleic and more linoleic acid, due to their sunflower oil content. It is known that a high linoleic acid content may produce relative tocopherol deficiency [5]. For that reason the Joint FAO/WHO Food Standards Programme [15] recommends that the lower limit of tocopherol content in milk formulas should depend on the level of linoleic acid.

In summary, our results provided data on the fatty acid composition of milk from Hungarian mothers and indicated that the levels of fatty acids in mature breast milk show little changes during lactation when the diet is nutritionally adequate.

Comparison of the data for human milk and Hungarian milk-based formulas showed differences in the contents of most saturated and unsaturated fatty acids. The present study confirmed the findings of many other authors that no formula may substitute human milk, which ensures an adequate source of fatty acid nutrients for normal nutrition of infants.

## Acknowledgements

Participation of Hungary in the WHO Collaborative Study on Volume and Composition of Breast Milk was directed by Dr. I. Őry and collection of human milk samples was organized by Prof. P. Cholnoky.

The authors wish to thank the health visitors who took part in the collection and the mothers who kindly supplied the milk samples. The technical assistance of Mrs. R. Tihanyi, Mrs. I. Ökrös, Mrs. V. Huszár, Mrs. E. Somogyi and Miss É. Maucha is gratefully acknowledged.

## References

1. Atkinson SA: Factors affecting human milk composition. J Can Dietet Assoc 40: 213, 1979
2. Contemporary patterns of breast-feeding. Report on the WHO Collaborative Study on Breast-feeding. WHO, Geneva 1981
3. Crawford MA, Hassam AG, Rivers JPW: Essential fatty acid requirements in infancy. Am J Clin Nutr 31: 2181, 1978
4. Droese W, Pape E, Stolley H: Zur Frage der Versorgung des Säuglings mit Fett und Fettsäuren. I. Fettgehalt und Fettsäuremuster in Frauenmilch und Kuhmilch. Eur J Pediatr 122: 57, 1976
5. Droese W, Pape E, Stolley H: Questions to the supply of young infants with fat and fatty acids. II. Fat content and fatty acid pattern in milk formulae for healthy infants in the first 6 months of life. Eur J Pediatr 123: 277, 1976
6. Forsum E, Lönnerdal B: Variation in the contents of nutrients of breast milk during one feeding. Nutr Rep Int 19: 815, 1979
7. Gibson RA, Kneebone GM: Fatty acid composition of human colostrum and mature breast milk. Am J Clin Nutr 34: 252, 1981
8. Gross SJ, David RJ, Bauman L, Tomarelli RM: Nutritional composition of milk produced by mothers delivering preterm. J Pediatr 96: 641, 1980
9. Gross SJ, Geller J, Tomarelli RM: Diurnal variation in nutritional composition of milk produced by mothers of preterm infants. Pediatr Res 14: 500, 1980
10. György PA: Biochemical aspects of human milk. Am J Clin Nutr 24: 976, 1971
11. Hall B: Changing composition of human milk and early development of an appetite control. Lancet 1, 779, 1975
12. Hall B: Uniformity of human milk. Am J Clin Nutr 32; 304, 1979
13. Jelliffe DB, Jelliffe EFP: Human milk in the modern world. Oxford University Press, 1979
14. Jensen RG, Clark RM, Ferris AM: Composition of the lipids in human milk: a review. Lipids 15: 345, 1980
15. Joint FAO/WHO Food Standards Programme, Codex Alimentarius Comission: Recommended international standards for foods for infants and children. FAO and WHO CAC/RS 72/74—1976
16. Krámer M, Szőke K, Lindner K, Tarján R: The effect of different factors on the composition of human milk and its variations. III. Effect of dietary fats on the lipid composition of human milk. Nutr Dieta 7: 71, 1965
17. Lemons JA, Hall D, Benson J, Simmons MA: Composition of preterm breast milk. Pediatr Res 13: 403, 1979
18. Schanler RJ, Oh W: Composition of breast milk obtained from mothers of premature infants as compared to breast milk obtained from donors. J Pediatr 96: 679, 1980
19. Szőke K, Krámer M, Lindner K: Eine zu Serien-Untersuchungen geeignete Methode zum raschen Verestern von Lipiden und Lipidfraktionen. Fette Seifen Anstrichm 67: 257, 1965
20. Tarján R, Krámer M, Szőke K, Lindner K, Szarvas T, Dworschák E: The effect of different factors on the composition of human milk and its variations. II. The composition of human milk during lactation. Nutr Dieta 7: 136, 1965
21. Timonen E, Åkerblom HK, Hasunen K, Kouvalainen K: Effect of diet on the fatty acid composition in human milk. Pediatr Res 13: 82, 1979

*Received 22 June 1982*

Anna Gere DEng
Gyáli út 3/A
H-1097 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 63—65 (1983)*

# Changes of the growth hormone level after a single small dose of somatostatin

F PÉTER, S SZENTISTVÁNYI *

Buda Children's Hospital, Budapest

Growth hormone (GH) secretion was studied in children after a single small intravenous (i.v.) dose of somatostatin (Somatotropin Release Inhibiting Factor, SRIF). After a short decrease of the GH level there was a slow increase culminating at 60 minutes, then again a decrease with the lowest point at 90 minutes. During the third hour the GH level showed a second peak; this was more frequent than the first one. It is concluded that a single small dose of somatostatin during the third hour after its administration can cause an increase of the GH level.

Pituitary GH secretion is regulated by two hypothalamic hormones, a stimulatory (GH-releasing factor, GRF) and an inhibitory one (somatostatin, SRIF) [2, 4]. SRIF has been characterized as a tetradecapeptide and it is commercially available in synthetized form [6]. This inhibitory factor suppresses GH and TSH and outside the pituitary it does not only inhibit the secretion of insulin and glucagon but also that of a large number of other gastrointestinal polypeptides [9]. Considerable work has been done on the in vivo effects of exogenous SRIF, but little is known about the changes of the GH level after a single bolus administration of SRIF. Because of its very short half life (2–4 minutes) it is mostly applied in infusion [2] and the GH level was estimated only in the first hour after terminating the infusion.

We have studied the late effect of a single small i.v. dose of SRIF on the GH level during three hours.

## Patients and Methods

Twenty-five healthy children and twelve GH deficient patients were studied. None of the healthy volunteers had a history of endocrine disease. GH was tested with the standardized RIA method of Pharmacia (Uppsala) 20 minutes and immediately before and 5, 10, 20, 30, 45, 60, 90, 120, 150 and 180 minutes after injecting 5 $\mu$g/kg of SRIF or physiological saline. After the first nine tests blood sampling was done only at –20 and 0 min and in the second and third hours. In the GH deficient children the GH level was studied at 0, 90, 150 and 180 minutes, and also at 210 minutes.

GH deficiency was diagnosed on the basis of short stature, bone age retardation, delayed growth, normal thyroid function, cytogenetic normality, negative insulin induced hypoglycaemia and DOPA tests (GH peak value-$<$ 14 mU/L).

* Present address: Royal Children's Hospital, Melbourne. Australia

## Results

The mean GH values of healthy children showed the inhibitory effect of SRIF on GH release during the first ten minutes, followed by a rebound during the next 50 minutes. The individual reactions were different in the second period; the peak occurred at 20 minutes in 7 children, at 30 in 3 children, at 45 in 6 children and at 60 minutes in 4 children, and the standard deviations were high (26.8—31.4). At 90 minutes there was a second low point with 5.8 ± 8.0 mU/L GH and then a second peak above 14 mU/L. (10 individual peaks out of 14 occurred at the last two samplings.)

Physiological saline did not provoke this undulation of the GH level except for an increase at 0 minute which was ascribed to the venous puncture.

None of the GH deficient patients had an increase of the GH level during the last period of the test (150—210 minutes).

## Discussion

The rebound of GH secretion has been observed in adults at the end of SRIF infusion in studies of 30—60 minutes duration [1, 3, 5]. In our experiments SRIF was given in a single small dose and the GH level was followed for three hours, to study the late effect of exogenous SRIF. A single intravenous injection of 5 μg/kg provoked an undulation of the GH level with a second peak at 150—180 minutes; this peak was observed more frequently than the rebound during the first hour.

Table I

GH level (mean ± S. D.) before and after 5 μg/kg somatostatin or physiological saline

| Minutes | GH mU/L | | | | | |
|---|---|---|---|---|---|---|
| | Healthy children | | | | GH deficiency somatostatin | No |
| | No | Somatostatin | phys. saline | No | | |
| —20 | (16) | 12.0±18.4 | 7.3±4.4 | (5) | — | |
| 0 | (20) | 14.6±17.0 | 12.3±0.5 | (4) | 1.9±2.0 | (12) |
| 5 | (9) | 7.6±7.6 | — | | — | |
| 10 | (11) | 5.8±5.6 | 5.0±1.7 | (2) | — | |
| 20 | (18) | 9.8±7.4 | 4.0±1.9 | (4) | — | |
| 30 | (10) | 17.8±28.4 | 1.5±0.1 | (2) | — | |
| 45 | (12) | 19.0±26.8 | 4.4±2.6 | (3) | — | |
| 60 | (9) | 20.6±31.4 | 0.8±0.3 | (2) | — | |
| 90 | (19) | 5.8±8.0 | 3.3±1.6 | (4) | 2.3±1.9 | (10) |
| 120 | (19) | 7.2±5.8 | 2.6±1.8 | (5) | — | |
| 150 | (13) | 12.0±8.0 | 0.9±0.4 | (3) | 2.4±2.2 | (12) |
| 180 | (14) | 16.0±24.1 | 2.8±1.8 | (5) | 2.6±2.1 | (12) |
| 210 | | — | — | | 2.5±1.8 | (8) |

It has been assumed that SRIF upsets the balance of endogenous GH regulating hormones if their production is sufficient and we have found a significant difference in the GH curves of normal and GH deficient children [7]. On the basis of this observation we have studied the effect of combined administration of somatostatin and DOPA to estimate the GH capacity [8].

Our hypothesis has been supported by some recent results. During insulin-induced hypoglycaemia a rise in the plasma endogenous somatostatin level was seen, culminating at 60 minutes [10] or during the second hour [11]. One group hypothesizes that this change of the somatostatin level after insulin hypoglycaemia is related to alterations in metabolic stimuli [11], but Martin supposes [4] that the increases in the GH level are dependent on GRF release and cannot be accounted for by a rebound release from endogenous somatostatin inhibition.

We thus believe that the peaks in the first and third hours are caused by a predominance of GRF and the endogenous somatostatin is responsible for the low point at 90 minutes [7, 8].

## References


1. Brazeau P, Wale W, Burgus R, Ling N, Butcher M, Rivier J, Guillemin R: Hypothalamic peptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 179: 77, 1973
2. Guillemin R: Hypothalamic hypophysiotropic peptides, known and unknown. J Endocrinol 90: 3P, 1981
3. Hall R, Besser GM, Schally AV, Coy DH, Evered D, Goldie DJ, Kastin AJ, McNeilly AS, Mortimer CH, Phenekos C, Tunbridge WMG, Weightman D: Action of growth hormone-release inhibitory hormone in healthy men and acromegaly. Lancet 2: 581, 1973
4. Martin JB: Functions of nervous system neurotransmitters in regulation of growth hormone secretion. Feder Proc 39: 2902, 1980
5. Mortimer CH, Carr D, Lind T, Bloom SR, Mallinson CN, Schally AV, Tunbridge WMG, Yeomans L, Coy DH, Kastin A, Besser GM, Hall R: Effects of growth hormone-release inhibiting hormone on circulating glucagon, insulin and growth hormone in normal, diabetic, acromegalic and hypo-pituitary patients. Lancet 1: 697, 1974
6. Mortimer CH: Growth hormone release--inhibiting hormone (GH-RIH, somatostatin). In: Clinical Neuroendocrinology (eds.: L. Martini, G. M. Besser) Academic Press, New York 1977. p 279
7. Péter F, Szentistványi S: Effect of single small dose somatostatin on GH release in children. Pediatr Res 12: 159, 1978 (Abstr)
8. Péter F: somatostatin and 1-Dopa loading for study of growth hormone reserve. Pediatr Res 12: 1094, 1978
9. Schally A V, Arimura A: Physiology and nature of hypothalamic regulatory hormones. In: Clinical Neuroendocrinology (eds L. Martini, G. M. Besser) Academic Press, New York 1977. p 1
10. Vinik AI, Levitt NS, Pimstone BL, Wagner L: Peripheral plasma somatostatin-like immunoreactive responses to insulin hypoglycaemia and a mixed meal in healthy subjects and in noninsulin-dependent maturity-onset diabetics. J Clin Endocrinol Metab 52: 330, 1981
11. Wass JAH, Penman E, Medbak S, Dawson AM, Tsiolakis D, Marks V, Besser GM, Rees LH: Immunoreactive somatostatin changes during insulin--induced hypoglycaemia and operative stress in man. Clin Endocrinol 12: 269, 1980


F. Péter MD
POB 14
1277 Budapest 23 Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 67—72 (1983)*

# Maturation of the fetal lung I. Phosphatidic acid phosphohydrolase in the fetal and newborn rat

Terezia KEREPESI

Department of Paediatrics, University Medical School, Debrecen

Phosphatidic acid phosphohydrolase (PAPase) activity was measured in the lungs, brain, liver and kidneys of fetal, newborn and adult rats. The highest activity was found in the kidneys. In one-day-old rats pulmonary enzyme activity was nearly as high as in the renal tissue. In four-days-old rats the highest activity was found in the 10% homogenate of the lung, the highest PAPase specific activity could be demonstrated in the mitochondria. In the fetal lung, the enzyme activity moderately increases from the 18th day of gestation up to birth; at birth 39—77% of the normal adult value was measured. Immediately after birth 150% activity is attained, thereafter a slow decrease can be shown throughout the first week of life but the values remain above the average adult value.

Immediately before birth a marked increase in the phospholipid content of the fetal lung can be shown. This is due to the activity of various enzymes. Two main pathways of pulmonary lecithin synthesis are known; choline incorporation, and methylation [3]. In the rat [15], rabbit [5], monkey [4] and in man [7] the major route is choline incorporation. A key enzyme of this pathway is phosphatidic acid phosphatase or phosphohydrolase (PAPase; EC. 3.1.3.4). It catalyses the hydrolytic cleavage of phosphatidic acid (PA) to diglyceride and orthophosphate ($P_i$): 1.2-diacyl-glycerol-3-phosphate+ + $H_2O$ → 1.2-diacyl-glycerol + Pi (Fig. 1).

PA is a precursor of 1.2-diglyceride, this in turn plays a key role in phospholipid biosynthesis. PAPase has been isolated from animal tissues [6], and its presence in the cytoplasmic membrane of Bacillus subtilis 168 has been demonstrated [8].

The aim of this work was to study the dynamics of lecithin synthesis in the neonatal lung, with special reference to PAPase activity and to the role of enzyme induction.

## MATERIAL AND METHOD

The experiments were carried out in Wistar rats having a gestation period of 22 days. Fetal age was calculated from the first sperm positive day. The fetuses were excised by Caesarean section under sterile conditions after short ether anaesthesia, placed in ice for some minutes, then killed before the first extrauterine respiratory movement. The newborn animals, 1, 2, 3, 4 resp. 6 days old, and the adult rats weighing 180—200 g were killed

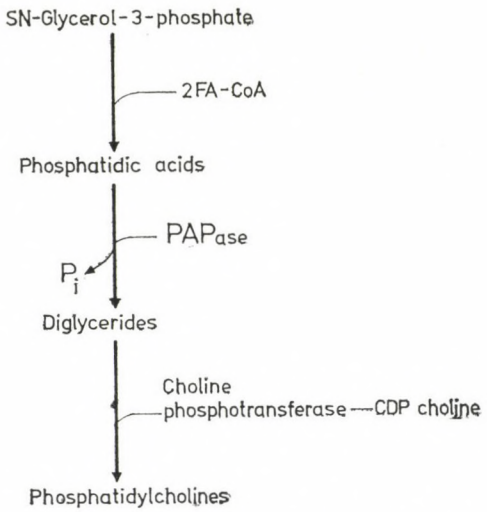



FIG. 1. Biosynthesis of phosphatidylcholine via CDP-choline pathway

by exsanguination. The lungs, liver, kidneys and brain were placed in ice immediately after removal and each organ was weighed on an analytical scale. The fetal and newborn lungs and kidneys were pooled; each pooled sample contained 4—6 fetal lungs or kidneys originating from one litter removed at the same gestational age. From the newborn animals 2—3 individual organs were pooled. Mean values for each five pooled samples were calculated.

For the studies L-alpha-phosphatidic acid (Sigma) isolated from egg-yolk and synthetic L-alpha-phosphatidic acid dipalmitoyl (Sigma) were used.

A 10% homogenate was prepared from the freshly removed organs. The organs were homogenized in 0.25 M sucrose in a teflon-headed homogenizer (Tissue grinder, Thomas, USA), then sonicated for 30 minutes (Lab. Sonic. 1510, Braun-Melsungen). The samples were kept in ice until starting the enzyme reaction. Subcellular particles were separated by fractionated centrifugation after Ravinuthala et al [11].

*PAPase assay* was carried out according to the method of Coleman and Hübscher [2] modified by ourselves: 1.5 μmol PA, 60 μmol maleate buffer pH 6.0 and the enzyme in a total volume of 250 μl were incubated at 37°C for 60 minutes. The reaction was stopped by addition of 250 μl 10% trichloroacetic acid. Inorganic phosphate was determined in the supernatant. All reactions were performed in duplicate. The blank did not contain PA. In previous assays we showed that incubation of PA without enzyme does not result in inorganic phosphate efflux. One unit of PAPase reflects 1 μmol inorganic phosphate liberated during one hour. Specific enzyme activity was calculated for 1 mg protein and one minute. The phosphatidic acid emulsion was prepared as follows: 10 μmol PA was dissolved in 0.1 ml hexane, then maleate buffer pH 6 was added and the solution sonicated for one minute. This resulted in a milky emulsion. The hexane was evaporated by fluid nitrogen.

Protein was measured according to Lowry et al [9]; for inorganic phosphate estimation the method of Bartlett [2] was used.

## Results

Table I shows the PAPase activity found in 10% homogenates of various organs removed from newborn rats. The maximum of enzyme activity was found between pH 6 and 7. Over 60 minutes there was a linear increase of liberated inorganic phosphate if the protein content was about 1 mg/ml. There was no difference between the two phosphatidic acid preparations; the use of L-alpha--phosphatidic acid of egg-yolk origin resulted in about 5% higher activity values.

In one-day-old newborn rats there was a considerable variation of enzyme activity between the kidneys, liver, lungs and brain. The highest activity was found in the kidneys while in the brain it was the lowest. The pulmonary enzyme activity hardly differed from that found in the renal tissue.

Table II indicates the subcellular distribution of PAPase in lungs of four-day-old rats. The highest activity was found in the 10% homogenate: 782 $\pm$ 28 nmol/min/g lung tissue while the highest specific activity was observed in the mitochondrial fraction: 21.3 $\pm$ 1.1 nmol/min/mg protein. No measurable inorganic phosphate was liberated into the supernatant.

The changes in PAPase activity during development of the lung are

Table I

**Distribution of PAPase in tissues of newborn rats. The results show the average $\pm$ S. D. for five separate experiments. Newborn tissues were taken from one-day-old rats**

| Tissue | $P_i$ formed $\mu$mol/h |
|---|---|
| Kidney | 0.62$\pm$0.01 |
| Lung | 0.6 $\pm$0.02 |
| Liver | 0.4 $\pm$0.016 |
| Brain | 0.34$\pm$0.012 |

Table II

Subcellular distribution of PAPase. The results are the average $\pm$ S. D. for four separate experiments. Newborn lungs were taken from 4-day-old rats

| Fraction | nmol/min/g lung | nmol/min/$m_o$ protein |
|---|---|---|
| Homogenate | 782$\pm$28 | 7.2$\pm$1.2 |
| Nuclei and debris | 353$\pm$18 | 6.9$\pm$0.9 |
| Mitochondria | 287$\pm$20 | 21.3$\pm$1.1 |
| Microsome | 120$\pm$18 | 10.1$\pm$3 |
| Supernatant | 0 | 0 |

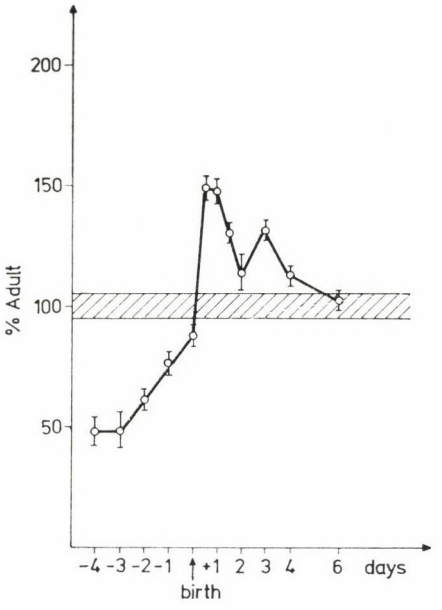



FIG. 2. PAPase activity during lung development. Each value is the average of 5 separate litters ± S. D. The activity is presented per lung weight. The adult values come to 699 nmol/min/g lung. The activity was measured in 10% homogenate

shown in Fig. 2. Enzyme activity increased moderately from the 18th day of gestation to term; at birth about 39—77% of the adult value was measured. A very sharp increase ensued immediately after birth, values as high as 150% of the adult level were attained. Thereafter a slow decrease was observed during the first week of life, but the levels remained higher than the adult mean all over this period.

## DISCUSSION

The key role of PAPase in fetal pulmonary metabolism was described by Schultz et al [12] in 1974. In rabbits, they found a fourfold increase of specific PAPase activity of lung homogenates and microsomes between the 23rd and 30th days of gestation. This was followed by a decrease after birth, and there were no changes in CDP-choline diglyceride transferase activity over this period of time.

Smith et al [13] were the first to demonstrate PAPase activity in the heart, kidneys, brain, liver and striate muscle of rats and in the liver of chickens. In our experiments PAPase activity was determined also in pulmonary tissue.

Meban [10] localized PAPase activity in the type II alveolar cells of the lung by histochemical methods. Ravinuthala et al [11] investigated the PAPase activity of subcellular fractions extracted from fetal and

adult rat lungs. They found the highest specific activity in the mitochondria in fetal lung cells while in adults the microsomes had the highest specific activity. In our experiments, specific activity was the highest in the mitochondria of four-day-old newborn rats ($21.3 \pm 1.1$ nmol/min/mg protein).

Spitzer et al [14] found that about 5—10% of all pulmonary cells are alveolar cells of type II. According to their studies in adult pigs, more than 40% of the total activity is concentrated in the lamellar bodies of type II alveolar cells. They assume that phosphatidylcholine is stored in the lamellar bodies after being synthesized on the perilamellar surface. In addition, PAPase activity is high also in the microsomes. In our experiments, a PAPase activity of $10 \pm 3$ nmol/min/mg protein was measured in the lungs of 4-day-old newborn rats, thus a marked activity was demonstrated both for mitochondria and microsomes. The highest PAPase activity calculated for wet pulmonary weight was observed in the homogenate. For this reason the comparative measurements performed in fetuses and newborns of various age were carried out in 10% homogenates of freshly removed lungs. Ravinuthala et al [11] found an about 70% activity in fetal lungs between the 18th day of gestation and term as compared with the corresponding adult activity level. In our experiments the corresponding figures were lower, between 40 and 77% of the adult values.

It is interesting that the events of birth induce a marked increase in enzyme activity speeding up lecithin synthesis in the alveolar membrane, this is then followed by a slight decrease on the 5th or 6th day of life. Presumably, the high oxygen content of the air perfusing the alveoli plays here an important role. The results of the present experiments may serve as a basis for further research into the role of postnatal changes in oxygen concentration.

## Acknowledgements

I am indebted to Dr P. Rády, Institute of Hygiene and Epidemiology, for valuable help.

## References

1. Bartlett GR: Phosphorus assay in column chromatography. J Biol Chem 234: 466, 1959
2. Coleman R, Hübscher G: Metabolism of phospholipids V. Studies of phosphatidic acid phosphatase. Biochim Biophys Acta 56: 479, 1962
3. Farrell PM: Regulation of pulmonary lecithin synthesis in respiratory distress syndrome. (ed. Villee CA, Villee DB, Zucherman J eds) Academic Press, New York 1973. p 311
4. Farrell PM, Avery ME: Hayline membrane disease Am Rev Respir Dis 111: 657, 1975
5. Gluck L, Scribney M, Kulovich MV: The biochemical development of surface activity in mammalian lung II. Pediatr Res 1: 247, 1967
6. Hajra AK, Agranoff BW: Phosphatidate phosphatase from pig brain. In: Methods in Enzymology Vol XIV Lowenstein J (ed.) Academic Press, New York 1969. 185
7. Hallman M, Gluck L: Development of the fetal lung J Perinat Med 5: 3, 1977
8. Krag SS, Robinson MD, Lennarz WJ: Biosynthesis of diglyceride from phos-

phatidic acid in the membranes of Bacillus subtilis. Biochim Biophys Acta 337: 271, 1974
9. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ: Protein measurement with Folin phenol reagent. J Biol Chem 193: 265, 1951
10. Meban C: Localization of phosphatidic acid phosphatase activity in granular pneumocytes. J Cell Biol 53: 249, 1972
11. Ravinuthala HR, Miller JC, Weinhold PA: Phosphatidate phosphatase activity and properties in fetal and adult rat lung. Biochim Biophys Acta 530: 347, 1978
12. Schultz FM, Jimenez JM, MacDonald PC, Johnston JM: Fetal lung maturation I. Phosphatidic acid phosphohydrolase in rabbit lung. Gynecol Invest 5: 222, 1974
13. Smith SW, Weis SB, Kennedy EP: The enzymatic dephosphorylation of phosphatidic acids. J Biol Chem 228: 915, 1957
14. Spitzer HL, Rice JM, MacDonald PC, Johnston JM: Phospholipid biosynthesis in lung lamellar bodies. Biochem Biophys Res Commun 66: 17, 1975
15. Weinhold PA: Biosynthesis of phosphatidyl choline during prenatal development of the rat lung. J Lipid Res 9: 262, 1968

*Received 26 June 1982*

T Kerepesi MD
POB 32
H-4012 Debrecen, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 73—78 (1983)*

# Serum ferritin level in infants and children with anaemia and malignant disease

I Ilyés, Judith Jezerniczky, T Tóth, S Csorba

Department of Paediatrics, University Medical School, Debrecen

Serum ferritin was determined by immunoradiometry in children aged 6 months to 3 years, immediately before leaving hospital where they had been treated for various acute, non-haematological diseases. A low value was found in 13% of them. Serum ferritin concentration is a sensitive method in differentiating between iron deficiency and infectious anaemia. A significantly higher mean value was found in children affected by malignant disease (acute lymphoid or myeloid leukaemia, various solid tumours).

Iron deficiency is a frequent disorder in infants and children even in countries with developed health care [17]. On the other hand, unnecessary iron treatment may cause undesirable side-effects [17]. Therefore, exact demonstration of iron deficiency is indispensable before initiating iron replacement; a sensitive and exact method for this purpose is determination of serum ferritin by immune radiometry [1, 15].

We have attempted to determine the incidence of iron deficiency in infants and children and to investigate the ferritin level of children affected by malignant disease.

## Material and Methods

Serum ferritin was determined by immune radiometry, utilizing the FERIRON kit (Ramco Laboratories Inc., Houston, Texas, USA). In the first step the ferritin of serum or of the standard solution is bound to antiferritin linked to a solid state immunosorbent. The second step consists of binding labelled anti-human ferritin to the complex. After elution of the unbound antibody, radioactivity is measured and compared to the values of a curve established by the use of standard solutions. Human ferritin isolated from human spleen was used as a standard and for antibody production. The antibody was produced in rabbits.

In addition to serum ferritin, serum iron (Fe), serum total iron-binding capacity (TIBC), the iron saturation index (SI per cent = Fe/TIBC$\times$100), haemoglobin and packed cell volume were determined.

In a first series the above mentioned tests were performed in 92 infants and children aged between 6 and 36 months. All had been treated for acute non-haematological diseases; the blood samples were taken immediately before discharge from hospital.

Serum ferritin was determined in addition in 25 blood samples of 23 children affected by malignancy. These patients were older than 2 years; 12 had acute

lymphoblastic leukaemia (ALL), 9 were affected by various solid malignant tumours, 2 suffered from acute myeloblastic leukaemia (AML) and of these, two blood samples each were taken. The results fo these patients were compared to those of an age-matched healthy group of children.

## Results

Figure 1 shows the results obtained in the first series; individual values are indicated. Twelve children had a ferritin level lower than 10 ng/ml, and 80 had a level exceeding this figure; low ferritin levels thus occurred in 13% of teh children. In seven children with a normal serum ferritin level anaemia characterized by low serum iron without increased TIBC was demonstrated. Thus, the total of 92 children could be grouped as follows; 73 non-anaemic, 12 iron deficient anaemic and 7 with infectious anaemia.

Serum ferritin, iron, TIBC and SI values of these three groups are shown in Table I, the other parameters are demonstrated in Table II. As can be seen, there was no obvious difference in iron level between the children affected by iron deficiency (as defined by low serum ferritin) and those with infectious anaemia. In infectious anaemia TIBC is not elevated and SI does not differ from that of non-anaemic children. In iron deficient children TIBC and SI values deviate from the normal values but the greatest difference can be shown in the serum ferritin value.

Fig. 2 illustrates the serum ferritin levels of children affected by malignancy and those of healthy con-

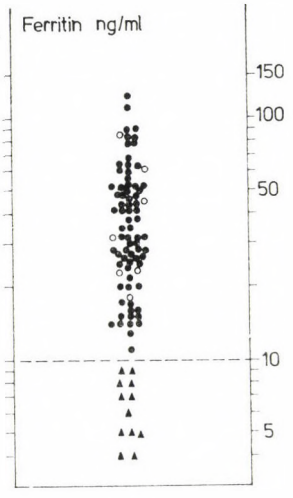



Fig. 1. Individual serum ferritin levels

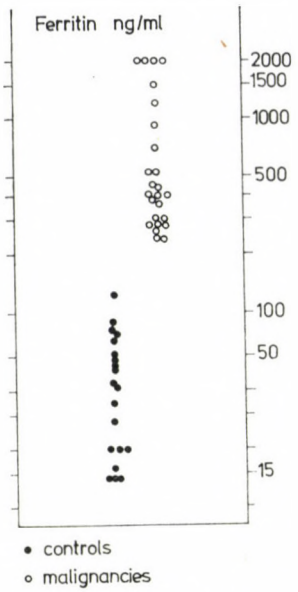



FIG. 2. Individual serum ferritin levels of healthy children and children affected by malignancies

TABLE I

Serum ferritin, serum iron, TIBC and SI in non-anaemic children and in children affected by infectious anaemia and iron deficiency anaemia

| Group | (n) | Ferritin, ng/ml | Serum iron, μmol/l | TIBC, μmol/l | SI, per cent |
|---|---|---|---|---|---|
| Non-anaemic | (72) | 40.1±23.7 | 16.6±4.1 | 50.2±12.7 | 33.6±12.4 |
| Infectious anaemia | (7) | 41.4±24.8 | 9.6±1.5 | 42.3±7.8 | 24.5±7.0 |
| Iron deficiency anaemia | (12) | 6.4±1.8 | 10.6±2.3 | 65.6±6.6 | 16.3±4.3 |

TABLE II

Statistical significance of differences in serum ferritin, serum iron, TIBC and SI between non-anaemic children, children affected by infectious anaemia or iron deficiency anaemia

| Pairs of groups | P value of the two-tailed t-test | | | |
|---|---|---|---|---|
| | Ferritin | Fe | TIBC | SI |
| Non-anaemic vs iron deficiency anaemia | <0.001 | <0.001 | <0.001 | <0.001 |
| Non-anaemic vs infectious anaemia | >0.05 | <0.001 | >0.05 | >0.05 |
| Iron deficiency anaemia vs infectious anaemia | <0.001 | >0.05 | <0.01 | <0.05 |

TABLE III

Serum ferritin level in normal children and in those affected by malignancies

| Groups | (n) | Serum ferritin, ng/ml mean ± SD | t-test |
|---|---|---|---|
| Controls | 20 | 42.1±30.6 | $P < 0.001$ |
| Malignancies | 25 | 736.0±626.0 | |
| Solid tumours | 9 | 1034.0±760.0 | $P < 0.05$ |
| ALL | 12 | 528.0±471.0 | |
| AML | 2* | 690.0 | |

* Two patients with two blood samples each

trols. Obviously, serum ferritin was markedly higher in the group affected by malignant disease. Table III demonstrates that the difference was statistically significant.

The mean value for children suffering from solid tumours was somewhat higher than the mean level of children with ALL; in these cases, however, the difference was not significant statistically.

## DISCUSSION

Ferritin is an iron-storing protein with a molecular weight of 450 000; it consists of a spheroid protein capsule and an iron-containing core. High concentrations are found in the liver, spleen and bone marrow [3]. Addison et al. [1] have shown that ferritin is present in the serum of healthy persons. Further work has elucidated that the serum ferritin level is closely related to the iron stores or the iron content of the tissues [4, 8, 13, 20]. The ferritin level is therefore a sensitive and rapid indicator of iron deficiency disease [8, 9].

Introduction of the immunoradiometric method has made serum ferritin measurements accessible to practice [1]. The method's sensitivity exceeds that of the radioimmunoassay since the reaction is carried out in the presence of antibody excess in contrast to RIA performed by the addition of an antigen excess. The kit of the firm Ramco (FER-IRON) is based on a modification of Miles et al. [15] of the original method described by Addison et al [1]. Binding of the antibody to plastic globules and the arrangement of the kit greatly facilitate the method. The method can be used in any laboratory equipped for RIA work.

We found a low ferritin level in 13% of the children between 6 and 36 months. This incidence does not attain the figures found by Schuler et al. [18] among children of similar age. The obvious reason of this difference lies in the fact that in our material many children were just recovering from acute infection, a condition characterised by an increased ferritin level [2] due to increased

iron influx to ferritin stores and decreased iron mobilization [12]. We think that screening for iron deficiency is best carried out in day care centres for healthy children.

In our experience, serum ferritin is a good discriminant between iron deficiency anaemia and infectious anaemia; the greatest difference between the two groups was demonstrated in this parameter. Exaggerated iron storage in infectious anaemia is the basis of differentiation between the two conditions [13].

In children with a serum ferritin level above 10 ng/ml and free from infectious anaemia the mean value was 40.1 ng/ml, with a range extending from 11 to 125 ng/ml. These values are in accordance with data in the literature [19].

Elevated serum ferritin levels were encountered in patients affected by malignant tumour or leukaemia [5, 6, 9, 11, 16]. Ferritin is therefore regarded as a tumour marker protein. In Hodgkin disease there is a fairly good correlation between the level of ferritin and the severity of the disease [10], and the high ferritin level may be accompanied by elevated serum levels of beta-2-microglobulin, e.g. in mesothelioma [7]. It has been assumed that the elevation of the serum ferritin level is due to the decreased utilization of iron; increased ferritin production has, however, also been demonstrated [21]. Increased levels of ferritin observed in malignant diseases may contribute to the decreased reactivity of certain cellular immune functions as demonstrated in experiments in vitro [14]. In our series, a considerably increased ferritin level was found, like in adults affected by malignant diseases [10]. Although no statistically significant differences could be demonstrated in the ferritin level of patients affected by solid tumours or leukaemia, solid tumour patients tended to have a higher serum level. The next step will be to study the correlation between the ferritin level on the one hand and immune functions, the beta-2-microglobulin level and the severity of the disease on the other hand.

## References


1. Addison GM, Beamish, MR, Hales CN, Hodgkins M, Jacobs A, Lewellin P: An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. J Clin Pathol 25: 326, 1972
2. Birgegård G, Hallgren R, Killander A, Stömberg A, Venge P, Wide L: Serum ferritin during infection. A longitudinal study. Scand J Haematol 21: 333, 1978
3. Bothwell TH, Finch CA, Iron metabolism. Little Brown and Co Boston 1962
4. Cook JD, Lipschitz DA, Miles LEM, Finch CH: Serum ferritin as a measure of iron stores in normal subjects Am J Clin Nutr 27: 681, 1974
5. Eshar Z, Order SE, Katz DH: Ferritin, a Hodgkin's disease associated antigen. Proc Natl Acad Sci USA 71: 3956, 1974
6. Hazard JT, Drysdale JW: Ferritinaemia in cancer. Nature 265: 755, 1977
7. Hotta T, Yoshikawa T, Fukumoto K, Yamaguchi K, Kondo M, Takamatsu T: Peritoneal mesothelioma with elevated serum ferritin and $B_2$ microglobulin levels. Jpn J Med 20: 114, 1981
8. Jacobs A, Miller F, Worwood M, Beamish MR, Wardrop CA: Ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. Br Med J 4: 206, 1972

9. Jakobs A, Worwood M: Ferritin in serum. Clinical and biochemical implication. N Engl J Med 292: 951, 1975
10. Jacobsen E, Engeset A, Sandstad B, Aas M: Serum ferritin and bone marrow haemosiderin in patients with malignancies and in healthy controls. Scand J Haematol 28: 264, 1982
11. Jones PAE, Miller FM, Werwood M, Jakobs A,: Ferritin in leukaemia and Hodgkin's disease. Br J Cancer 27: 212, 1973
12. Konijn AM, Hershko C: Ferritin synthesis in inflammation pathogenesis of impaired iron release. Br J Haematol 37: 7, 1977
13. Lipschitz DA, Cook JD, Finch CA: A clinical evaluation of serum ferritin as an index of iron stores. N Engl J Med 290: 1213, 1974
14. Matzner Y, Hershko C, Polliak A, Konijn AM, Izak G: Supressive effect of ferritin on in vitro lymphocyte function. Br J Haematol 42: 345, 1979
15. Miles LEM, Lipshitz DA, Bieber CP, Cook JD: Measurement of serum ferritin by a 2-site immunoradiometric assay. Anal Chem 61: 209, 1974
16. Oertel J, Shultz E, Korinth E, Heilhecker A: Ferritinkonzentration im Serum bei Patienten mit malignen Lymphomen. Klin Wochenschr 55: 1109, 1977
17. Oski FA, Stockman JA: Anemia due to inadequate iron sources or poor iron utilization. Pediatr Clin North Am 27: 237, 1980
18. Schuler D, Kiss É, Velkey L, Németh K, Mann V: Iron deficiency and supplementation in infancy Orv Hetil 123: 91, 1982
19. Siimes M, Addiego, JE, Dallman PR: Ferritin in serum. Diagnosis of iron deficiency and iron overload in infants and children. Blood 43: 581, 1974
20. Walters GO, Miller FW, Worwood M: Serum ferritin concentration and iron stores in normal subjects. J Clin Pathol 26: 770, 1973
21. White GP, Worwood M, Parry DH, Jakobs A: Ferritin synthesis in normal and leukaemia leucocytes. Nature 250: 584, 1974

*Received 7 July 1982*

I Ilyés MD
POB 32
H-4012 Debrecen, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 79—83 (1983)*

# The position of the diabetic child in society

L Barta, Mária Molnár, L Madácsy, Magda Barta-Bedő, Anna Körner

First Department of Paediatrics, Semmelweis University Medical School, and Institute of Nutrition, Budapest, and County Hospital, Miskolc

A total of 108 diabetic children and 153 controls has been examined by explorative methods and questionnaires. According to the results the relationship between the diabetic child and his surroundings is not satisfactory. The sporting possibilities of the diabetic child are scanty, often without reason. All this may be in relation with the erroneous knowledge on diabetes of the child and his environment. The diabetic children familiar with their disease are in a more advantageous position. In consequence diabetic children need more attention and care. Well-trained experts and teams have to direct their way of life.

Most parents of diabetic children are extremely worried and protect their children in an unhealthy way, whereas their upbringing is a very hard task. The connection of diabetic children with their parents, siblings and with friends is often inadequate or even bad. The knowledge on diabetes of the child and his environment is often insufficient [1, 2, 3, 4, 5, 6].

The aim of the present study was to clarify some factors which might be helpful for the integration of diabetic children into the healthy population. We have studied their activities and personality and their possibilities of making sports.

## Material and Methods

A total of 108 diabetic children, 57 boys and 51 girls, and 153 controls, 74 boys and 79 girls, participated in the study. Of these, 10—14% were between 10—11 years of age, 55—60% between 11—13 years and 30—35% between 14—15 years of age in both groups. Determination of their attitudes was carried out by using explorative methods and questionnaires, to clarify the following problems.

1. The relation to the parents, siblings and friends;
2. their desires and expectations of their future life;
3. what do the diabetics know about their illness;
4. to what extent is the life of the diabetic influenced by his illness;
5. relation between school achievement and the knowledge about diabetes;
6. relation between the quality of treatment and the knowledge about diabetes;
7. the difference between the two groups concerning physical activity and sports.

Statistical analysis was carried out by the $\chi^2$ test; occasionally the Jeats modification was used.

## Results

Table I represents the connexion of the examined children with their parents, siblings and friends. An inadequate relationship occurred sig-

nificantly more frequently in the diabetic group.

To obtain data about their personality, the children were encouraged to place 10 wishes (Table II) in an order of importance according to their imagination. The wishes put by the patients in the first three places were evaluated together. These represent the value orientation of these children. Table III shows the results. Diabetic children have a high estimate of health, friendship and a loving peaceful home, whereas healthy children prefer success, good school results and adventures.

The following questions were asked from diabetic children to clarify their awareness of their illness;

1. What are the symptoms of hyperglycaemia?
2. What are the symptoms of hypoglycaemia?
3. What are the consequences of a lowering of the insulin dose?
4. What are the consequences of elevating the insulin dose?
5. What happens if the patient forgets to give himself insulin?
6. What happens if forbidden foods are consumed?
7. What happens if meals are skipped?
8. What types of insulin exist? What are their characteristics?
9. What are the consequences of acetonuria?

Excellent answers received 2 points, insufficient ones 1 point, incorrect ones 0 point. Well informed were considered the children who scored between 14 and 18, moderately

TABLE I

Relation to parents and siblings

| Diabetics (n = 108) | | Healthy controls (n = 153) | |
|---|---|---|---|
| Adequate | 81 | adequate | 146 |
| Inadequate | 27** | Inadequate | 7** |

** $p < 0.001$

TABLE II

Ten wishes the children had to classify

To be a good scholar
To have good friends
To have interesting adventures
To be healthy
To have a peaceful loving home
To have much money
To be clever and highly educated
To be successful with girls/boys
To be very strong
To travel and see foreign countries

TABLE III

The wishes put in the first three places

| Wishes | Controls (n = 153) | Diabetics (n = 108) | p |
|---|---|---|---|
| Health | 79 | 88 | $< 0.001$ |
| Friendship | 15 | 25 | $< 0.001$ |
| Success | 19 | 2 | $< 0.001$ |
| Peaceful home | 46 | 65 | $< 0.001$ |
| Clever educated | 36 | 43 | n.s. |
| Studies | 65 | 43 | n.s. |
| Travels | 30 | 18 | n.s. |
| Adventures | 8 | 3 | n.s. |
| Much money | 8 | 5 | n.s. |
| Strength | 6 | 2 | n.s. |

TABLE IV

School achievement and familiarity with diabetes

| School achievement | Case number | Well informed |
|---|---|---|
| Excellent-good (5—4) | 53 | 45 |
| Satisfactory (under 4) | 55 | 30* |

*$p < 0.05$

informed those who reached a score between 8 and 14, and uninformed those with less than 8 points.

Table IV shows the connexion between school achievements and the knowledge about diabetes, while Table V represents the relation between the quality of treatment and the knowledge about the illness. Those diabetic children were considered well treated, whose urine was durably free from acetone and the daily discharge of sugar remained under 20 g. Moderately well treated were those who often discharged more than 20 g of sugar, but acetonuria was infrequent so that they did not need admission to hospital. Treatment was considered inadequate if acetonuria was frequent and the daily sugar discharge exceeded 20 g considerably. Most children of the last group failed to report regularly at the clinic.

Table VI shows the participation in physical activity. Significantly more diabetic children participated in light physical training in school, whereas significantly more healthy children were involved in training and sport races.

Table VII represents the wishes and the reality concerning sport activities in the two groups. They differed highly significantly. The majority of diabetic children, especially the girls, were not capable of physical activities

and sports in accordance with their desires. Some of the boys would have liked to participate in sports which are not recommended for diabetics (water-polo, boxing, horse-riding) and the girls had no opportunity to play volley-ball or to learn swimming etc. This may explain the differences

TABLE V

Familiarity with diabetes and the quality of treatment

| Quality of treatment | Informed about diabetes | | |
|---|---|---|---|
| | Well | Adequately | Inadequately |
| Excellent | 40 | 9 | 3 |
| Adequate | 10 | 4 | 1 |
| Inadequate | 4* | 3 | 5* |
| $\Sigma$ | 54 | 19 | 9 |

*$p < 0.001$

TABLE VI

Participation in physical training

| | Controls (n = 153) | Diabetics (n = 108) | p |
|---|---|---|---|
| Physical training in school | 140 | 86 | $< 0.001$ |
| Light physical training in school | 1 | 16 | $< 0.001$ |
| Exemption from physical training | 9 | 5 | n.s. |
| Extra physical training | 39 | 4 | $< 0.001$ |
| Race sportlers | 31 | 7 | $< 0.001$ |

TABLE VII

The desired sport cannot be done

| Diabetic group n = 107, Boys = 56, Girls = 51) | | Control group (n = 147, Boys = 70, Girls = 77) | |
|---|---|---|---|
| 60* | | 28* | |
| Boys | Girls | Boys | Girls |
| 23 | 37 | 13 | 15 |

* $p < 0.001$

TABLE VIII

| Table-tennis was selected as the desired sport by boys | Badminton was selected as the desired sport by girls |
|---|---|
| Out of 56 diabetics by 10 | Out of 51 diabetics by 11 |
| Out of 70 controls by 1 | Out of 77 controls by 0 |

shown in Table VIII. Diabetic boys considered table-tennis and the girls badminton as serious sport activities whereas healthy children had entirely different wishes and imaginations concerning sports.

## Discussion

The inadequate relationship of the diabetic child with relatives and friends indicates their desire for a quiet home, peace and friendship; they do not seek adventures and success as their healthy companions do.

It is basically important for the diabetic child to be familiar with his condition. Successful treatment and good school achievements are in close correlation in this respect. Well-treated good scholars belonged to the well-informed group.

Diabetic children have great difficulties in making sports and physical activity, as physical instructors and coaches do not take the responsibility to deal with them. It would be of basic importance to change this situation and in cooperation with instructors to make it possible for the diabetics to participate in suitable sport and after careful consideration in the case of good results even in sport races. If the physicians, teachers, psychologists and parents cared more about this problem, the unpleasant situation of the diabetic children could be altered in the majority of the cases. Diabetic summer camps are advantageous because the child learns to take care of himself during excursions, entertainments and sport. They learn about their illness, the adequate diet, and the right way of living.

The whole family of a diabetic child ought to be well aware of the diabetic condition. These factors could be of great help for the young patient to face reality, to avoid separation from their companions and to realize that sports, excursions and the other pleasures of life are open for them.

## References

1. Bruch H: Psychological aspects of diabetic children. In: Proc. 3rd Congress of the International Diabetes Federation. K Oberdisse, K Jahnke (eds). Thieme, Stuttgart 1959
2. Fällström K: On the personality structure in diabetic school-children. Acta Paediatr Scand Suppl 251, 1974
3. Jochmus I: Die psychische Entwicklung diabetischer Kinder und Jugendlicher. Arch Kinderheilk Suppl 66. Enke, Stuttgart 1971
4. Karp M, Manor, M, Laron Z: What do juvenile diabetics and their family know about diabetes. In: Z Laron (ed.): Habilitation and rehabilitation of juvenile diabetics H E Stenfort Kroese, Leiden 1970. p 83
5. Koski ML: The coping processes in childhood diabetes. Acta Paediatr Scand Suppl 198, 1969
6. Ludvigsson J: Socio-psychological factors and metabolic control in juvenile diabetes Acta Paediatr Scand 66: 431, 1977

*Received 3 July 1982*

Prof L Barta MD
Bókay J u 53
H-1083 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 85—90 (1983)*

# Clinical diagnosis of malformation syndromes: syndromatology in paediatrics

J MÜCKE

Section of Human Genetics, Department of Paediatrics,
Medical Faculty of Karl Marx University, Leipzig, GDR

The term malformation syndrome should be retained for designation of characteristic symptom complexes of clear-cut pathogenesis. Classification of disorders into any of the three categories deformation, malformation respectively dysplasia or into any combination of them leads to better insight into morphological syndromes.

Ten rules of the diagnostic procedure have been formulated and illustrated by the example of the Beckwith-Wiedemann syndrome. Disturbed organogenesis is usually accompanied by multiple signs of dysmor phy, a careful search for malformations is therefore desirable. In the case of malformation syndromes interfering with growth and development continuous care of the patient is indispensable.

The term syndrome is quite familiar for the practising paediatrician. Individual symptoms and symptom patterns observed in the patient are compared with generally recognized conditions and possibly classified as known syndromes. Dysmorphic syndromes are not infrequently identified at first glance, without the use of the machinery of laboratory investigations. On the other hand, the load of descriptions of new syndromes represents an ever increasing obstacle to clear sight. Standard works and syndromological atlases are nowadays indispensable for the paediatrician and geneticist [2, 5, 8, 12, 15, 16, 17]. Only between 1958 and 1975 about 2000 new entities were recognized and in recent times 300 to 400 new syndromes have been described every year [4]. Quite obviously, a new orientation of the term syndrome has become necessary.

## *Syndrome versus disease*

The definition still partly accepted for a syndrome being a complex of symptoms combined more frequently than expected on the basis of pure coincidence is in contradiction to a formal pathogenetic explanation of syndromes. Syndromes are now regarded as conditions of unitary pathogenesis of variable or unknown aetiology. This means a sharp distinction of syndromes from diseases, in the latter both pathogenesis and aetiology are uniform and known (Figure 1).

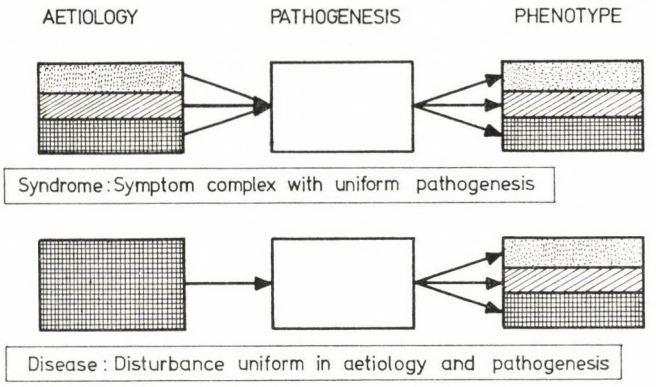



FIG. 1. Graphic distinction between syndrome and disease

Originally, the term syndrome (syn= = together, dromos = run, drive) only refers to co-appearance of clinical signs. As a diagnosis, the term also comprises the possibility of diagnostic and therapeutic measures. This means a certain similarity to the term disease, here also the label is associated with certain diagnostic and therapeutic tools.

According to these definitions, many syndromes have become diseases of clarified aetiology during the last years, quite often without real consequences in therapeutic strategy. For instance, the adrenogenital syndrome, the biochemical basis of which is now known in full detail, has preserved the word syndrome in its name in spite of being regarded nowadays as a disease. On the other hand, nobody would call cystic fibrosis of the pancreas a syndrome although its basic defect is still unclear and it may have a heterogeneous aetiology.

Therefore it appears that a sharp distinction between syndrome and disease is not always practicable. Nonetheless, it is not always necessary because it would have no diagnostic or therapeutic impact.

*Nomenctalure*

International efforts to establish a system of clinical syndromes were reflected in a nomenclature proposed by a committee of the National Institute of Health in Bethesda in 1975 [1]. According to this, a malformation is a primary structural defect resulting from a localized fault of morphogenesis, e.g. hare-lip. Malformation syndromes are recognizable patterns having in all probability the same cause and cannot be traced back to a single localized fault in morphogenesis, e.g. Down-syndrome. Associations are patterns that cannot be regarded as an autochthonous syndrome entity.

The term anomalad, a malformation leading to secondary structural changes (Robin anomalad = Robin syndrome) has not been widely accepted in Europe [6].

For better understanding the pathogenesis of syndromes, Spranger [13, 14] has offered a classification into three categories, malformation, deformity and dysplasia.

A primary malformation such as a neural tube defect, is based on a developmental disturbance of embryonal structures. In secondary malformations a loss of normal developmental potential is caused by an external damaging factor, e.g. in embryopathies. A deformity is the consequence of a localized change in primarily normal structures, with a preserved possibility of subsequent return to normality, e.g. contractures, amnial ligations. Dysplasia, generalized (e.g. ectodermal dysplasia) or local (e.g. naevi) is characterized by abnormal development of single tissues or cell types. The three possible forms may also be combined.

Quite independently of the discussion of the terminology of syndromes, we have to cope with this term in everyday practice whether it depicts a known syndrome, a combination of symptoms, or a disease.

*Basic rules*

Most experts use certain general rules in the diagnostic procedure clarifying malformation syndromes. A system of rules will be illustrated by the example of the Beckwith-Wiedemann Exomphalos-Macroglossia-Gigantism (EMG) syndrome in the following paragraphs.

The EMG syndrome is clearly of genetic origin and can be classified as a dysplasia. Its characteristic features are a conspicuous facies, omphalocele and gigantism sometimes accompanied by general organomegaly and/or hemihypertrophy.

*(i)* In malformation or maldevelopment syndromes the patient's phenotype has always to be compared with that of all first degree relatives. Not too rarely, only a conspicuous familial feature is the case and not a syndrome.

Comparison of the phenotypic appearance of the relatives may help in establishing the mode of inheritance. In the case of the EMG syndrome, which is not seldom sporadic, the mode of inheritance is quite heterogeneous, all subtilities of the family tree must therefore be taken into consideration before giving genetic advice (Figures 2 and 3).

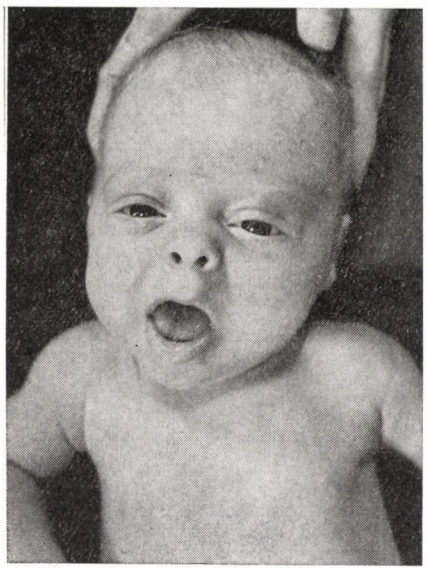
*(ii)* In most cases not all possible symptoms of a syndrome are present in the individual patient.

Classical exomphalos is, for instance, rather a rarity within the EMG syndrome. In fact, recently a case lacking all three cardinal symptoms has been described [18].

*(iii)* The individual components of the syndrome have different weights. Unweighted summing up of the single symptoms cannot be allowed in syndrome classification.

The typical face of the newborn affected by the EMG syndrome is a very important feature which cannot be outweighed by the lack of even three cardinal symptoms; macroglossia has the highest diagnostic value among all symptoms of the EMG syndrome.

*(iv)* More than three minor malformations such as gothic palate, ear dysplasia, supernumerary mamillae,



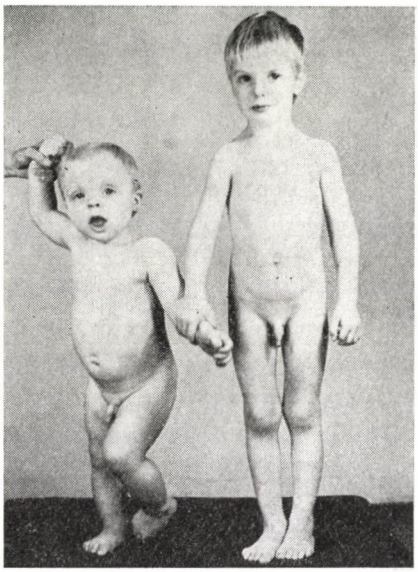


FIG. 2 and 3. Infant with Beckwith-Wiedemann EMG syndrome at two months and one year of age. Sibling exhibiting mid-face hypoplasia, malformed ears and teleangiectasic naevus in the occipital region, minor symptoms of the syndrome

hypertelorism, four-finger crease, point to deranged organogenesis and thereby to possible major malformations. The latter must be looked for carefully in such cases.

Fourteen out of hundred newborn babies have at least one minor dysmorphic sign [7, 9], a variant without functional impairment; three or more minor anomalies can be found in only five out of thousand [7]. In patients afflicted by the EMG syndrome urogenital malformation is more common, therefore urography is indicated in these cases.

*(v)* Unclear syndromes with unimpaired mental faculty are very exceptionally due to an autosomal chromosome aberration; the scarce exceptions to this rule do not make it invalid.

Such exceptions are usually partial trisomies, thus anomalies without loss of genetic material. Children affected by 18p trisomy, mosaic trisomy 8 and partial trisomy of the distal segment of chromosome 22, all having normal intelligence, have been described. Up to now no chromosomal anomalies have been encountered in children with EMG syndrome.

*(vi)* Metabolic studies in malformation syndromes and chromosome analysis in well-defined and well-known morphological syndromes are usually not indicated.

The EMG syndrome is rather an exception to this rule. Newborn babies affected by the syndrome tend to develop severe hypoglycaemia leading to subsequent cerebral damage. In contrast, chromosomal aberrations have frequently been described in the Prader-Willi syndrome. Since the patients affected by this disorder do not exhibit salient features during the neonatal period, it has been ascribed to various damaging factors. Quite recently,

a deletion of the long arm of chromosome 15 has been found in patients with Prader-Willi syndrome [3]. Thus, all patients suspect to have this disorder should be subjected to chromosomal analysis.

*(vii)* Objective measurements should be used for quantification of measurable deviations occurring in dysmorphy syndromes, e.g. angular index of the eyes, interorbital index, intermamillary index, length of ears, penis length, dermatogram. Such measurements must be evaluated with caution in newborns.

In cases with EMG, photographs are recommended for follow-up. Changes described in section viii can best be evaluated by this method.

*(viii)* Shape and extent of dysmorphic phenomena are age-dependent. In the course of development harmonization may ensue. A careful follow-up is highly recommended from the fourth week to the sixth year of life.

Epicanthus, occurring also in normal newborns, usually disappears by school age. Similarly, macroglossia of EMG syndrome is as a rule counterbalanced by catch-up growth of the skull, so that it usually represents no functional obstacle by school age [11]. Premature resection of the tongue is thus contraindicated. Our own studies have shown that the classical picture of the EMG syndrome cannot be found in adult patients.

*(ix)* Not infrequently, malformation syndromes are associated with a postnatal derangement in developmental dynamics, e.g. an increased risk of cancer or progression of organ affection. Such syndromes need careful follow-up, including psychological guidance of the whole family.

The EMG syndrome has long been known for increased risk of malignancies, Wilms tumour, adrenal cancer and other neoplasms. Similarly, the risk is somewhat higher among first degree relatives [10].

*(x)* Diagnosis of a certain syndrome must be based on appropriate criteria since the correct diagnosis has deep implications in both therapy and genetic counselling.

Macgroglossia observed in a newborn is an alarming symptom, so its cause must be clarified. In differential diagnostics glycogenosis type II and hypothyroidism must be taken into account. Decision on a possible EMG syndrome with less conspicuous hypertrophy and omphalocele may be postponed.

## References


1. Classification and nomenclature of morphological defects Lancet 1: 513, 1975
2. Goodmann R, Golin JR: Atlas of the Face in Genetic Disorders. Mosby, Baltimore 1977
3. Ledbetter DH: Deletion of chromosome 15 as a cause of the Prader-Willi syndrome. N Engl J Med 304: 325, 1981
4. Leiber B: Die Nosologie auf dem Weg zu neuen Ordnungs-systemen: Syndrome und Syndromatologie. Internist (Berlin) 16: 56, 1975
5. Leiber B, Olbrich G: Die klinischen Syndrome. 6. Aufl, Urban und Schwarzenberg, München 1981
6. Lenz W: Was ist ein Syndrom? Monatsschr Kinderheilkd 126: 248, 1978
7. Marden PM, Smith DW, McDonald MJ: Congential anomalies in the newborn infant, including minor variations. J Pediatr 64: 356, 1964
8. McKusick VA: Mendelian Inheritance in Man. 5th ed, The John Hopkins Univ. Press, Baltimore 1978
9. Méhes K: Klinische Bedeutung der Minoranomalien. In: Klinische Genetik in der Pädiatrie. I. Symposion Kiel.

(Hrsg: Tolksdorf M, Spranger J) Georg Thieme Verlag, Stuttgart 1979
10. Mücke J, Bahrke A: Genealogische Untersuchungen bei Familien mit EMG-Syndrom. In press
11. Mücke J, Martin J, Bührdel P, Sandig KR: Das Exomphalos-Gigantismus-Syndrom. Allgemeine und klinische Aspekte. Dtsch Gesundh-Wes 33: 2332, 1978
12. Smith D: Recognizable Patterns of Human Malformations. Saunders, Philadelphia 1976
13. Spranger J: Syndrome. Klinische Erfassung und Bedeutung. Monatschr Kinderheilkd 126: 252, 1978
14. Spranger J: Sinn und Unsinn der Syndrome. In: Klinische Genetik in der Pädiatrie. I. Symposion Kiel. (Hrsg: Tolksdorf M, Spranger J) Georg Thieme Verlag, Stuttgart 1979
15. Spranger JW, Langer jr LO, Wiedemann HR: Bone Dysplasias. An Atlas of Constitutional Disorders of Skeletal Development. VEB Gustav Fischer Verlag, Jena 1974
16. Wiedemann HR, Grosse JR, Dibbern H: Das charakteristische Syndrom. FK Schattauer Verlag, Stuttgart, New York 1976
17. Wittkowski R, Prokop O: Genetik erblicher Syndrome und Mißbildungen. 2 Aufl, Akademie Verlag, Berlin 1975
18. Wöckel W, Scheibner K, Lageman A: A variant of the Wiedemann-Beckwith syndrome. Eur J Pediatr 135: 319, 1981

*Received 20 July 1982*

J Mücke MD
Kinderklinik der Karl-Marx-Universität
Oststraße 21—25
7050-Leipzig, DDR

*Acta Paediatrica Hungarica, 24 (1), pp 91—99 (1983)*

# Aetiological monitor of congenital abnormalities: A case-control surveillance system

A Czeizel, Andrea Pázsy, Judit Pusztai, Magdolna Nagy

Department of Human Genetics, National Institute of Hygiene, Budapest

An Aetiological Monitor of Congenital Abnormalities was launched in Hungary on 1 January 1980 with the purpose to obtain aetiological information parallel with the reporting of congenital abnormalities. A questionnaire is sent to all mothers having babies with well defined major congenital abnormalities within one month after being reported to the Register. Diseases during pregnancy, drugs taken during pregnancy as well as employment and type of work made by the pregnant are studied. According to the data of the first year, progestogens were taken in 33.4% and oestrogen in 10.8% of all pregnancies. Other data indicate that the drugs studied mean either no teratogenic risk or, if there is any risk, it is very small.

Within the scope of the Hungarian Centre for Congenital Anomaly Control the Hungarian Congenital Abnormality Monitor has been operating since 1973 [1]. It was initiated by the WHO and is part of the International Clearinghouse for Birth Defects Monitoring Systems involving 18 countries [4]. Eleven so-called indicator congenital abnormalities are evaluated monthly and quarterly as well as regionally, in 20 administrative units in Budapest and 19 counties, in order to detect clusters as soon as possible.

For example, in the frequency of congenital limb reduction abnormalities a 30% increase was observed in Hungary in 1975 [3]. An epidemiological study of approximately 3 years duration was needed to identify the causes of this cluster [2]. Possibly as a result of the preventive counter-measures the "epidemic" disappeared by 1979—80. The 3 years necessary for solving the problem seemed, however, too long a time, and this has urged us to start a new programme, the Aetiological Monitor or a Case-Control Surveillance System. It was launched on 1 January 1980, following pilot studies in 1979.

The purpose of the Aetiological Monitor is to obtain aetiological information nearly parallel with the reporting of congenital abnormalities. Simultaneously the Aetiological Monitor gives opportunity to check and to complete or correct the data of the Hungarian Congenital Malformation Register, and to inform the parents about the causes of their child's anomaly as well as the possibility of treatment and the risk of the next pregnancy. Thus, the Aetiological Monitor is suitable for the extension of the efficacy of the Centre Congenital Anomaly Control.

## Function of the Aetiological Monitor

A reply-paid postal questionnaire is sent to all mothers having babies (index patients) with well defined major congenital abnormality within one month after being reported to the Register. The questionnaire involves

1. personal data of the index patient (these are filled out by our staff on the basis of the Hungarian Congenital Malformation Register and the mothers are asked to check them);

data not reported previously to the Register, such as

2. mother's data (date of birth, occupation, marital status, outcome of previous pregnancies);

3. father's data (date of birth, occupation);

4. data of the pregnancy studied

a) diseases during pregnancy,

b) drugs taken during pregnancy,

c) employment and type of work during pregnancy

(these are specified and given according to the weeks of pregnancy. In order to standardize the answers, a printed sheet with a list of diseases and drugs is enclosed; the mothers are asked to read them before they reply);

5. family data (if there are any congenital anomalies or inherited diseases among the first, second and third degree relatives);

6. parents' opinion about the suspected cause of their child's anomaly.

Together with the questionnaire an explanatory letter is enclosed asking the mother to send us every medical document connected with her pregnancy (e.g. prenatal care booklet) or the child's abnormality; these documents are returned after two weeks. The material sent to the parents includes the "General Advices for Family Planning" and the list of Genetic Counselling Clinics and their consulting hours, in order to offer help in the next pregnancy. Finally, we enclose a description of the specific congenital abnormality of the individual index child together with some useful information about possible causes, recurrence risk, prevention, etc.

Of course, the data from the Aetiological Monitor can only be evaluated when compared to adequate control cases. For this reason, two "negative" control cases are matched to every index patient according to birth week, sex and the district of the parents' residence. The selection of matched control cases is done by the Central Statistical Office. Since in the experience of the 1979 pilot study, parents of control cases are less ready to send back the questionnaire than the parents of index cases, two controls are approached. Control parents receive a similar packet of information, with the same list of drugs as that sent to the index cases, except for the description of the specific congenital abnormality. Index patients with Down syndrome of well-known aetiology are evaluated as "positive" control cases.

The questionnaires filled in and sent back are coded. Particular stress

is laid on the validity of medical data, thus the completeness and accuracy of the answers are checked on the basis of the medical documentation. After data processing the material is evaluated by computer. Statistical evaluation is presently being done by $X^2$ test of four fields contingency tables with Yates correction when needed, and by the Fisher-test. The threshold level for $X^2$ should be set lower than $p = 0.05$ due to multiple testing.

## Data in the year 1980

In 1980, 7011 newborns/infants were reported with congenital abnormalities. From this number 1859 index patients were omitted because their notification arrived after the 30th day following birth, and it was not possible to find matching controls. In 2724 cases the questionnaire was not sent to the parents because the anomaly reported was not important from the medical aspect. The distribution of these anomalies was as follows.

1555 congenital dislocation of hip (as in the majority of the reported cases it only means a predisposition)

577 Congenital inguinal hernia
276 Naevus/haemangioma
225 Hydrocele
91 Other hernias

Thus, 2428 questionnaires had been sent out and 1849 (76.2%) were answered. As to the rest, 62 letters were sent back by the post as undeliverable and 517 parents failed to respond. Only those questionnaires were evaluated in which every question was correctly answered. Finally 1711 questionnaires were evaluated, i.e. 24.4% of the total material and 72.3% of the selected index patients with correct address.

Out of the 4856 controls, the questionnaire was mailed to the parents of 4632 matched control cases; 224 cases were excluded because some data needed for matching were lacking, and a few because they had congenital anomalies. The response rate was 58.2%, i.e. 2694 parents answered. In 83 cases the address was incorrect and 1855 parents failed to respond. Of the questionnaires 173 were excluded, owing to deficient data. Finally, 2521 matched control cases were evaluated.

In this paper the data for the first year are presented according to drugs taken during pregnancy, diseases and occupation.

### *Drugs taken during pregnancy (Table I)*

*(i)* Evaluation of the control group showed the following:

a) Progestogens (allyloestrenol or hydroxyprogesterone capronate) were used in 33.4% of all pregnancies. We were surprised by this figure because we felt that their use in Hungary may have paralleled the decline in USA, UK, Sweden and other countries. In considering the risk/benefit ratio, the efficacy of progestogens in hormone support ther-

TABLE I

| Drugs | Control group | Malformation | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | AN EN SB | CL | CP | LR | PY SY | EX | OA | AA |
| Oestrogen + Pill | 273 | 13 | 11 | 2 | 5 | 14 | 8 | 0 | 4 |
| | 10.8% | 10.0% | 10.5% | 3.9% | 14.7% | 12.2% | 21.1% | 0 | 20.0% |
| Progestogen | 843 | 49 | 26 | 26 | 14 | 44 | 12 | 8 | 10 |
| | 33.4% | 37.7% | 24.8% | 51.0% | 41.2% | 38.3% | 31.6% | 53.3% | 50.0% |
| Other hormones | 105 | 7 | 5 | 4 | 3 | 6 | 0 | 1 | 3 |
| | 4.2% | 5.4% | 4.8% | 7.8% | 8.8% | 5.2% | 0 | 6.7% | 15.0% |
| Antibiotics | 589 | 40 | 27 | 12 | 14 | 33 | 6 | 4 | 11 |
| | 23.4% | 30.8% | 25.7% | 23.5% | 41.2% | 28.7% | 15.8% | 26.7% | 55.0% |
| Sulfonamides | 61 | 4 | 4 | 3 | 3 | 5 | 1 | 0 | 1 |
| | 2.4% | 3.1% | 3.8% | 5.9% | 8.8% | 4.3% | 2.6% | 0 | 5.0% |
| Antiemetics | 238 | 11 | 12 | 7 | 2 | 9 | 9 | 0 | 1 |
| | 9.4% | 8.5% | 11.4% | 13.7% | 5.9% | 7.8% | 23.7% | 0 | 5.0% |
| Antipyretics-antiphlogistics | 347 | 25 | 21 | 11 | 13 | 19 | 9 | 2 | 6 |
| | 13.8% | 19.2% | 20.0% | 21.6% | 38.2% | 16.5% | 23.7% | 13.3% | 30.0% |
| Analgetics | 38 | 3 | 2 | 0 | 1 | 2 | 0 | 0 | 1 |
| | 1.5% | 2.3% | 1.9% | 0 | 2.9% | 1.7% | 0 | 0 | 5.0% |
| Sedatives-hypnotics | 729 | 43 | 30 | 12 | 12 | 37 | 15 | 8 | 8 |
| | 28.9% | 33.1% | 28.6% | 23.5% | 35.3% | 32.2% | 39.5% | 53.3% | 40.0% |
| Spasmolytics | 206 | 10 | 8 | 7 | 6 | 10 | 5 | 2 | 2 |
| | 8.2% | 7.7% | 7.6% | 13.7% | 17.6% | 8.7% | 13.2% | 13.3% | 10.0% |
| Antiepileptics | 6 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 |
| | 0.2% | 0.8% | 1.0% | 3.9% | 0 | 0 | 0 | 0 | 0 |
| Vitamins, iron, calcium | 1592 | 83 | 62 | 20 | 16 | 69 | 25 | 12 | 10 |
| | 63.1% | 63.8% | 59.0% | 39.2% | 47.1% | 60.0% | 65.8% | 80.0% | 50.0% |
| Other drugs | 683 | 43 | 28 | 14 | 9 | 28 | 11 | 6 | 5 |
| | 27.1% | 33.1% | 26.7% | 27.5% | 26.5% | 24.3% | 28.9% | 40.0% | 25.0% |
| No drug taken | 268 | 11 | 8 | 9 | 0 | 13 | 3 | 0 | 1 |
| | 10.6% | 8.5% | 7.6% | 17.6% | 0 | 11.3% | 7.9% | 0 | 5.0% |
| Total | 2521 | 130 | 105 | 51 | 34 | 115 | 38 | 15 | 20 |

AN — Anencephaly; EN — Encephalocele; SB — Spina bifida; CL — Cleft lip; CP — Cleft palate; LR — Limb reduction; PY — Polydactyly; SY — Syndactyly; EX — Exomphalos; OA — Oesophageal atresia; AA — Anal atresia; MC — Microcephaly; HY — Hydrocephaly; AM, CA, EY — Eye anomalies; CF — Club foot; HS —

apy is, at most, confined to a small group of women, estimated at approximately 4% of those with threatened abortion, who have corpus luteum deficiency while the possibility of increasing the risk of hypospadias in the male children of mothers given progestogens during pregnancy has been widely disputed in the literature [5] and according to the prevailing opinion, if there is any risk, it must be a small one.

b) Oestrogen use during pregnancy amounted to 10.8%. We expected a

| Groups | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MC HY | AM CA EY | CF | HS | HD | DI | RA CK | PS | UT | EG | Down's disease | Other malfor-mation | Total |
| 7 | 0 | 29 | 25 | 38 | 4 | 0 | 3 | 15 | 1 | 10 | 37 | 226 |
| 16.7% | 0 | 14.6% | 12.8% | 14.6% | 18.2% | 0 | 12.0% | 13.0% | 33.3% | 13.3% | 15.0% | 13.2% |
| 18 | 3 | 90 | 84 | 97 | 7 | 3 | 8 | 43 | 2 | 24 | 95 | 663 |
| 42.9% | 42.9% | 45.5% | 43.1% | 37.2% | 31.8% | 23.1% | 32.0% | 37.4% | 66.7% | 32.0% | 38.5% | 38.8% |
| 1 | 0 | 4 | 9 | 11 | 2 | 1 | 1 | 4 | 0 | 4 | 19 | 85 |
| 2.4% | 0 | 2.0% | 4.6% | 4.2% | 9.1% | 7.7% | 4.0% | 3.5% | 0 | 5.3% | 7.7% | 4.9% |
| 17 | 3 | 51 | 50 | 71 | 5 | 7 | 3 | 27 | 0 | 26 | 72 | 455 |
| 40.5% | 42.9% | 25.8% | 25.6% | 27.2% | 22.7% | 53.8% | 12.0% | 23.5% | 0 | 34.7% | 29.1% | 26.6% |
| 1 | 1 | 7 | 5 | 10 | 0 | 1 | 0 | 1 | 0 | 3 | 12 | 62 |
| 2.4% | 14.3% | 3.5% | 2.6% | 3.8% | 0 | 7.7% | 0 | 0.9% | 0 | 4.0% | 4.9% | 3.6% |
| 4 | 0 | 20 | 21 | 22 | 3 | 2 | 3 | 6 | 1 | 10 | 20 | 163 |
| 9.5% | 0 | 10.1% | 10.8% | 8.4% | 13.6% | 15.4% | 12.0% | 5.2% | 33.3% | 13.3% | 8.1% | 9.5% |
| 4 | 2 | 31 | 36 | 52 | 4 | 5 | 6 | 14 | 0 | 23 | 69 | 352 |
| 9.5% | 28.6% | 15.7% | 18.5% | 19.9% | 18.2% | 38.5% | 24.0% | 12.2% | 0 | 30.7% | 27.9% | 20.6% |
| 4 | 0 | 3 | 7 | 7 | 0 | 0 | 1 | 3 | 0 | 4 | 1 | 39 |
| 9.5% | 0 | 1.5% | 3.6% | 2.7% | 0 | 0 | 4.0% | 2.6% | 0 | 5.3% | 0.4% | 2.3% |
| 16 | 3 | 77 | 78 | 89 | 5 | 5 | 3 | 37 | 2 | 22 | 100 | 602 |
| 38.1% | 42.9% | 38.9% | 40.0% | 34.1% | 22.7% | 38.5% | 12.0% | 32.2% | 66.7% | 29.3% | 40.5% | 35.2% |
| 3 | 1 | 14 | 17 | 16 | 3 | 3 | 4 | 13 | 0 | 11 | 25 | 160 |
| 7.1% | 14.3% | 7.1% | 8.7% | 6.1% | 13.6% | 23.1% | 16.0% | 11.3% | 0 | 14.7% | 10.1% | 9.4% |
| 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 10 |
| 0 | 0 | 0.5% | 0.5% | 0.4% | 0 | 0 | 4.0% | 0 | 0 | 0 | 0.8% | 0.6% |
| 25 | 6 | 125 | 116 | 161 | 15 | 6 | 15 | 58 | 3 | 42 | 167 | 1036 |
| 59.5% | 85.7% | 63.1% | 59.5% | 61.7% | 68.2% | 46.2% | 60.0% | 50.4% | 100.0% | 56.0% | 67.6% | 60.6% |
| 17 | 3 | 53 | 63 | 86 | 7 | 6 | 7 | 27 | 1 | 29 | 72 | 515 |
| 40.5% | 42.9% | 26.8% | 32.3% | 33.0% | 31.8% | 46.2% | 28.0% | 23.5% | 33.3% | 38.7% | 29.1% | 30.1% |
| 2 | 1 | 16 | 15 | 19 | 2 | 2 | 3 | 18 | 0 | 6 | 12 | 141 |
| 4.8% | 14.3% | 8.1% | 7.7% | 7.3% | 9.1% | 15.4% | 12.0% | 15.7% | 0 | 8.0% | 4.9% | 8.2% |
| 42 | 7 | 198 | 195 | 261 | 22 | 13 | 25 | 115 | 3 | 75 | 247 | 1711 |

Hypospadias; HD — Heart defect; DI — Diaphragmatic hernia; RA — Renal agenesis; CK — Cystic kidney; PS — Pyloric stenosis; UT — Undescended testicles; EG — External genital malformation.

much lower frequency in view of the recommendations that sex hormones had to be avoided during pregnancy. The possibility of a teratogenic risk of sex hormones has been widely studied and now it is thought that there is no risk [7] although its possibility cannot be excluded. Since oestrogens are now counterindicated for both pregnancy testing and as abortion inducers, the 10.8 % frequency seems to be unnecessarily and inexplicably high. Still, the figure included some women who had become pregnant

TABLE II

| Disease Groups | Control group | Malformation: ANEN SB | CL | CP | LR | PY SY | EX | OA | AA | MC HY |
|---|---|---|---|---|---|---|---|---|---|---|
| Threatened abortion | 144 | 4 | 7 | 4 | 0 | 5 | 1 | 1 | 3 | 2 |
| | 5.7% | 3.1% | 6.7% | 7.8% | 0 | 4.3% | 2.6% | 6.7% | 15.0% | 4.8% |
| Toxaemia | 139 | 6 | 5 | 1 | 2 | 1 | 2 | 1 | 0 | 3 |
| | 5.5% | 4.6% | 4.8% | 2.0% | 5.9% | 0.9% | 5.3% | 6.7% | 0 | 7.1% |
| Kidney and urinary disease | 158 | 10 | 5 | 1 | 5 | 16 | 3 | 0 | 2 | 4 |
| | 6.3% | 7.7% | 4.8% | 2.0% | 14.7% | 13.9% | 7.9% | 0 | 10.0% | 9.5% |
| Influenza and respiratory diseases | 564 | 59 | 44 | 22 | 12 | 32 | 8 | 7 | 8 | 16 |
| | 22.4% | 45.4% | 41.9% | 43.1% | 35.3% | 27.8% | 21.0% | 46.7% | 40.0% | 38.1% |
| Rubella | 1 | 0 | 2 | 0 | 0 | 1 | 2 | 0 | 1 | 0 |
| | 0.0% | 0 | 1.9% | 0 | 0 | 0.9% | 5.3% | 0 | 5.0% | 0 |
| Heart disease | 114 | 10 | 8 | 0 | 2 | 4 | 4 | 2 | 1 | 2 |
| | 4.5% | 7.7% | 7.6% | 0 | 5.9% | 3.5% | 10.5% | 13.3% | 5.0% | 4.8% |
| Hyper or hypothyrodism | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | 0.1% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5.0% | 0 |
| Epilepsy | 5 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.2% | 0.8% | 0.9% | 3.9% | 0 | 0 | 0 | 0 | 0 | 0 |
| Diabetes | 3 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 0.1% | 0 | 0.9% | 0 | 2.9% | 0 | 0 | 0 | 0 | 0 |
| Anaemia | 261 | 7 | 4 | 1 | 1 | 6 | 1 | 0 | 1 | 2 |
| | 10.4% | 5.4% | 3.8% | 2.0% | 2.9% | 5.2% | 2.6% | 0 | 5.0% | 4.8% |
| Alimentary tract diseases | 39 | 6 | 4 | 1 | 0 | 1 | 1 | 0 | 0 | 3 |
| | 1.6% | 4.6% | 3.8% | 2.0% | 0 | 0.9% | 2.6% | 0 | 0 | 7.1% |
| Other diseases | 592 | 25 | 20 | 15 | 11 | 25 | 9 | 1 | 7 | 7 |
| | 23.5% | 19.2% | 19.0% | 29.4% | 32.3% | 21.7% | 23.7% | 6.7% | 35.0% | 16.7% |
| No disease | 1118 | 38 | 34 | 15 | 13 | 46 | 17 | 7 | 5 | 15 |
| | 44.3% | 29.2% | 32.4% | 29.4% | 38.2% | 40.0% | 44.7% | 46.7% | 25.0% | 35.7% |
| Total | 2521 | 130 | 105 | 51 | 34 | 115 | 38 | 15 | 20 | 42 |

while taking oral contraceptives; the reasons for this include inadvertent usage, interaction with other drugs, gastroenteritis, etc., and a number of such exposed pregnancies are unavoidable.

c) The 28.9% frequency of sedatives and hypnotics also seems to be high.

d) "Other drugs" were taken by 27.1%. Detailed analysis of this group will have to be undertaken, although it is doubtful if any statistically significant results will emerge because of the small number of cases in the subgroups.

e) Vitamins, iron and calcium were taken by 63.1% of all pregnant women. This rate was lower than expected in view of the recommenda-

| Group | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AM CA EY | CF | HS | HD | DI | RA CK | PS | UT | EG | Down | Multiple | Other malfor-mation | Total |
| 0 | 12 | 11 | 12 | 1 | 0 | 0 | 3 | 0 | 3 | 10 | 7 | 86 |
| 0 | 6.1% | 5.6% | 4.6% | 4.5% | 0 | 0 | 2.6% | 0 | 4.0% | 6.4% | 7.8% | 5.3% |
| 0 | 9 | 17 | 7 | 0 | 1 | 2 | 5 | 0 | 6 | 7 | 3 | 78 |
| 0 | 4.5% | 8.7% | 2.7% | 0 | 7.7% | 8.0% | 4.3% | 0 | 8.0% | 4.5% | 3.3% | 4.6% |
| 0 | 14 | 15 | 13 | 2 | 2 | 2 | 5 | 0 | 7 | 13 | 11 | 130 |
| 0 | 7.1% | 7.7% | 5.0% | 9.1% | 15.4% | 8.0% | 4.3% | 0 | 9.3% | 8.3% | 12.2% | 7.6% |
| 2 | 55 | 56 | 91 | 8 | 10 | 9 | 26 | 1 | 26 | 72 | 32 | 596 |
| 28.6% | 27.8% | 28.7% | 34.9% | 36.4% | 76.9% | 36.0% | 22.6% | 33.3% | 34.7% | 45.9% | 35.6% | 34.8% |
| 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 12 |
| 0 | 0.5% | 0 | 0.4% | 0 | 0 | 0 | 0 | 0 | 5.3% | 0 | 0 | 0.7% |
| 0 | 11 | 16 | 18 | 0 | 0 | 1 | 3 | 0 | 5 | 10 | 5 | 102 |
| 0 | 5.6% | 8.2% | 6.9% | 0 | 0 | 4.0% | 2.6% | 0 | 6.7% | 6.4% | 5.6% | 6.0% |
| 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 5 |
| 0 | 0.5% | 0 | 0.4% | 0 | 0 | 0 | 0 | 0 | 0 | 0.6% | 1.1% | 0.3% |
| 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 9 |
| 0 | 0 | 0.5% | 0.4% | 0 | 0 | 4.0% | 0 | 0 | 0 | 0.6% | 1.1% | 0.5% |
| 0 | 0 | 2 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 11 |
| 0 | 0 | 1.0% | 0.8% | 0 | 7.7% | 0 | 0 | 0 | 0 | 1.9% | 1.1% | 0.6% |
| 0 | 7 | 9 | 8 | 1 | 0 | 0 | 5 | 0 | 2 | 8 | 5 | 68 |
| 0 | 3.5% | 4.6% | 3.1% | 4.5% | 0 | 0 | 4.3% | 0 | 2.7% | 5.1% | 5.6% | 4.0% |
| 0 | 1 | 4 | 6 | 0 | 1 | 1 | 4 | 0 | 0 | 6 | 2 | 41 |
| 0 | 0.5% | 2.0% | 2.3% | 0 | 7.7% | 4.0% | 3.5% | 0 | 0 | 3.8% | 2.2% | 2.4% |
| 3 | 40 | 46 | 65 | 3 | 0 | 7 | 25 | 0 | 17 | 26 | 21 | 373 |
| 42.8% | 20.2% | 23.6% | 24.9% | 13.6% | 0 | 28.0% | 21.7% | 0 | 22.7% | 16.6% | 23.3% | 21.8% |
| 3 | 90 | 68 | 89 | 11 | 3 | 10 | 50 | 2 | 26 | 50 | 29 | 621 |
| 42.8% | 45.4% | 34.9% | 34.1% | 50.0% | 23.1% | 40.0% | 43.5% | 66.6% | 34.7% | 31.8% | 32.2% | 36.3% |
| 7 | 198 | 195 | 261 | 22 | 13 | 25 | 115 | 3 | 75 | 157 | 90 | 1711 |

tion that all pregnant women should receive these drugs.

*(ii)* Evaluation of the index patients revealed that there were no statistically significant differences in drug taking between the two groups. Still, there were trends of associations between some drugs and some types of lesion, e.g. an excess of limb reduction defects in the children of women who took salicylates (38.2%) as compared to the controls (13.8%) [6], and a very small excess of progestogen users in the mothers of hypospadic children (43.1%) as compared to the controls (33.4%). These results could, however, easily have been due to chance. In any case, the drugs studied carry either no teratogenic risk whatever or, if there is

any risk, it is exceedingly small. Thus the custom of interrupting wanted pregnancies because of exposure to drugs has to be considered erroneous.

*Maternal diseases during pregnancy (Table II)*

In the control group, 44.3% of the women did not mention any disease. By the remaining 1304 subjects 2023 diseases were mentioned. The "Others" group had the highest frequency but there was no typical correlation with any specific type of disease. Second in frequency were influenza and other respiratory diseases. Third was anaemia, but its prevalence of 10.4% is suspected to be less than the true incidence. The group of kidney and urinary diseases was mainly comprised of cystopyelitis. The rate of threatened abortion and toxaemia of pregnancy seems reliable as it corresponds to the registered national figures. Diseases suspected to be important from the teratological aspect were rarely mentioned.

When we look at the data of the mothers of index patients there was no significant difference in the distribution of diseases as compared to the control group, except for a small excess observed in the respiratory (5%) and anaemia (2.5%) groups. The impact of recall bias owing to the different motivation of mothers could, however, not be excluded. When we analysed the congenital abnormality groups separately, respiratory diseases were found to be more frequent in the ASB, OA, RA, CK and Multiple groups; and kidney and urinary diseases were more frequent in the LR and PY/SY groups. These diseases will carefully be observed in the future to determine whether the present apparent associations are confirmed, although the literature gives no support to this possibility.

*Maternal occupation during pregnancy*

The distribution of occupations during pregnancy did not show any aetiological relationship.

When running the Aetiological Monitor programme it was interesting to see how eager the malformed children's parents were to obtain information. Almost every second parent asked questions of different kinds. (Which shows the deficiency of information given in obstetric institutions.) We tried to answer them correctly although the capacity of our staff is hardly sufficient for this purpose.

ACKNOWLEGEMENTS

We are indebted to Dr. I. Őry from the Hungarian Ministry of Health, to Mrs. Nyitrai, president of the Central Statistical Office, to the Hungarian Red Cross, and the National Cooperation of Drug Factories for making this programme possible. Finally, we thank Dr. R. A. Wiseman for critical evaluation of the manuscript.

REFERENCES

1. Czeizel A: The Hungarian Congenital Malformation Monitoring System. Acta Paediatr Acad Sci Hung 19: 225, 1978
2. Czeizel A, Keller I, Bod M: An aetiological evaluation of increased occurrence of

congenital limb reduction abnormalities in Hungary, 1975—78. In press
3. Czeizel A, Pazonyi I: Increase of upper limb reduction deformities in Hungary. Lancet 1: 706, 1976
4. Flynt JW, Hay S: International Clearinghouse for Birth Defects Monitoring Systems. Contrib Epid Biostatist 1: 44, 1979
5. Källen B, Winberg J: An epidemiological study of hypospadias in Sweden. Acta Paediatr Scand (Suppl) 293: 1, 1982
6. McNiel JR: The possible teratogenic effect of salicylates on the developing fetus. Clin Pediatr 12: 347, 1973
7. Wilson JG, Brent RL: Are female sex hormones teratogenic? Am J Obstet Gynecol 141: 567, 1981

*Received 15 July 1982*

A Czeizel MD
Gyáli út 2
1091 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (1), pp 101—108 (1983)*

# Book reviews

RODEWALD, A., ZANKL, H. *Hautleistenfibel.* 135 pages with 45 figures. Gustav Fischer Verlag, Stuttgart—New York 1981. Price DM 34.—

Classical studies on dermatoglyphics, such as the papers and books published by Purkinje, Galton, Cummins, Penrose, etc., have attracted the attention of anthropologists, criminologists and human geneticists. They soon aroused interest in the medical world as well. The interest of paediatricians has, however, culminated after the human chromosomal aberrations had been discovered. Along with the introduction of chromosome investigations of malformed subjects, dermatoglyphic data were zealously collected over more than two decades. At the beginning of this era, in medical circles one often heard the saying that dermatoglyphics was the poor man's karyotype, which was to mean that dermatoglyphic analysis would be used instead of karyotyping. By now, fascinating rich collections of data have been summarized and evaluated by a number of authors. None of them could convince the paediatricians on the diagnostic value of dermatoglyphics. In this respect, the aim set by the authors of this book, however well it is presented, can hardly be achieved.

Magda OSZTOVICS

*Rheumatic valvular disease in children.* Herausgegeben von J. B. BORMAN und M. S. GOTSMAN. IX + 231 Seiten mit 105 Abbildungen und 43 Tabellen. Springer Verlag, Berlin—Heidelberg—New York 1980. Preis DM 98,—

Seit der von Markovitz und Gordis im Jahre 1972 verfaßten Monographie „Rheumatic Fever" ist dieses Buch das erste, das die Fortschritte in der Ätiologie, Pathologie, Diagnostik sowie der medikamentösen und chirurgischen Behandlung des rheumatischen Fiebers zusammenfassend darstellt. Die Herausgeber leben als Leiter der Thoraxchirurgischen bzw. Kardiologischen Klinik der Hebrew Universität in Jerusalem, — in einem Land, wo das rheumatische Fieber auch heutzutage ein aktuelles Problem bedeutet. Es ist das Verdienst der Herausgeber, daß sie zur Mitarbeit hervorragende, international anerkannte Autoritäten gewinnen konnten.

Die Thematik verteilt sich streng proportional zwischen dem medizinischen und dem chirurgischen Teil. Der medizinische Teil besteht aus folgenden Kapiteln:

1. Epidemiologie und Prävention des rheumatischen Fiebers,
2. Akute rheumatische Karditis,
3. Pathologie der rheumatischen Herzklappenfehler,
4. Spontanverlauf des rheumatischen

Fiebers im Kindesalter. Dieses Thema wird in folgender Gliederung besprochen:

a) Spontanverlauf in den westlichen Ländern vor der Einführung der Penicillinprophylaxe,

b) Veränderung des Spontanverlaufes infolge der Einführung der modernen Therapie,

c) rheumatisches Fieber in unentwickelten Ländern und Entwicklungsländern,

d) Spontanverlauf der rheumatischen Klappenfehler.

Das Kapitel „Präoperative Beurteilung des Kindes mit rheumatischem Klappenfehler" stellt den hervorragendsten Teil des Buches dar. Es befaßt sich mit der Bewertung der physikalischen Untersuchung, des EKG, des Röntgenbefundes, Echokardiogramms, der Herzkatheterisierung und Angiokardiographie. Die eindeutige und klare Stellungnahme in der Frage der Operationsindikation der rheumatischen Klappenfehler bietet dem Kinderarzt unschätzbare Hilfe auf dem Gebiet der erworbenen Vitien.

Der chirurgische Teil besteht aus den folgenden Kapiteln:

1. Anästhesie und Unterstützung der Atmung,
2. Geschlossene Mitralkomissurotomie bei Kindern,
3. Rekonstruktionschirurgie der rheumatischen Herzklappenfehler bei Kindern unter 12 Jahren,
4. Mitralklappenersatz bei Kindern,
5. Aortenklappenersatz bei Kindern,
6. Chirurgie der multivalvulären Krankheit bei Kindern,
7. Künstliche Herzklappen. Vergleich der vier Grundtypen.
8. Langzeitbehandlung des Kindes nach der Operation eines rheumatischen Herzklappenfehlers.

Man kann mit der Behauptung des Vorwortes völlig einverstanden sein: „Das Buch kann das Interesse des Epidemiologen, des Pathologen, des Pädiaters, Kardiologen und Chirurgen gleichfalls erwecken".

J. KAMARÁS

*Kardiotokographie.* Diagnostische Methoden in der Perinatologie. Herausgegeben von W. M. FISCHER. 3., überarbeitete und erweiterte Auflage. XVIII + 602 Seiten mit 280 Abbildungen und 27 Tabellen Georg Thieme Verlag, Stuttgart 1981. Preis DM 160,—

Das Buch ist die dritte ergänzte Auflage des in den Jahren 1973 und 1976 erschienenen Handbuches. Die einzelnen Kapitel wurden von anerkannten Autoritäten verfaßt.

Das ausgezeichnete, didaktische Werk faßt die vielschichtige Diagnostik der verschiedenen Phasen des perinatalen (ante, sub- und postnatalen) Zeitabschnittes zusammen. Es werden die technischen Grundlagen der Untersuchungsmethoden, die Interpretation der Ergebnisse, die Fehlermöglichkeiten, die Diagnostik der Risikoschwangerschaften und deren Schwierigkeiten eingehend besprochen. Mit Hilfe von originalen ante- und intrapartualen Kardiotokogrammen wird dies in einem Atlas-Teil illustriert.

Das Buch gliedert sich in fünf größere Kapitel, von denen im ersten die Erfassung von Schwangerschaften mit erhöhtem Risiko behandelt wird. Das zweite Kapitel befaßt sich mit der Überwachung der Schwangerschaft und Geburt. Das nächste große Kapitel ist den Grundlagen und der klinischen Wertigkeit der Kardiotokographie gewidmet. Sodann folgt die klinische Demonstration von ante- und intrapartualen Kardiogrammen. Im fünften Kapitel erhalten wir eine zusammenfassende Schilderung der Technik, der Registrierprinzipien und -fehler von Kardiotokografen. Die Grundlagen der sog. On-line Überwachung werden im sechsten Kapitel erörtert. Abschließend wird noch die vielseitige Überwachung des Neugeborenen besprochen.

Die auf den neuesten Stand gebrachte vorliegende Auflage des in jeder Hinsicht ausgezeichneten Buches soll als Hilfsquelle für Geburtshelfer, Perinatologen,

Pädiater und für das Hilfspersonal der entsprechenden Spezialabteilungen dienen.

B. Zsolnai

Lintermans, J. P., Dorp, W. G. van: *Differential diagnosis in pediatric echocardiography.* XVI + 234 pages with 110 figures and 20 tables. Springer-Verlag, Berlin—Heidelberg—New York 1981. Price DM 128.—

This monograph occupies a prominent place in paediatric cardiology as among the many books on the subject this one discusses the echocardiographic (M mode and sector scan) differential diagnostics in the clearest way and in all details.

The first part deals with the qualitative anatomy of the heart. Here the use of the most up-to-date terminology is certainly an advantage. The deviations of echocardiographic from normal anatomy are explained by three possibilities. These are 1) changes in position of the represented structures and in this relation the pathologic atrioventricular — large vessel situations are described; 2) changes in the mutual relations of the structures: this point is illustrated by the atrioventricular — semilunar discontinuities due to different causes, and by the atrioventricular valves appearing without septum; 3) appearance in the echocardiogram of structures absent under normal conditions, such as pericardial fluid, tumour, common pulmonary venous return, etc.

The second part deals with the quantitative anatomy. Here the pathological valve movements and the possibilities of echocardiographic analysis of the structures are explained. The third part of the book discusses the details of functional echocardiography including the technique of contrast echocardiography and the measurement of systolic intervals and of ventricular function. In an appendix we find a very useful list of normal echocardiographic data obtained by the authors in 425 normal children.

The book presupposes some basic knowledge of the reader concerning echocardiography and paediatric cardiology and so it does not touch upon the physics of ultrasound, the technique of echocardiography or the normal findings. We believe that this attractive monograph will offer much help and plenty of information to every paediatric cardiologist and quite especially to those interested in congenital heart defects.

Krisztina Kádár

*Modern trends in human leukemia IV.* Neth, R., Gallo, R. C., Graf, T., Mannweiler, K., Winkler, K. editors. XXV + 557 pages with 252 figures. Springer Verlag, Berlin—Heidelberg—New York 1981. Price DM 168.—

The book contains the proceedings of a joint meeting of the German Society for Haematology and Oncology and the German Centre of Cancer Research, held in Wilsede in 1980. The papers given by the invited authors, a number of them of international reputation, are divided under the four headings, clinical aspects, cytogenetics, cell biological and virological and molecular biological studies. The introductory Frederick Stohlman lectures were given by G. Klein who discussed oncogenic virus transformation and cytogenetic changes in lymphomas, and H. S. Kaplan who discussed Hodgkin disease. The clinical part offers much information on preleukaemia, diagnostic therapeutical and prognostic factors. Of especial interest for the paediatric oncologist are the paper on some new therapeutical lines such as the use of interferon, bone marrow transplantation, medium dose methotrexate, low dose cytosine arabinoside and of hyperthermia. In the second part the properties of leukaemic cells in patients and cell lines are described. In these a great help was obtained from the rapid development of the methods of cell isolation and culturing. Special mention is due to the

studies on the maturation of leukaemic cells obtained from patients, although this could not be brought into any relation with the clinical course of their disease. Several papers deal with the changes elicited by the Epstein-Barr virus, and some discuss gene mapping and genetic manipulations. The retroviruses isolated from humans and their pathologic role is somewhat neglected while we find several studies of animal retroviruses and the properties of their genes and gene products.

On the whole, the book gives an excellent review of the now important problems, results, hypotheses and outlooks of therapy and research. It is an important lecture and source of recent data for every physician interested in malignancies.

D. SCHULER

P. WUNDERLICH: *Differentialdiagnostik von Kinderkrankheiten* 2., bearbeitete Auflage. 192 Seiten mit 11 Abbildungen und 19 Tabellen. Gustav Fischer Verlag, Jena 1981. Preis M 12,50

Die erste Auflage der Arbeit ist 1977 unter dem Titel Kinderärztliche Differentialdiagnostik erschienen. Das vorliegende, für die Reihe "Für die medizinische Praxis" ergänzte Buch wendet sich in erster Reihe an Ärzte, die keine Pädiater sind doch auch Kinder behandeln. Es gliedert sich in zwei Teile, a) allgemeine Gesichtspunkte zur Differentialdiagnostik und b) Differentialdiagnose einzelner Symptome.

Im ersten Teil wird die Wichtigkeit der entsprechenden Anamnese betont. Ausführlich werden die Häufigkeit der Symptome, die Technik der Untersuchungen, die Besonderheiten der verschiedenen Altersgruppen geschildert, wobei jene der Neugeborenen und die der Pubertät hervorgehoben werden.

Der zweite Teil umfaßt die rationelle Diagnostik nach verschiedenen Leitsymptomen, wie z. B. Fieber, Schmerzen, Husten und Atemnot, Erbrechen, Durchfall, Blässe, Zyanose, Schwellungen, Krämpfe, Lähmungen, Blutungen usw. Die wichtigsten Ursachen werden jeweils angeführt und der Gang der Diagnostik angedeutet.

In einer knappen, doch übersichtlichen Form wird für den jungen Arzt oder Studenten die schnelle Orientierung gesichert, wenn er in der Praxis mit Symptomen konfrontiert ist, von denen ausgehend er sich zur Diagnose und Einleitung therapeutischer Maßnahmen entscheiden muß.

K. SCHMIDT

DENHOFF, E., FELDMAN, S. A.: *Developmental Disabilities*. 280 pages Marcel Dekker, Inc., New York 1981. Price SFr. 78.—

This book, consisting of 9 chapters and 3 appendices, is somewhat unusual in its aspects. The first two chapters describe the concept of developmental disability and the associated neuroanatomical, neurophysiological and biochemical basic notions. The remaining chapters are devoted to the major disabilities (cerebral palsy, mental retardation, epilepsy, psychoses, sensory disorders) and minor disabilities (minimal brain damage, attentional deficit disorder, specific learning disability), their clinical course and drug and dietary treatment.

Developmental disability is a new concept, at least in Europe, but the classification method of the authors is logical and didactically useful. Another attractive aspect of the book is that it includes many social and educational problems.

The most valuable parts are those discussing the problems of pharmacology, so chapters 3 and 5 and the pharmacotherapeutic parts in chapters 6 and 8, and the appendices. In this field, however, one has to object to the absence of anxiolytic drugs and the cursory discussion of pharmacogenetics. More space should have been devoted to the fetal alcohol syndrome, the

prostaglandins and especially the adverse side effects of drugs. As to this last item, all that is said about its important aspects is a short classification extending to not more than 15 lines. At the same time, the many pharmacotherapeutical advices and some data in Appendix 1 are the proof of the authors' excellent theoretical knowledge and practical experience concerning the drug therapy of developmental disabilities. Chapter 4, discussing the principles of their dietary therapy, is certainly the weakest part of the book and in any case iron, fluorine and vitamin D would have deserved more attention and more space. At the same time, chapter 9 that deals with related questions, is rather extensive and interesting. Among others, it discusses Feingold's suggestion that hyperactivity in certain children was due to food additives and salicylates and omission of these substances from the diet would mean a cure of the condition. This concept is now generally rejected but its excellent presentation and discussion in the book is a good example of the authors' critical acumen.

It is rather unfortunate that the references quoted are practically all from American authors and the works of some internationally well-known authorities are neglected. Still, in view of its original concept and some original and individual points of view the book will be of interest to all those engaged in the study, therapy, care and rehabilitation of children with "developmental disabilities".

I. Szórády

R. Sachsenweger: *Stereo-Sehübungen* 3. Auflage. 62 Seiten mit 80 Abbildungen und 2 Stereobrillen. Gustav Fischer Verlag, Stuttgart—New York 1982. DM 16,—

Das Bilderbuch wurde für Kinder im Alter von 4—10 Jahren verfaßt, mit dem Ziel, das stereoskopische Sehen zu üben. Mit Hilfe der beiliegenden zweifarbigen Pappbrillen entstehen beim beidäugigen Sehen räumliche Bilder. Die Mehrzahl der Bilder bereitet den Kindern Spaß, die Aufgaben sind interessant und auch für Kleinkinder lösbar; einige sind aber zu schwer. Ein Teil der Bilder eignet sich zur Prüfung des binokularen Simultansehens, andere dienen zur Übung des Stereosehens. Ferner eignet sich das Bilderbuch, das Sehen nach Schieloperationen zu schulen und auch die Beobachtungs- und Konzentrationsfähigkeit normalsichtiger Kinder zu fördern. Das Lösen aller Aufgaben ist nur bei inaktem beidäugigem Sehen möglich. Das bedeutet, daß Sehfehler früh aufgedeckt werden können, das Sehvermögen jedoch nicht korrigiert werden kann.

Edith Szalay

*Renal transport of organic substances* Greger, R., Lang, F., Silbernagl, S. editors. XI + 314 pages with 81 figures. Springer-Verlag, Berlin—Heidelberg—New York 1981. Price DM 74.—

This book consists of 19 papers originally given by 29 mostly well-known authorities at a conference held in Innsbruck, Austria, in the summer of 1980. The first 6 chapters discuss the biochemical, electrophysiological, membrane structural and morphological problems of glomerular filtration and tubular reabsorption and secretion. The rest of the papers deals with the fate in the human kidney of glutamine and ammonia, amino acids and oligopeptides, proteins, urea, D-glucose, organic cations, PAH, lactate, oxalate, urate, drugs and hormones. The last chapter contains some pertaining comparative physiological data.

The book offers an excellent review of up-to-date knowledge concerning the renal handling of organic solutes and thus represents a good source of information which is really important to specialists working in the most diverse fields. It will be welcomed by internists who wish to treat their patients suffering from gout

on a modern basis, by the paediatricians, clinical chemists and geneticists interested in the diagnostics and treatment of congenital disturbances of amino-acid metabolism, and by the nephrologists and urologists who will obtain much new information of the mechanics and pathology of the development of renal calculi.

M. Miltényi

*Herz und Kreislauf.* Redigiert von J. Stoermer. XIV + 188 Seiten mit 30 Abbildungen und 9 Tabellen. Springer Verlag, Berlin—Heidelberg—New York 1982. Preis DM 32,—

Durch die beträchtliche Entwicklung der Kinderkardiologie in den vergangenen Jahren hat sich auch die Indikation der Herzkatheterierung und Herzoperationen verändert. Die neuen Untersuchungsmethoden — wie z. B. die Echokardiographie — haben die diagnostischen Möglichkeiten erweitert, und neue Operationsverfahren sind entwickelt worden. Der Kinderarzt muß sich in diesen Fragen gründlich auskennen, und der vorliegende Band bietet hierzu die entsprechenden Informationen.

Das Buch gliedert sich in 11 Kapitel. Einleitend werden die wichtigsten genetischen Probleme der kongenitalen Herzfehler (ätiologische Klassifikation, genetische Familienberatung) und die heutige Nomenklatur erläutert. Ein Kapitel ist den spezialen Fragen der pädiatrischen kardiologischen Diagnostik gewidmet. Von den noninvasiven Methoden werden u. a. die transkutane $PO_2$-Messung, der Hyperoxietest, die Szintigraphie, von den invasiven Verfahren die Herzkatheterierung und die sich anschließenden Untersuchungen wie Indikatordilution, pharmakologische Untersuchungen mit Indikation bzw. Kontraindikationen behandelt. Ein gesonderter Teil befaßt sich mit der Echokardiographie im Kindesalter; die mit der M-mode und zweidimensionalen Echokardiographie diagnostizierbaren Herzfehler sind in einer praktischen Tabelle zusammengefaßt. Das sich mit der Elektrokardiographie des His-Bündels befassende Kapitel schildert die methodologischen Probleme, Indikationen und die normalen Zeitintervalle auf dem EKG. In weiteren Kapiteln werden Hypertonie und Karditis des Kindesalters besprochen. Von besonders praktischem Wert ist das sich mit der Prophylaxe der Endokarditis bei angeborenen Herzfehlern befassende Kapitel, wo auch die Indikationen der Prophylaxe und das Schema der American Heart Association angeführt werden. Die letzten drei Kapitel behandeln die chirurgischen Möglichkeiten bei Kammerseptumdefekt, bei Transposition der großen Arterien und bei der Tricuspidalisatresie. Über letztere wird so eingehend berichtet, daß dieses Thema bereits die Zielsetzung des Buches überschreitet; diese Tatsache demonstriert gut, daß der Kinderarzt mit den Fortschritten in der Kardiologie und den Veränderungen in der Betrachtungsweise im klaren sein muß, — da ja dieser noch vor kurzem als unheilbar angesehene Herzfehler heute in vielen Fällen korrigiert werden kann, falls die Diagnosestellung rechtzeitig erfolgt.

Das Buch bietet eine klare, gedrängte Zusammenfassung der modernen kinderkardiologischen diagnostischen Aufgaben. Es wendet sich an Pädiater, kann jedoch auch von jungen Kardiologen mit Nutzen verwendet werden.

L. Lozsádi

U. Lorenz: *Antepartale Lungenreifebestimmung durch Fruchtwasseranalyse.* VIII + 84 Seiten mit 46 Abbildungen. Springer Verlag, Berlin—Heidelberg—New York 1982. Preis DM 40,—

Die Monographie ist eine ausgezeichnete Zusammenfassung der seit den 70-er Jahren sich rasch verbreiteten Untersuchung der Lungenreife aus dem Fruchtwasser. In dem in 6 Kapitel gegliederten

Buch werden einleitend der biochemische Reifeprozeß der Lunge und die Atmungsstörungen erörtert. Dann werden die einzelnen Bestimmungsverfahren, deren Auswertung und praktische Anwendung besprochen. Anhand von tierexperimentellen und klinischen Beobachtungen wird die Wirkung von Steroiden auf die Phospholipide der Lunge und die morphologische und funktionelle Reife der fetalen Lunge behandelt. Wie die Ergebnisse der Fruchtwasseranalyse bei verschiedenen schwangerschaftspathologischen Zuständen — wie z. B. Diabetes mellitus, Rh-Sensibilisierung, Retardation der Frucht, Frühgeburt nach vorzeitigem Blasensprung — zu bewerten sind, wird auch kurz angedeutet.

Zahlreiche praktische Hinweise, etwa 200 Literaturangaben und mehrere nützliche Abbildungen fördern den Wert der Monographie.

L. Lampé

M. Maahs: *Erkrankungen der Atemwege.* 111 Seiten mit 23 Abbildungen. Verlag Volk und Gesundheit, Berlin 1982. Preis M 4,30

Die Broschur wendet sich an Krippenerzieherinnen und Gesundheitsfürsorgerinnen.

Die kindlichen Erkrankungen der Atemwege stellen heute etwa 50% der ambulanten Kranken und 75% der Krankheiten von Krippenkindern dar. Die mit dem Problem konfrontierte Erzieherin muß deshalb einige Kenntnisse auf diesem Gebiet aufweisen können. Von anatomischen und immunologischen Gegebenheiten ausgehend werden also die Symptome dieser Erkrankungen, die notwendige Untersuchung und Behandlung geschildert. Auch auf ganz praktische Probleme wird eingegangen, z. B. wann ein Arzt in Anspruch genommen und was bis zum Eingriff des Arztes vorgenommen werden soll. Auf die bei Säuglingen oft symptomlos, doch mit schweren Folgen einhergehende Pneumonie und Otitis wird besonders aufmerksam gemacht. In dem Teil, der sich mit der Therapie befaßt, werden einige Medikamente und deren Dosierung, ferner allgemeine Versorgungsrichtlinien angegeben. Schließlich bietet das Büchlein zur Adaptation der nach der Krankheit in die Krippe zurückkehrenden Kinder zahlreiche Ratschläge.

Das Buch ist sehr nützlich, dürfte jedoch für den erstrebten Zweck zu ausführlich sein.

G. Póder

*Morphologische Abdominaldiagnostik im Kindesalter.* Herausgegeben von D. Weitzel und J. Tröger. X + 206 Seiten mit 138 Abbildungen. Springer Verlag, Berlin—Heidelberg—New York 1982. Preis DM 88,—

Die neueren nicht invasiven Untersuchungsverfahren, so die Ultraschalldiagnostik, die Isotopdiagnostik und die Computertomographie haben in der pädiatrischen Diagnostik bedeutende Veränderungen gebracht. Dies bezieht sich in erster Linie auf die Erkennung abdominaler Erkrankungen.

Die Herausgeber des Bandes haben ein Symposium über die kindliche Abdominaldiagnostik veranstaltet, und die Monographie ist aus dem Material dieser Veranstaltung entstanden. Der überwiegende Teil der Beiträge stammt aus der Mainzer Klinik, sodaß diese die Erfahrungen und Ansichten dieser Arbeitsgruppe widerspiegeln.

Das Buch besteht aus drei größeren Teilen: der erste überblickt die gastroenterologischen Beziehungen einschließlich Leber, Pankreas und Milz; im zweiten kürzeren Teil werden die abdominalen traumatologischen Fragen behandelt; der dritte Teil ist den in der Pädiatrie besonders wichtigen Fragen der zeitgemäßen Untersuchungsmethoden der Niere und ableitenden Harnwege gewidmet.

Die Monographie bietet wohl gesonderte Zusammenfassungen über die ein-

zelnen Verfahren, dennoch dürfte jenes Problem am interessantesten sein, wie und wann sich die konventionellen Verfahren den neuen Methoden anschließen sollen. Es liegt auf der Hand, daß auf allen Indikationsgebieten, wo die nicht invasiven die invasiven Verfahren ersetzen können, die Ersteren bevorzugt werden müssen. Das erfordert natürlich eine veränderte Betrachtungsart und die Abweichung von der gewohnten Routine, was sich ziemlich langsam durchsetzt, wie das aus den Diskussionen hervorgeht.

Die Echographie wird mit besonderer Betonung behandelt, wobei auf die nicht völlig ausgenützten Möglichkeiten der Ultraschalldiagnostik hingewiesen wird. Hervorzuheben sei ein Beitrag von D. Weitzel, in dem die mit Ultraschall bestimmten Maße der Leber, Milz und Niere im Kindesalter angegeben werden.

Das Buch wendet sich an Kinderärzte, die sich zur Zeit mit den neuen Verfahren und deren Indikationen befreunden, ferner Kinderchirurgen, die genauere präoperative Diagnosen dankbar begrüßen und schließlich an Radiologen, deren Aufgabe es ist, im Besitz dieser Methoden — auf Grund morphologischer Angaben — die Therapie oft entscheidende Kenntnisse zu vermitteln.

Z. HARKÁNYI

H.-R. WIEDEMANN MIT F.-R. GROSSE und H. DIBBERN: *Das charakteristische Syndrom. Ein Atlas für Klinik und Praxis.* 2. Auflage. XXXI + 413 Seiten mit 204 Abbildungstafeln. Schattauer-Verlag, Stuttgart—New York 1982. Preis DM 154.—

Wenn man eine Rezension über die »überarbeitete und erweiterte« neue Auflage eines Buches schreibt, muß man meistens lange nachsehen, was eigentlich überarbeitet und was erweitert wurde. Mit diesem Buch hat man keine solche Probleme. Das Format ist viel größer geworden und das Buch ist mindestens doppelt so dick als seine erste Ausgabe. Anstatt 100 enthält nämlich diese Ausgabe fast 200 Syndrome und die Seitenzahl ist auch das Doppelte des vorherigen. Der Unterschied liegt nicht an einer veränderten Beschreibung der Krankheiten: Nach wie vor findet man die Beschreibung eines Syndroms, das an der gegenüberliegende Seite mit 2 bis 15 charakteristischen Photographien demonstriert wird. Die Erweiterung ergibt sich aus einer Fülle neu aufgenommener Syndrome. Manche davon, wie das Pfeiffersche, das Carpentersche, das Scheuthauer-Mariesche usw. wurden in die erste Ausgabe nicht aufgenommen, einige wohl darum, da sie zu der Zeit noch nicht beschrieben worden sind, wie z. B. die mesomele Dysplasie oder das pseudohydrozephale Progeroidsyndrom. Andere sind dagegen nie beschriebene verblüffende Krankheitsbilder, wie ein Syndrom von Taubheit, Radiushypoplasie und psychomotorischer Entwicklungshemmung, ein anderes, das mit ektodermaler Dysplasie, Hypotrichosis mit Pili torti und Syndaktylie einhergeht, oder ein Syndrom mit Daumentriphalangie, Thrombozytopathie und Schwerhörigkeit, und noch viele Andere. Der Text der Beschreibungen wurde auch sorgfältig überarbeitet, und die Referenzien sind bis Mitte 1982 ergänzt. Die Bilder sind demonstrativ, nur hätte vielleicht der Autor einen typischeren Kranken mit fazialer Hemiatrophie als das abgebildete Mädchen einfügen und auch bei der gerade durch ihn beschriebenen Thalidomidembryopathie anstatt des jetzigen Bildes eine Tetra-Amelie oder noch eher eine Tetraphokomelie präsentieren können.

Das ausgezeichnete Buch wird jedem Pädiater und Genetiker und allen, die sich mit Familienberatung beschäftigen, ein unentbehrliches Nachschlagewerk sein.

P. V. VÉGHELYI

*Small Intestine* edited by V. S. CHADWICK and S. PHILLIPS. 355 pages. Butterworth Scientific, London 1982. Price £ 21.00

In this book that contains papers from a multinational team of experts and is edited by a senior lecturer of the Post-

graduate Medical School in London and the director of the gastroenterology unit of the Mayo Clinic, even the best informed specialist will find some interesting data which were unknown to him. The chapters have apparently been selected so as to present only subjects in which there have been important recent advances. This is clearly seen from the lists of references at the end of every chapter: few of the papers quoted have appeared before the last decade and data published in 1981 or even 1982 are no rarity.

The chapters are centred around 5 subjects. The first one deals with development, ultrastructure, biochemistry, in vitro methods (mainly small intestinal organ cultures and their technique), small intestinal immune mechanisms and endocrine functions including the recently isolated PHI and PYY in addition to the eight generally known intestinal hormones, and further the motility of the small intestine and the effect of invading microorganisms. The second subject concerns the immonologically related diseases. The first of these chapters deals with some parasites; it is said that the thymus has a central role in the resistance to enteric parasites in mice and rats and IgA and IgG would also have a role in it, and also that the carbohydrate composition of the brush border is affected in trichinelliasis. There is an interesting and detailed review from Algeria of alpha chain disease and a chapter on the intestinal effects of graft-vs-host-disease. Although involvement of the small intestine is a rarity in chronic GVHD, five patients with severe malabsorption have been observed by the authors. Fat excretion amounted to 50—70% in spite of a normal villous architecture and lymphatic blockade due to submucosal fibrosis was assumed to have been the responsible factor. The next two chapters deal with the different forms of vasculitis on the basis of case reports, and with atopy of the gut.

Neuroendocrine disorders form the next subject. The first chapter discusses the hormonal diarrhoeas. In four patient with Zollinger—Ellison syndrome the authors of the chapter found near the Treitz angle a flow exceeding 3 to 5 times the upper limit of normal; 75% of this was reabsorbed by the small intestine and the rest of the overload by the colon. In mastocytosis, prostaglandin overproduction was found to be an important factor. In endocrine cholera (WDHA syndrome) the source of the diarrhoea was found in the small intestine. The next two chapters deal with intestinal motility. Infectious agents are the subject of the following two chapters of which the first gives an account of the up to now futile attempts at finding the cytotoxicity-inducing agent in Crohn's disease and ulcerative colitis, and the second chapter presents a review of the enteric pathogens causing acute disease. There is a striking statement here: is it really true that disease and death due to diarrhoea take toll of 500 million children annually in developing countries? The last chapter of the book gives a good review of mostly recent data concerning protein-calorie malnutrition, vitamin and trace element deficiencies and, finally, the effects of dietary fibre on the small bowel.

The book will be especially interesting for pathophysiologists and clinicians studying the functions of the small intestine, but practising gastroenterologists will also find it useful.

P. V. VÉGHELYI

*The Medical Annual 1982/83* edited by SIR RONALD BODLEY SCOTT. Wright PSG, Bristol—London—Boston 1982. 387 pages. Price £ 15.00

This 100th issue of the popular Medical Annual is a memorable book. In the Preface, Sir Ronald Bodley Scott who as the successor of Tidy has been the editor for 24 years and whose name was so tightly connected with the Annual, announces that this volume will be the last one published under his editorial care. And less than two months later Sir Ronald was killed in a road accident.

The Annual has always reviewed the advances that have occurred during each year in all the fields of medicine. The same is done in its present issue with the difference that here perhaps more than the usual space is devoted to the changes and developments that have taken place in the special fields in the last 25 years. The peadiatrician will be interested in the chapter on children's diseases. Its first subject is the home monitoring of diabetic control by the use of blood sampling devices and BM test strips. The next subject is cow's milk protein intolerance; on two pages an excellent summary is given of the present knowledge concerning the pathomechanism and management of the condition. The next paragraph discusses the effect on young children of maternal depression, an up-to-date problem that has been studied especially since some 5 years ago Zax et al had shown that babies born to depressed women have lower Apgar scores and suffer more fetal death than those born to normal mothers. The further subjects of this part are whooping cough immunization, congenital pyloric stenosis, intrassusception, extrahepatic biliary atresia, rupture of the spleen, solitary thyroid nodules, urinary diversion, undescended testes, trace elements and finally total body water. The further chapters also offer many points of interest for the paediatrician. To quote some of them, even the practitioner will find many new data in the reviews on fibreoptic sigmoidoscopy, the leukaemias and lymphomas, cardiac surgery, ENT diseases, the endocrine glands, chemotherapy of infections, vaccines, prostaglandin, cholecalciferol, subarachnoid haemorrhage, advances in clinical nutrition, laser treatment of haemangiomas, new techniques in radiology, tropical rotavirus and campylobacter gastroenteritis, and nutrition and vitamins. In one word, the book will be of much use to practising and clinical paediatricians and paediatric surgeons.

P. V. VÉGHELYI

PRINTED IN HUNGARY

Akadémiai Nyomda, Budapest

# INSTRUCTIONS TO AUTHORS

*Form of manuscript*

Two complete copies of the manuscript including all tables and illustrations should be submitted. Manuscripts should be typed double-spaced with margins at least 4 cm wide. Pages should be numbered consecutively.

Manuscripts should include the title, authors' names and address of the institution where the work was done.

An abstract of not more than 200 words should be supplied typed before the text of the paper.

*Abbreviations* should be spelled out when first used in the text. *Drugs* should be referred to by their WHO code designation (Recommended International Nonproprietary Name); the use of proprietary names is unacceptable.

The *International System of Units* (SI) should be used for all measurements.

*References*

References should be numbered in alphabetical order and only the numbers should appear in the text (in parentheses). The list of references should contain the name and initials of all authors (the use of et al. instead of authors' name in the reference list is not accepted); for journal articles the title of the paper, title of the journal abbreviated according to the style used in Index Medicus, volume number, first page number and year of publication; for books the title followed by the publisher and place of publication.

**Examples:**

Kerpel-Fronius E, Gács GK: Serum insulin values in infants. Acta Paediatr Acad Sci Hung 16:197, 1975

Crosse VM: The Preterm Baby. Churchill Livingstone, Edinburgh and London 1971

Detter JC: Biochemical variation. In: Textbook of Human Genetics, ed. Fraser O, Mayo O, Blackwell Scientific Publications, Oxford 1975, p. 115

*Tables and illustrations*

*Tables* should be comprehensible to the reader without reference to the text. The headings should be typed above the table.

*Figures* should be identified by number and authors' name. The top should be indicated on the back. Their approximate place should be indicated in the text. Captions should be provided on a separate page.

*Proofs and reprints*

Reprints and proofs will be sent to the first author unless otherwise indicated.

A hundred reprints of each paper will be supplied free of charge.

The name and address of the first author should be given after the list of references.

CONTENTS

Prognostic value of sleep analysis in newborns with perinatal hypoxic brain injury *I György* ..... 1

Intrauterine growth retardation ultrasonic diagnosis: *G Pap, J Szőke, L Pap* .... 7

The D-xylose test in coeliac disease *H Bodánszky, K Horváth, G Horn* ..... 17

Renal aspects of neonatal sodium homeostasis *E Sulyok, F Varga* ..... 23

Maternal regulation of fetal growth *P Tóth, K Keszei, K Méhes* ..... 37

Evolution of serum $C_3$, IgG, IgA and IgM levels of healthy mothers and their mature newborns during the early neonatal period *G Balla, L Karmazsin* 41

Fatty acid composition of human milk and milk-based formulas in Hungary *A Gere, E A Bernolák, Ö Gaál, P Cholnoky, I Őry* ..... 53

Changes of the growth hormone level after a single small dose of somatostatin *F Péter, S Szentistványi* ..... 63

Maturation of the fetal lung I. Phosphatidic acid phosphohydrolase in the fetal and newborn rat *T Kerepesi* ..... 67

Serum ferritin level in infants and children with anaemia and malignant disease *I Ilyés, J Jezerniczky, T Tóth, S Csorba* ..... 73

The position of the diabetic child in society *L Barta, M Molnár, L Madácsy, M Barta-Bedő, A Körner* ..... 79

Clinical diagnosis of malformation syndromes: syndromatology in paediatrics *J Mücke* 85

Aetiological monitor of congenital abnormalities: A case- control surveillance system *A Czeizel, A Pázsy, J Pusztai, M Nagy* ..... 91

Book reviews ..... 101

**Index: 26.021**

FORMERLY ACTA PAEDIATRICA ACADEMIAE SCIENTIARUM HUNGARICAE

# Acta Paediatrica Hungarica

VOLUME 24, NUMBER 2, 1983



**Akadémiai Kiadó, Budapest**
ACTA PAEDIATR. HUNG. HU ISSN 0001-6527

# ACTA PAEDIATRICA

## HUNGARICA

A Quarterly of the Hungarian Academy of Sciences

Editor

P. V. VÉGHELYI

---

*Acta Paediatrica* publishes original reports of studies in paediatrics and borderline fields.

Manuscripts and editorial correspondence should be addressed to

*ACTA PAEDIATRICA*
Bókay J. u. 53.
H-1083 Budapest
Hungary

*Subscription information*

Orders should be addressed to

KULTURA Foreign Trading Company
P. O. Box 149, Budapest
H-1389

or its representatives

*Acta Paediatrica* is published in yearly volumes of four issues by

AKADÉMIAI KIADÓ

Publishing House of the Hungarian Academy of Sciences
Alkotmány u. 21.
H-1054 Budapest

*Acta Paediatrica Hungarica, 24 (2), pp. 111—118 (1983)*

# Thyrotropin and prolactin response to thyrotropin-releasing hormone in healthy and asphyxiated full-term neonates

F Ruppert, M Adonyi, T Ertl, E Sulyok, K Zámbó, I F Csaba and F Varga

Woman and Child Welfare Institute of the City Health Service of Pécs, Department of Obstetrics and Gynaecology, and Central Nuclear Laboratory of University Medical School, Pécs

To evaluate the effect of perinatal asphyxia on the pituitary response to thyrotropin-releasing hormone (TRH) in full-term newborn infants, serum thyrotropin (TSH) and prolactin (PRL) levels were measured before and 30 and 180 min after i.v. administration of 40 $\mu$g TRH. Birth weight, gestational and postnatal age were similar in the healthy (group NA) and in the asphyxiated (group A) babies. Hormone levels were determined by radioimmunoassay using commercial kits.

It was demonstrated that the basal TSH level was slightly higher and the basal PRL level significantly ($p < 0.05$) higher in group A than in group NA. In response to TRH administration in group A a marked increase in PRL occurred from 6781 $\pm$ 887 to 11 072 $\pm$ 1318 and 9636 $\pm$ 1024 mU/l at 0, 30 and 180 min, respectively. A similar response was seen in group NA; the values, however, remained significantly lower during the TRH-test. The respective PRL values at 0, 30 and 180 min were 4672 $\pm$ 411, 7945 $\pm$ 343 ($p < 0.05$) and 5963 $\pm$ 372 mU/l ($p < 0.05$).

TRH administration also resulted in a significant elevation of the serum TSH level from 6.20 $\pm$ 1.30 to 49.02 $\pm$ 7.25 ($p < 0.01$) and 18.72 $\pm$ 6.35 mU/l ($p < 0.05$) in group A, and from 3.90 $\pm$ 0.57 to 24.01 $\pm$ 3.81 ($p < 0.01$) mU/l in group NA, but in group NA the 180 min TSH value of 6.07 $\pm$ 1.25 mU/l did not differ statistically from the basal level ($p > 0.1$).

It is concluded that the pituitary PRL and TSH reserves are maintained in full-term newborn infants recovering from perinatal asphyxia whose biochemical findings are indicative of subclinical hypothyroidism.

Neonatal serum TSH undergoes a sharp rise after birth reaching the peak at 30 minutes. This is followed by a rapid decline during the first 24 h and then a much slower decrease over the next two days [6, 7]. This pituitary response appears to be stimulated by cooling the extrauterine environment. High prolactin (PRL) values have also been found in newborn infants [13, 23] and since the rise in PRL secretion is associated with a concomitant increase of serum TSH, it has been hypothesised that during the early period of life there is a TRH surge which releases both TSH and PRL [23]. Jacobsen et al. [15, 16] found that in the first week of life the relative responses of serum TSH to TRH in euthyroid full-term, preterm and small-for-gestational age newborns were equal to that of adults and older children [2, 8, 14]. More recently Delitala et al [3, 4] applying TRH stimulation tests could demonstrate an adequate neonatal PRL and

TSH reserve despite the high basal PRL and TSH values found in human neonates.

In view of the observation that hypoxia decreases thyroid function [9, 20] whereas it does not cause any significant change in the plasma PRL level in fetal sheep [19], the present study was undertaken to evaluate the basal TSH and PRL levels and their response to TRH stimulation during the early neonatal period in healthy and asphyxiated full-term neonates.

## Materials and Methods

Studies were carried out in 11 asphyxiated and 11 healthy full-term newborn infants. The asphyxiated infants (group A) had a mean birth weight of 3211 g (range, 2970–3500 g) and mean gestational age of 39.0 weeks (range, 38–40 weeks). The birth weight and gestational age of infants of the non-asphyxiated group (group NA) ranged from 2890 to 3500 g (mean, 3264 g) and from 38 to 41 weeks (mean, 39.5 weeks), respectively.

Gestational age was calculated from the mother's menstrual history and was confirmed by physical examination of the infants. All were full-term with appropriate weight for dates.

The infants were born after uncomplicated pregnancy and normal vaginal delivery.

Asphyxiated infants had a one-minute Apgar score of $\leq 6$ and mean actual pH of 7.12 (range, 7.03–7.18) requiring $O_2$ administration for several hours, but all were in a good condition during the period of investigation.

Infants of group NA had Apgar scores of more than 7 at one-minute of age and after the routine care in the delivery room they remained well during the whole neonatal period.

None of the mothers had received drug therapy known to influence thyroid function and their family history did not reveal thyroid disorders.

Determinations were performed at mean postnatal ages of 97 h and 95.2 h in groups A and NA, respectively.

In order to eliminate the possible influence of a circadian TSH and PRL rhythm, all tests were started at 9.00 a.m. while the infants were kept in thermally controlled environment.

Synthetic TRH (Hoechst GA) was administered intravenously in a dose of 40 $\mu$g. Blood samples were obtained prior to and 30 and 180 min after TRH injection. Blood was centrifuged immediately and serum stored at $-20$ °C until analysis. Serum TSH was measured by RIA using Amersham kits according to the method of Martin and Landon [18]. Serum PRL measurements were also made by RIA using commercial kits manufactured by Serono.

Informed parental consent was obtained for the study.

The results were expressed as mean $\pm$ SE and statistical evaluation was done by using Student's $t$-test. When necessary the coefficient of correlation and the equation of regression were also calculated.

## Results

Clinical data and the results of TRH-test in infants with and without perinatal asphyxia are given in detail in Tables I and II.

Changes in mean serum TSH and PRL levels in response to TRH administration are shown in Fig. 1 *(a, b)*. It can be seen that the basal TSH level was slightly higher and the basal PRL level significantly ($p < 0.05$) higher in group A than in group NA. In response to TRH administration in group A a marked increase occurred in PRL from 6781 $\pm$ 887 to 11072 $\pm$ $\pm$ 1318 and 9636 $\pm$ 1024 mU/l at 0, 30 and 180 min respectively. A similar response was seen in infants of group NA, the values, however, remained significantly lower during the TRH-test. The respective PRL values at 0, 30 and 180 min were 4672 $\pm$ 411, 7945 $\pm$ 343 ($p < 0.05$) and 5963 $\pm$ $\pm$ 372 mU/l ($p < 0.05$), respectively.

TABLE I

Clinical data and the results of TRH-test in infants with perinatal asphyxia

| No. | Sex | Gestational age weeks | Birth weight g | Postnatal age h | Apgar score | | TRH-test | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Se-PRL, mU/l | | | Se-TSH, mU/l | | |
| | | | | | 1 | 5 | 0 | 30 | 180 | 0 | 30 | 180 |
| | | | | | min | | min | | | | | |
| 1 | M | 39 | 3 450 | 96 | 3 | 9 | 9 200 | 16 000 | 9 200 | 9.2 | 46.8 | 11.9 |
| 2 | M | 38 | 2 970 | 88 | 1 | 9 | 10 600 | 16 800 | 12 200 | 4.2 | 13.4 | 4.6 |
| 3 | M | 38 | 3 250 | 98 | 4 | 9 | 9 800 | 12 800 | 14 000 | 3.4 | 58.0 | 70.0 |
| 4 | F | 38 | 3 290 | 108 | 5 | 8 | 11 000 | 16 800 | 16 200 | 5.2 | 64.0 | 12.0 |
| 5 | F | 40 | 3 330 | 90 | 6 | 9 | 4 000 | 13 200 | 10 600 | 4.8 | 70.4 | 12.0 |
| 6 | F | 39 | 3 500 | 87 | 6 | 8 | 6 800 | 7 800 | 7 800 | 3.1 | 20.0 | 6.1 |
| 7 | F | 38 | 3 120 | 91 | 1 | 9 | 2 800 | 6 000 | 6 000 | 7.6 | 42.1 | 5.2 |
| 8 | F | 40 | 3 150 | 103 | 6 | 9 | 6 000 | 7 400 | 7 000 | 18.0 | 62.0 | 46.0 |
| 9 | F | 40 | 3 030 | 107 | 4 | 8 | 6 000 | 7 000 | 6 800 | 4.6 | 74.0 | 22.0 |
| 10 | M | 39 | 2 980 | 95 | 3 | 9 | 4 800 | 6 000 | 6 000 | 4.4 | 76.0 | 12.0 |
| 11 | M | 40 | 3 260 | 104 | 3 | 9 | 3 600 | 12 000 | 10 200 | 3.8 | 12.6 | 4.1 |

TABLE II

Clinical data and the results of TRH-test in infants without perinatal asphyxia

| No. | Sex | Gestational age weeks | Birth weight g | Postnatal age h | Apgar score | | TRH-test | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Se-PRL, mU/l | | | Se-TSH, mU/l | | |
| | | | | | 1 | 5 | 0 | 30 | 180 | 0 | 30 | 180 |
| | | | | | min | | min | | | | | |
| 1 | M | 40 | 3 170 | 96 | 9 | 10 | 3 600 | 7 800 | 4 400 | 3.6 | 17.4 | 7.2 |
| 2 | M | 41 | 3 300 | 84 | 9 | 10 | 3 600 | 7 200 | 5 000 | 8.4 | 50.2 | 11.6 |
| 3 | F | 40 | 3 500 | 86 | 9 | 10 | 6 800 | 8 800 | 7 000 | 4.8 | 40.0 | 9.2 |
| 4 | F | 40 | 3 160 | 98 | 9 | 10 | 3 200 | 6 200 | 4 600 | 2.4 | 24.0 | 7.4 |
| 5 | F | 40 | 3 130 | 108 | 9 | 10 | 6 000 | 9 200 | 5 400 | 4.2 | 36.0 | 10.5 |
| 6 | F | 39 | 3 500 | 90 | 9 | 10 | 4 400 | 8 800 | 8 000 | 3.2 | 15.4 | 2.2 |
| 7 | M | 40 | 3 470 | 88 | 9 | 10 | 3 200 | 7 200 | 4 600 | 1.8 | 24.0 | 1.8 |
| 8 | F | 38 | 2 890 | 90 | 9 | 10 | 4 400 | 7 800 | 6 600 | 3.6 | 16.0 | 2.4 |
| 9 | F | 40 | 3 140 | 98 | 9 | 10 | 6 000 | 7 600 | 6 800 | 4.1 | 12.0 | 11.0 |
| 10 | M | 39 | 3 270 | 104 | 9 | 10 | 3 800 | 6 800 | 6 200 | 1.5 | 16.5 | 2.0 |
| 11 | M | 38 | 3 380 | 106 | 9 | 10 | 6 400 | 10 000 | 7 000 | 5.4 | 12.7 | 1.5 |

TRH administration also resulted in a significant elevation of serum TSH level from 6.20 ± 1.30 to 49.02± ± 7.25 ($p < 0.01$) and 18.72 ± 6.35 mU/l ($p < 0.05$) in group A, and from 3.90 ± 0.57 to 24.01 ± 3.81 mU/l ($p < 0.01$) in group NA, but in group NA the 180 min TSH value of 6.07 ± 1.25 mU/l did not differ statistically from the basal level ($p < 0.1$).

Figure 2*a* demonstrates a significant positive relationship of TSH to PRL during TRH stimulation test ($r = 0.52$ $p < 0.01$) indicating that the common hypothalamic control mechanism was functioning in healthy neonates.

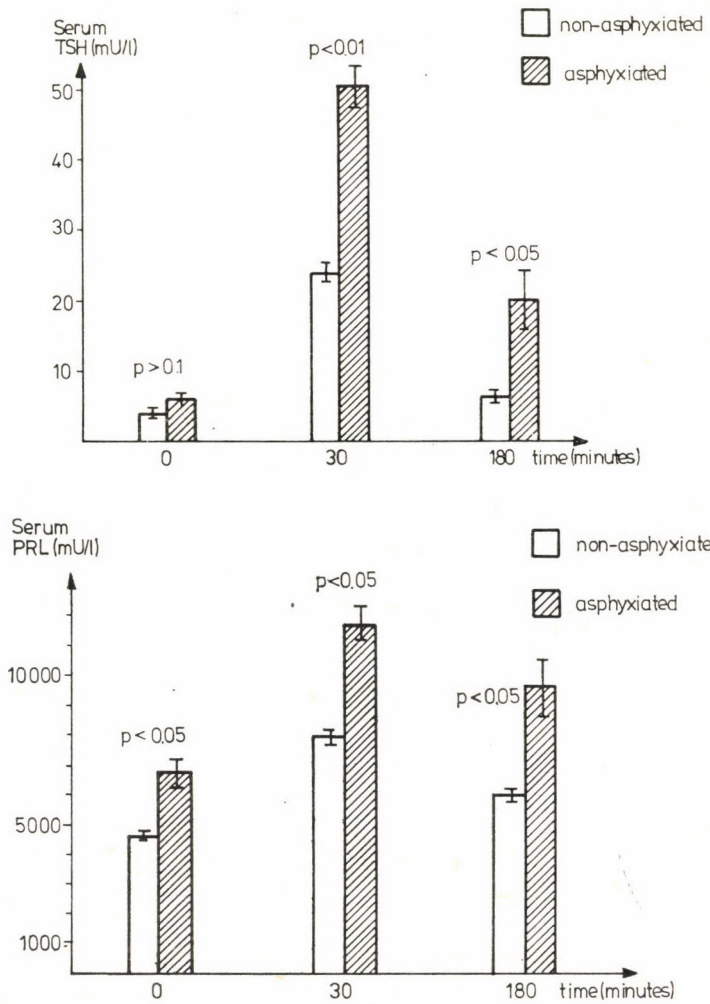



FIG. 1. Serum PRL *(a)* and TSH *(b)* response to TRH administration in healthy and asphyxiated full-term newborn infants

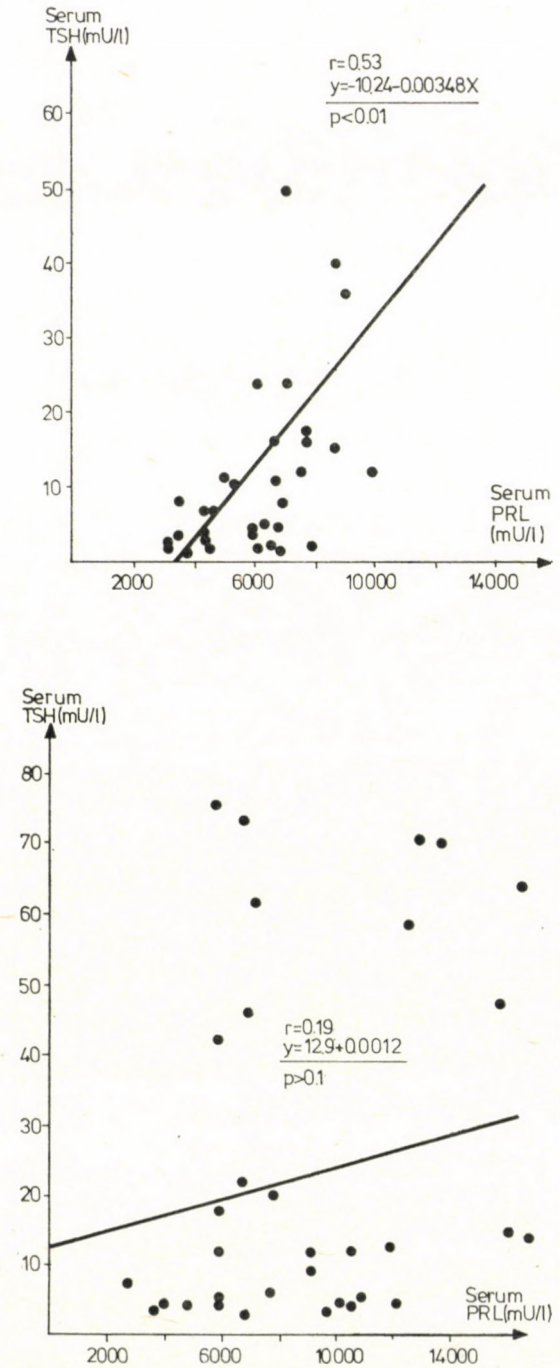



FIG. 2. Relationship between serum TSH and PRL during TRH stimulation test in healthy and asphyxiated full-term newborn infants

In asphyxiated newborn infants this relationship could not be seen (Fig. 2*b*). This finding may be interpreted as showing that perinatal hypoxia modulates differently the pituitary TSH and PRL secretion in response to TRH.

## Discussion

The present results are in good agreement with the previous finding of normal pituitary reserves of TSH and PRL in human newborn infants [4, 11, 15, 16].

Prior to TRH administration the basal values of TSH did not differ in the asphyxiated neonates from those in healthy infants. Few data are available as to the influence of hypoxia on TSH secretion. Moshang et al [20] reported low serum TSH and normal $T_3$ and $T_4$ levels in children with acute hypoxia and a slightly elevated TSH and significantly depressed $T_3$ and $T_4$ levels in those with chronic hypoxia. These findings have been regarded to indicate the adaptation of the hypothalamic-pituitary-thyroid axis to hypoxia in order to increase the resistance to hypoxia by the hypothyroid state [9, 26].

Similarly, a transient elevation of TSH and a significant decrease of the thyroxine level were observed in newborn infants with respiratory distress syndrome [21, 24]. It is reasonable to speculate that the impaired thyroid function associated with hypoxaemia may be a defence mechanism to decrease the metabolic rate and oxygen consumption in newborn infants whose oxygenization is compromised [17].

Jacobsen et al [15] also reported higher TSH levels in asphyxiated neonates but those infants were delivered by Caesarean section and it is difficult to say whether it was the surgical delivery itself or the underlying conditions that contributed to the rise of serum TSH [5].

Neonatal TRH challenge tests were performed by Jacobson et al [15, 16] and by Delitala et al [4]. Their results are in agreement with the present ones in that in healthy newborns the relative TSH response to TRH was equal to that of adults in spite of the elevated basal TSH concentration.

A further important point in our study was the demonstration of elevated serum PRL in newborn infants, in particular in those who had recovered from perinatal asphyxia.

The clinical significance of the high serum PRL is not completely understood [1, 13, 23]. The findings presented by Smith et al [25] and Gluckmann et al [10] seem to indicate that PRL may contribute to maturation of the fetal lung by demonstrating a significantly lower cord PRL concentration in premature infants who developed respiratory distress syndrome than in those who did not suffer from RDS. Furthermore, Grosso et al [12] found higher PRL levels in infants delivered by pre-eclamptic women than in those delivered by normotensive women, suggesting that chronic fetal distress associated with

pre-eclampsia may induce increased fetal PRL production.

PRL is generally regarded as a stress hormone [22, 23] and its high values in the immediate neonatal period may be considered a non-specific pituitary response to labour and delivery as a stress. Perinatal asphyxia means a further stress and may account for the significantly higher PRL levels found in asphyxiated neonates.

In response to TRH stimulation the PRL response was unaltered in spite of the high base-line level. This observation indicates that perinatal asphyxia does not impair the pituitary PRL reserves.

## References


1. Aubert, ML, Grumbach, MM, Kaplan SL: Ontogenesis of human fetal hormones. III Prolactin. J Clin Invest 56: 155, 1975
2. Costom BH, Grumbach MM, Kaplan SL: Effect of thyrotropin-releasing factor on serum thyroid-stimulating hormone. J Clin Invest 90:2219, 1971
3. Delitala G, Meloni T, Masala A, Alagna S, Devilla L, Corti C: Dynamic evaluation of prolactin secretion during the early hours of life in human newborns. J Clin Endocrinol Metab 46:880, 1978
4. Delitala G, Meloni T, Masala A, Corti R: Thyrotropin, prolactin and growth hormone response to synthetic thyrotropin-releasing hormone in newborn infants. Biol Neonate 33:236, 1978
5. Engberg S, Gustavson K-H, Jacobson L, Söderström R: Elevation of TSH during the early neonatal period. J Pediatr 93:1030, 1978
6. Fisher DA, Dussault JH, Sack J, Chopra IJ: Ontogenesis of hypothalamic pituitary thyroid function and metabolism in man, sheep and rats. Recent Prog Horm Res 33:59, 1977
7. Fisher DA, Odell WD: Acute release of thyrotropin in the newborn. J Clin Invest 48:1670, 1969
8. Foley TP, Jacobs LS, Hoffmann W, Daughaday WH, Blizzard RM: Human prolactin and thyrotropin concentrations in the serums of normal and hypopituitary children before and after administration of synthetic thyrotropin-releasing hormones. J Clin Invest 51: 2143, 1972
9. Galton VA: Some effects of altitude on thyroid function. Endocrinology 91: 1393, 1972
10. Gluckman PD, Ballard PL, Kaplan SL, Liggins GC, Grumbach MM: Prolactin in umbilical cord blood and the respiratory distress syndrome. J Pediatr 93: 1011, 1978
11. Greenberg AH, Czernichow P, Reba RC, Tyson J, Blizzard RM: Observations on the maturation of thyroid function in early fetal life. J Clin Invest 49:1790, 1970
12. Grosso DS, MacDonald CP, Thomasson JE, Christian CD: Relationship of newborn serum prolactin levels to the respiratory distress syndrome and maternal hypertension. Am J Obstet Gynecol 137:569, 1980
13. Gujda HJ, Friesen HG: Serum prolactin levels in humans from birth to adult life. Pediatr Res 7:534, 1973
14. Hiba J, Del Pozo P, Gennazzoni A, Pusterla F, Dancranjan I, Sidiropulos D, Gunti J: Hormonal mechanism of milk secretion in the newborn. J Clin Endocrinol Metab 44:973, 1977
15. Jacobsen BB, Andersen HJ, Dige-Petersen H, Hummer L: Thyrotropin response to thyrotropin-releasing hormone in full-term, euthyroid and hypothyroid newborns. Acta Paediatr Scand 65:433, 1976
16. Jacobsen BB, Andersen HJ, Dige-Petersen H, Hummer L: Pituitary-thyroid responsiveness to thyrotropin-releasing hormone in preterm and small-for-gestational age newborns. Acta Peadiatr Scand 66:541, 1977
17. Klein AH, Foley B, Kenny FM, Fisher DA: Thyroid hormone and thyrotropin responses to parturition in premature infants with and without the respiratory distress syndrome. Pediatrics 63: 380, 1979
18. Martin MJ, Landon J: The use of a ammonium sulphate and dextran together with second antibody at the separation stage in radioimmunoassay. In: Radioimmunoassay in Clinical Biochemistry, ed. Pasternak CA, Heyden and Son Ltd., London 1975, p. 269
19. McMillen IC, Jenkin G, Robinson JS, Kingston EJ, Thorburn GD: Prolactin concentrations in fetal and neonatal sheep: effect of TRH, hypoxia and

chlorpromazine. J Endocrinol 75:548, 1977
20. Moshang ThJr, Change KH, Kaplan MM, Utiger RD, Takahashi O: Effects of hypoxia on thyroid function test. J Pediatr 97:602, 1980
21. Nivelon J-L, Tenenbaum D, Sandre D, Dauvergne M, Touzery Cl, Pelletier J-P: Détresse respiratoire et fonction thyroidienne du nouveau-né. Pediatrie 34:473, 1979
22. Noel GL, Suh HD, Stone J, Frantz AG: Human prolactin and growth hormone release during surgery and other conditions of stress. J Clin Endocrinol Metab 35:340, 1972
23. Sack J, Fisher DA, Wang CC: Serum thyrotropin, prolactin and growth hormone levels during the early neonatal period in the human infant. J Pediatr 89:298, 1976
24. Schönberger W, Grimm W, Gempp W, Dinkel E: Transient hypothyroidism associated with prematurity, sepsis and respiratory distress. Eur J Pediatr 132: 85, 1979
25. Smith YF, Mulon DK, Hamosh M, Scanlon JW, Hamosh P: Serum prolactin and respiratory distress syndrome in the newborn. Pediatr Res 14:93, 1980
26. Zarrow MX, Hiestand WA, Stemler FW, Wiebers SE: Comparison of effects of experimental hyperthyroidism and hypothyroidism on resistance to anoxia in rats and mice. Am J Physiol 167: 171, 1951

*Received May 7, 1982*

F Ruppert MD
Munkácsy u. 19
H-7621 Pécs, Hungary

*Acta Paediatrica Hungarica, 24 (2), pp. 119–130 (1983)*

# Accidents in schoolchildren: epidemiologic, aetiologic and prognostic considerations

M Sillanpää,[1] P Terho,[2] Helena Westerén[2] and Harriet Pisirici[1]

[1]Department of Public Health, University of Turku, and
[2]Turku City Health Department, Turku, Finland

A prospective follow-up study of school accidents occurring to 21 712 city pupils and to 1584 rural pupils aged 7–18 years during the school year 1977–78 was carried out. The facilities of the pupils to be referred to the school policlinics were practically as good to all pupils. The incidence of accidents was in Turku 363 per 1000 pupils aged 7–12 years and 233 per 1000 pupils aged 13–18 years. Minor injuries were in 84.2% of cases located in the extremities. In the great majority, they were slight sprains and strains (46.9%) or cutaneous lacerations and bruises (40.0%). More severe injuries were found in 4.9% among the Turku pupils and in 2.1% of those in Lieto. The accidents met by boys was almost double that found for girls. Individual exercise and sports turned out to involve approximately the same degree of risk as team sports. The site of injury was most commonly either the upper extremity (38%), lower extremity (28%), the head (22%) or the eyes (4%), the remaining 8% of injuries having been to the trunk. More than two thirds of the cases could be treated in two or three visits to nurse or doctor, the treatment period being two to seven days in the majority of cases. No delayed effects such as postconcussive headache or other psychosomatic symptoms occurred during the follow-up period of three years.

The World Health Organization has devoted particular attention to accidents occurring to children for some time, and to their prevention. Finland ranks among the first countries worldwide in the frequency of high accident mortality to both preschool and school-age children [17], even though a slight decreasing trend may now be found. In the case of the latter, accidents cause fairly frequent absences from school and form a considerable part of the school physician's and the school nurse's daily work [1, 11]. In spite of this, there has been little research on accidents to children at school.

Reliable information on the accidents occurring to children is needed to allow to find out the causes of school accidents and develop preventive methods and first aid readiness. The purpose of the present study is to study the school accidents occurring during the school year 1977–78 to pupils aged 7 to 18 years, attending the primary and secondary schools in two municipalities in southwestern Finland, i.e. in the city of Turku and the adjoining rural municipality of Lieto. In addition to the incidence and character of the accidents, the study is concerned with the effect of these accidents on the

pupils' schoolwork (absences), and with the possibly resulting permanent disabilities.

## Study population

The city of Turku has about 165 000 inhabitants, somewhat over one-third of whom live in the inner city. Part of the area administratively incorporated in the city is rural-like, with small population centres. In the school year 1977–78, Turku had 39 primary schools (for pupils aged 7 to 12 years), 14 lower secondary schools (age groups 13 to 15) and 11 upper secondary schools (age groups 16 to 18). The lower and upper secondary schools usually operate in the same building, forming an integrated administrative unit. There were a total of 54 school buildings. The pupils attending these schools totalled 21 712, girls accounting for 10 912 and boys for 10 800.

The rural municipality of Lieto (approx. 9500 inhabitants), a typical municipality in rural southwestern Finland, had in that year a total of eight schools: primary education was provided by seven and lower and upper secondary education by one. These schools had a total of 1584 pupils, or 778 girls and 816 boys.

The distribution of the pupils among the different types of school in the two municipalities is shown in Table 1.

The pupils' accidents were recorded in the autumn term, which started on August 15 and ended on December 20, 1977, and in the spring term, from January 5 to May 31, 1978. In February the pupils had one week winter vacation. School was from Monday to Friday, only exceptionally on Saturdays.

## Methods

"School accidents" refer here to all injuries incurred by the pupils during the two terms on the way to or from school, during lessons or during recesses. The study was prospective in nature, with regard to both the primary data and the following three-year follow-up. For the purposes of data collection a questionnaire was drawn

Table I

Distribution of pupils by type of school in the city of Turku and the rural municipality of Lieto

| Type of school | Girls | | Boys | | Both | |
|---|---|---|---|---|---|---|
| | Turku | Lieto | Turku | Lieto | Turku | Lieto |
| Primary school (age groups 7–12) | 5 755 | 393 | 6 253 | 470 | 12 008 | 863 |
| Lower secondary school (age groups 13–15) | 3 555 | 272 | 3 315 | 259 | 6 870 | 531 |
| Upper secondary school (age groups 16–18) | 1 602 | 113 | 1 232 | 87 | 2 834 | 190 |
| Total | 10 920 | 778 | 10 800 | 816 | 21 712 | 1 584 |

up which, in addition to demographic data, recorded in detail the place and time of the accident and other data related to the event. The effects of the accident, the location of the injury, the treatment provided for it and its permanent consequences were also recorded. In cases of accident, the victim was first sent to the school nurse, who filled in this questionnaire. If a medical examination was considered necessary, the pupil was referred to the school physician, who completed the questionnaire and provided the treatment. If the school physician considered that adequate treatment was not possible in the school policlinic, the patient was sent to a hospital outpatient department.

Each school in both Turku and Lieto has its own school nurse; in large and medium-sized schools she sees pupils on a daily basis at that school, while in small schools she is available two to four times a week. If the accident occurs at the time when the nurse is not available, the teacher has the right and the duty to send the pupil to the school policlinic. A taxi for instance may be used as needed. The distance of the school from the school policlinic and the physician has thus proved in practice to be insignificant as a factor affecting the rate of referral to the policlinic. The impression of these school physicians in both Turku and Lieto, according to their own report, is that the pupils of the small schools are sent to the school policlinic even more readily on those days on which the school nurse has no consulting hours than on other days.

On the basis of the treatment required, the injuries were classified into two categories: injuries which required examination and treatment by a physician, and minor injuries, regarded by the school nurse as needing no further care. Minor injuries were recorded only for the pupils in the city of Turku.

## Results

Over the school year the 21 712 pupils in the Turku schools suffered a total of 6603 accidents. If the accidents had been evenly distributed, they would have occurred to not quite one in three (30.4%) of the pupils. The incidence of accidents among the 7–12-year old children in the primary schools (363 per 1000 pupils) was, however, considerably higher than that among the 13–18-year old pupils of the secondary schools (233 per 1000 pupils).

Treatment was provided by the school nurse in 84% of all the accidents met by the Turku schoolchildren, by the school physician in 13% and in the hospital in 3% of cases. The school accidents in Lieto, totalling 35, were treated by the school physician in 88% of cases, by a private practitioner in 6% and in the hospital likewise in 6% of cases.

*Minor injuries* were by far most commonly located in the extremities: almost one-half (46.0%) were in the upper extremities and a somewhat lower percentage (38.2%) in the lower extremities. The rest of the injuries were in the head (8.9%), in the eyes (2.9%) or on the trunk (4.0%). The great majority of the minor injuries were either slight sprains and strains (46.9%) or cutaneous lacerations and bruises (40.0%). Minor injuries in the head occurred in 12.4% of the subjects and the rest were mainly concussion injuries to the trunk or extremities.

The school nurses treated minor injuries in the first-aid facilities of the schools. These injuries interfered very little with schoolwork, only seldom causing at most a 1–2-day absence from school.

*More severe injuries.* Injuries referred to a school physician occurred in 1059 pupils in Turku and in 35 in Lieto. The accident incidence among the Turku pupils (4.9%) was more

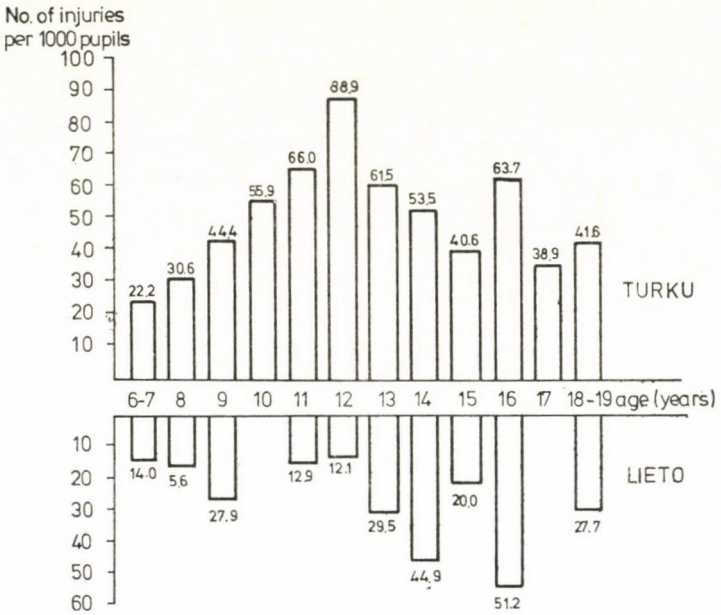

No. of injuries
per 1000 pupils
100
90
80
70
60
50
40
30
20
10
22.2
30.6
44.4
55.9
66.0
88.9
61.5
53.5
40.6
63.7
38.9
41.6
TURKU
6-7
8
9
10
11
12
13
14
15
16
17
18-19 age (years)
10
20
30
40
50
60
14.0
5.6
27.9
12.9
12.1
29.5
44.9
20.0
51.2
27.7
LIETO

FIG. 1

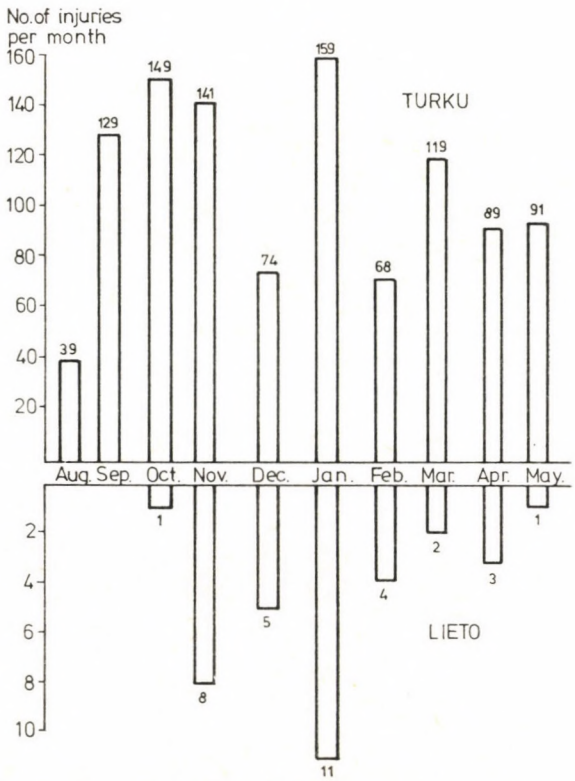

No.of injuries
per month
160
140
120
100
80
60
40
20
39
129
149
141
74
159
68
119
89
91
TURKU
Aug.
Sep.
Oct.
Nov.
Dec.
Jan.
Feb.
Mar.
Apr.
May.
2
4
6
8
10
1
8
5
11
4
2
3
1
LIETO

FIG. 2

than double that found in Lieto (2.1%).

In Turku these injuries were somewhat less frequent in the primary-school children, aged 7–12 (42 per 1000 pupils), than in the secondary-school pupils aged 13–18 (57 per 1000 pupils). The distribution of accidents by age in the Turku and Lieto pupils is shown in Figure 1. In Turku the peak occurred in the 12-year-old group, while in Lieto the frequency was highest in the group aged 16.

In Turku the frequency of accidents met by boys was almost double (60 per 1000 boys) that found for girls (37 per 1000 girls). A similar relationship was recorded also in Lieto (27 per 1000 and 17 per 1000, respectively).

Figure 2 shows that accidents happened most commonly in October and November and from January through March. The accident risk was somewhat higher on the first few days of the week (Table II). Most accidents happened between 9 a.m. and 2 p.m., at which time the majority of pupils were simultaneously at school (Figure 3).

TABLE II

Incidence of accidents by day of week

| Location | Mon | Tue | Wed | Thu | Fri |
|---|---|---|---|---|---|
| Turku | 212 | 231 | 227 | 202 | 172 |
| Lieto | 14 | 5 | 2 | 7 | 7 |
| Total | 226 | 236 | 229 | 209 | 179 |

Table III shows the situations in which the accidents occurred. They were most common during classes, particularly during physical education classes. In the Turku schools, individual exercise and sports (209

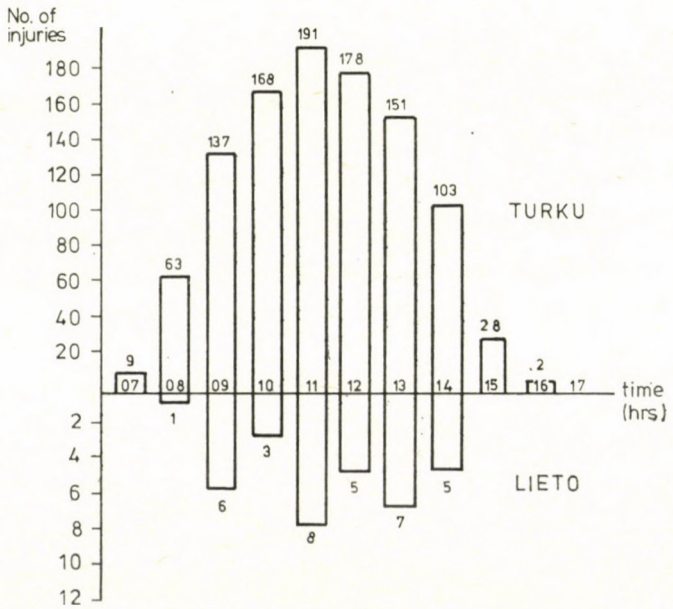



FIG. 3

TABLE III

Situation in which the school accident occurred

| Situation | | | Turku | | Lieto | |
|---|---|---|---|---|---|---|
| | | | No. | Per cent | No. | Per cent |
| On the way to or from school | | | 103 | 9.7 | 0 | |
| Classes | | | 526 | 49.8 | 22 | 62.9 |
| — physical education | | 431 | | | 18 | |
| — gymnastics | 97 | | | | 4 | |
| — basketball | 87 | | | | 4 | |
| — track and field | 59 | | | | 3 | |
| — skating | 50 | | | | 0 | |
| — football | 42 | | | | 0 | |
| — icehockey | 21 | | | | 5 | |
| — other game | 72 | | | | 2 | |
| — skiing | 3 | | | | 0 | |
| — manual training | | 51 | | | 2 | |
| — other classes | | 44 | | | 2 | |
| Recess | | | 428 | 40.5 | 13 | 37.1 |
| — school yard | | 233 | | | 6 | |
| — stairs | | 75 | | | 4 | |
| — other place | | 120 | | | 3 | |
| Total | | | 1057 | 100.0 | 35 | 100.0 |

TABLE IV

Nature of injuries according to sex in Turku schools

| Injury | Girls | | Boys | | Both | |
|---|---|---|---|---|---|---|
| | No. | Per cent | No. | Per cent | No. | Per cent |
| Sprain or strain | 210 | 53 | 253 | 39 | 463 | 44 |
| Concussion injury to head | 63 | 16 | 95 | 14 | 158 | 15 |
| Fracture, rupture | 55 | 14 | 79 | 12 | 134 | 13 |
| Wound | 29 | 7 | 149 | 23 | 178 | 17 |
| Cutaneous laceration, bruise | 25 | 6 | 39 | 6 | 64 | 6 |
| Foreign body | 11 | 3 | 17 | 3 | 28 | 3 |
| Other injury | 6 | 1 | 21 | 3 | 27 | 2 |
| Total | 399 | 100 | 653 | 100 | 1052 | 100 |

TABLE V

Main treatment method of injuries

| Treatment method | Turku | | Lieto | |
|---|---|---|---|---|
| | No. | Per cent | No. | Per cent |
| Elastic bandage/Tensoplast | 268 | 26 | 10 | 29 |
| Splinting | 252 | 24 | 8 | 23 |
| Bed rest | 160 | 15 | 5 | 14 |
| Bandaging of the wound | 91 | 9 | 3 | 8 |
| Suturing of the wound | 89 | 8 | 6 | 17 |
| Medication | 59 | 6 | 0 | |
| Plaster cast | 46 | 4 | 1 | 3 |
| Other treatment | 28 | 3 | 1 | 3 |
| No treatment | 54 | 5 | 1 | 3 |
| Total | 1047 | 100 | 35 | 100 |

accidents) turned out to involve approximately the same degree of risk as team sports (222 accidents). In Lieto the corresponding figures were 7 and 11. During recess the school yard was naturally the most common scene of accidents.

The site of injury was most commonly either the upper extremity (38%) or the lower extremity (28%); these injuries, together with those to the head (22%) and the eyes (4%), accounting for over 90% of all accidents. The rest consisted of injuries to the trunk (8%).

There was some variation in the nature of the injury in the two sexes (Table IV). Sprains and strains were common injuries in girls, occurring in over half (53%) of cases for girls compared to only 39% for boys. Another clear difference was in the occurrence of various types of wounds, which were more than three times as common in boys (23%) as in girls (7%).

The methods of treatment (Table V) naturally depended on the nature of the injury; elastic bandage or splinting were thus the main method of treatment in every second case. In one case out of seven, bed rest formed sufficient treatment. Half of the wounds were treated by bandaging; medication, suturing and plaster casts were seldom necessary.

TABLE VI

Number of examination and treatment visits in individual accidents

| No. of visits | Cases | |
|---|---|---|
| | No. | Per cent |
| 1 | 227 | 23 |
| 2 | 478 | 48 |
| 3 | 178 | 18 |
| 4—12 | 113 | 11 |
| Total | 996 | 100 |

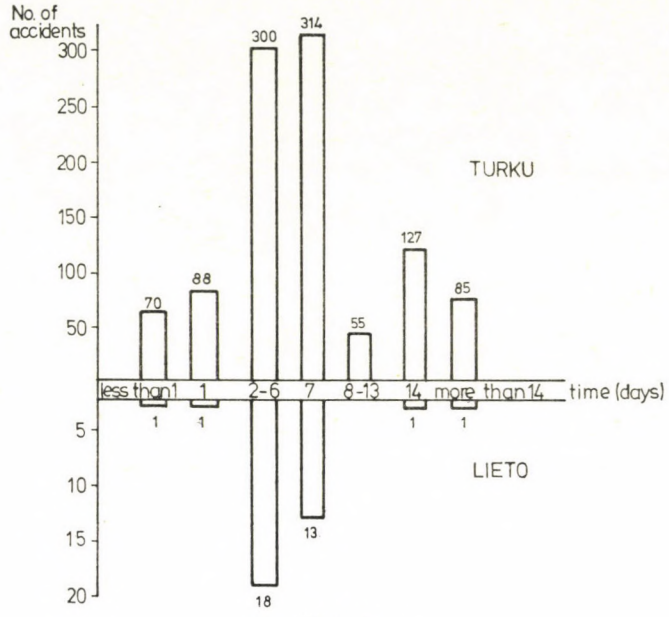

No. of accidents
300
250
200
150
100
50
5
10
15
20
70
88
300
314
55
127
85
1
1
18
13
1
1
TURKU
LIETO
less than 1
1
2-6
7
8-13
14
more than 14
time (days)

FIG. 4

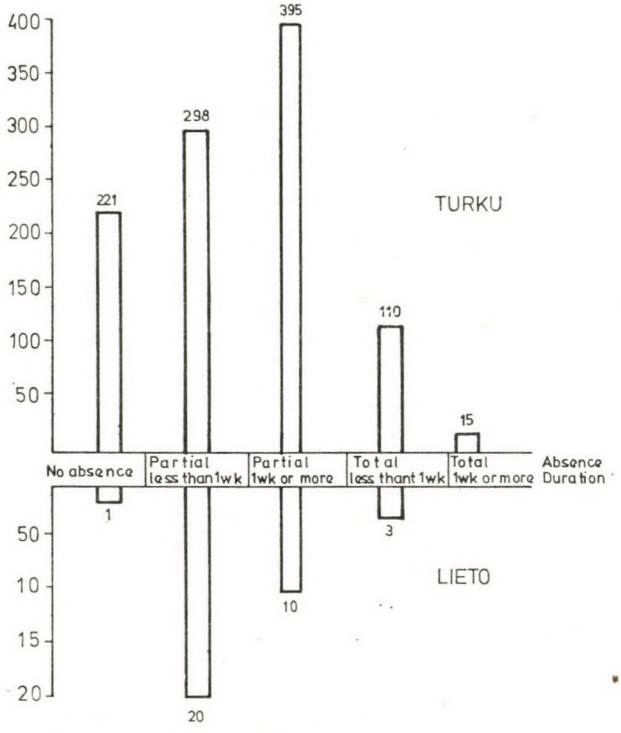

400
350
300
250
200
150
100
50
50
10
15
20
221
298
395
110
15
1
20
10
3
TURKU
LIETO
No absence
Partial less than 1wk
Partial 1wk or more
Total less than 1wk
Total 1wk or more
Absence Duration

FIG. 5

One or two treatment visits were enough for over two thirds of the Turku schoolchildren; one out of five needed three visits and one out of ten four or more visits (Table VI). The duration of the treatment period was, however, in the great majority of cases two to seven days in both Turku and Lieto (Fig. 4). Treatment periods of over two weeks' duration, on the other hand, were rare, accounting for less than 10% of cases in both Turku and Lieto. The effect on schoolwork (Figure 5) was slight; in only 12% of cases in Turku and 3% in Lieto did schoolwork have to be interrupted entirely for more than one day, while 21% of the former and 3% of the latter suffered no interruption.

The injuries almost always healed in a couple of weeks, with a few exceptions in which treatment lasted two to three months. No fatal accidents occurred during the school year, nor were any permanent disabilities or defects incurred. There were also no delayed effects such as postconcussive headache or other psychosomatic symptoms found during the three-year follow-up.

## Discussion and Conclusions

Due to their common occurrence, accidents in children have been studied in recent years fairly extensively, and from various points of view. The research has concerned the accident incidence rates and factors affecting them [6–9], accident recurrence in certain children [10] and, in particular, the possibilities of accident prevention [2,3,5]. Only rarely has attention been paid to school-related accidents [4, 6]. The school years, however, include a certain period during which the child is not yet able to cope with traffic as well as an adult; he also lives through puberty and learns to identify himself and others both as individuals and as a member of a group. Accident-proneness is known to be related, among other factors, to the social environment [7], and the school presumably plays its own role in this respect.

The total accident frequency of 30.4% found in the present study corresponds closely to the total frequency of 34.0% obtained for school pupils in Helsinki in the same school year 1977–78 [14]. Both figures may be below average, since the winter of 1977-78 was milder than usual in Finland, and winter sports activity in the schools, as well as injuries caused by such sports, were therefore less common than normally. This assumption, on the other hand, conflicts with the low school accident frequency of 2.9% obtained for schoolchildren who were referred to a physician in Helsinki during the winter of 1967–68, with plenty of snow, as compared to the almost equally low frequency of 3.0% obtained in the same city in the winter of 1968–69, in which there was a normal amount of snow, and with the relatively low frequency of accidents in the winter months compared to the other months in Helsinki [12], where the criteria of remittance were similar to the present study. In the

latter too, from January to March, accidents were frequent.

Since accidents requiring medical examination affect the child's shoolwork much more than do the slight scratches and strains treated by the school nurse, attention was paid mainly to the injuries of those children who were referred to the school policlinic. These occurred in the present study in 4.9% of the pupils in Turku and in 2.1% of those in the rural municipality of Lieto.

Although the differences between individual schools were not studied in greater detail, attention was nevertheless drawn to the lower accident frequency for small schools. Variations in this frequency have been studied previously e.g. in Helsinki schools; in a study of inner-city schools in the school year 1966–67, for instance, it was found to be 3.7% in schools with over 1000 pupils and 3.0% in schools with fewer than 1000 pupils. In the suburbs of Helsinki the corresponding figures were 2.7% and 2.6%; accident frequencies are thus evidently lower in smaller communities [15]. Both the smaller size of the schools and the rural-like environment probably provide an explanation for the low frequency in the Lieto school as well.

According to both the present study and previous reports [4, 14, 16], the ratio of accidents between boys and girls appears to be 1.5 to 1, and they are evidently more common in prepuberty than at an earlier age.

According to the present results, the accident risk is somewhat higher on the first few days of the week, a finding which is consistent with the figures for the schools in the city of Helsinki [13].

Half of the accidents in Turku (49.8%) occurred during lessons, somewhat over one third (40.5%) during recess and the rest (9.7%) on the way to or from school. In Lieto the traffic was evidently safer, since not a single accident happened there on the way to school. Recesses were likewise more tranquil than in Turku; 37.1% of the accidents occurred during recess and 62.9% during lessons. When compared to the Helsinki schools, 32.0–39.4% of the accidents met by the Helsinki school pupils in the school years 1962–74 occurred during lessons, 53.5–60.0% during recesses and 7.1–9.4% on the way to or from school [12–15]. Thus in approximately 10% of cases the accident occurs when the child is on his way to school or returning home. In the study carried out by Thiele et al [16] the figure was as high as 15.4%.

Among the different school subjects, physical education is well known to involve a higher accident risk than other subjects. In the present study 40.8% of all accidents met by Turku pupils occurred during physical education classes. In Helsinki in the school years 1976–79 such accidents accounted for 35–47% of all accidents. Thiele et al [16] reported similarly that 43.1% of all accidents had occurred in connection with school sports. It is interesting to note that in the present study accidents occurred almost as frequently in connec-

tion with individual exercise or sports (19.8%) as with team sports (21.0%). The quantitative ratio of the two modes, however, could not be worked out in the study.

During recess, injuries are incurred most commonly in the school yard; in the present study 22.0% of the injuries in Turku and 17.1% of those in Lieto occurred there. In the same school year, 28% of all injuries of the school pupils in the city of Helsinki were incurred in school yards. The figure is somewhat higher than that found in the present study and is probably mainly a reflection of the greater prevalence of violence in the Helsinki schools compared to Turku and Lieto. Such violence is also referred to by Thiele et al [16]; in their study 39.2% of injuries were incurred during recess. School violence is not, however, something new, as 42.3–47.3% of the injuries in the Helsinki schools in the school years 1962–74 were incurred in school yards. School yards which are too small or which involve unsuitable structural factors may contribute to the incidence of these injuries. These factors were not, however, dealt with in the present study.

In the great majority of cases the injury was a bruise, strain, sprain, open wound or fracture. Injuries to the eyes, for instance, occurred in a few per cent of cases [14].

The accidents necessitated one or two treatment visits in approximately 70% of cases and more than two in the others. The number of visits is thus relatively low; yet the injuries caused considerable absences from school. These were, however, often partial, for instance release from physical education or manual training. Twelve per cent of the pupils in Turku and 3% of those in Lieto had to stay at home for at least one week.

The injuries were mild in so far as no deaths or permanent disabilities resulted. Out of the approximately 63,000 pupils in Helsinki in the school year 1977–78 one died through a school accident and several had to be hospitalized for a few weeks or undergo surgical procedures. Against this background too the injuries can be considered mild.

## References


1. Arsdell WR van, Roghmann KJ, Nader PR: Visits to an elementary school nurse. J Sch Health 42:142, 1972
2. Baker SP: Prevention of childhood injuries. Med J Aust 1:466, 1980
3. Berfenstam R: Prevention of childhood accidents in Sweden. With special attention to the work of the joint committee for prevention of accidents. Acta Paediatr Scand [Suppl] 275:88, 1979
4. Bojlén K: Skader i skolen. Skolhygien Tidskr 50:113, 1962
5. Christiansson G: Barnolycksfall — att förebygga och behandla. (Childhood accidents — prevention and treatment.) Studentlitteratur, Lund 1980
6. Gratz RR: Accidental injury in childhood: a literature review on pediatric trauma. J Trauma 19:551, 1979
7. Gustafsson LH: Så skadas barn: Epidemiologiska studier av olika faktorers betydelse för uppkomsten av barnolycksfall. (How children are injured: Epidemiological studies of the importance of different factors for childhood accidents.) Acta Univ Upsaliensis No. 230, 1975
8. Gustafsson LH: Childhood accidents: Three epidemiological studies on the etiology. Scand J Soc Med 5:5, 1977

9. Høyer SE, Wollebaek E: Ulycker hos barn. Registrering ved et sentralsykehus. (Accidents in children. Registration in a central hospital.) Tidsskr Norsk Laegeforen 99:1783, 1979
10. Jones JG: The child accident repeater. A review. Pediatrics 19:284, 1980
11. McKevitt RK, Nader PR, Williamson MC, Berrey R: Reasons for health office visits in an urban school district. J Sch Health 47:275, 1977
12. Report from Helsinki City Health Department 1970
13. Report from Helsinki City Health Department 1971–73
14. Report from Helsinki City Health Department 1979
15. Statistics of accidents of Helsinki City Health Department 1966.67
16. Thiele K, Leithe J, Bodewig HO: Kindergarten- und Schulunfälle—Ursachen bei Kinderunfällen in einer Deutschen Stadt mit 50 000 Einwohnern in den Jahren 1971–1975. (Kindergarten and school accidents—causes in childhood accidents in a German town with 50,000 inhabitants in the years 1971–1975.) Hefte Unfallheilkd 130:97, 1978
17. WHO Statistical Report Series 30:1, 1977

*Received August 2, 1982*

Prof M Sillanpää MD
Dept of Public Health
University of Turku
SF-205 20 Turku, Finland

*Acta Paediatrica Hungarica, 24 (2), pp. 131–136 (1983)*

# Disaccharidases in coeliac disease

K Horváth, Gabriella Horn, Hedvig Bodánszky, Katalin Tóth and S Váradi

Second Department of Paediatrics, Semmelweis University Medical School, Budapest

In 30 children presenting with complaints characteristic of malabsorption in whom congenital enzyme deficiency could be excluded, determination of the enzymes lactase, saccharase and maltase was performed in the tissue sample obtained by jejunal biopsy; histology was also carried out in all cases. In 23 cases the diagnosis of coeliac disease could subsequently be confirmed, in the other 7 cases the diagnosis could neither be rejected nor established with certainty. All three enzymes had a decreased activity in cases displaying subtotal or total villous atrophy, the most sensitive among them being lactase: in 69% of cases no lactase activity could be shown while saccharase and maltase were absent in 29 respectively 4% of the cases.

No close correlation exists between the light-microscopic findings and the activity of enzymes since total absence of enzyme activity may be associated with only moderate villous atrophy. Lack of disaccharidase activity in the upper section of the small bowel does not necessarily mean disaccharide malabsorption exhibiting clinical symptoms, it only indicates a reduced capacity of disaccharide splitting.

It has been concluded that routine determination of disaccharidase activities is not justified within the diagnostic procedure of coeliac disease

Digestion of carbohydrates is ried out by a sequence of enzymatic cleaving procedures. The last step of these is the splitting of disaccharides to monosaccharides. The disaccharidases, the enzymes performing this process, are sited on the luminal surface of the epithelial cells lining the small bowel, in the neighbourhood of the microvillous structure [10].

Congenital absence of disaccharidases, in other words, congenital lactase, saccharase or isomaltase deficiency are rare conditions [8, 15]. Acquired forms are much more frequent. Secondary lactase deficiency is a common problem; it is frequently due to gastroenteritis [1] but may also be preceded by marasm, coeliac disease, cow's milk protein intolerance, immunodeficiency or a surgical intervention [14]. In adults, disaccharidase deficiency may evolve after gastric resection. Secondary saccharase and especially maltase deficiency are rather infrequent conditions.

In infancy, carbohydrate intake is mostly covered by the disaccharides lactose and saccharose and later a higher proportion of polysaccharides is consumed. The proportion of disaccharides within all carbohydrates ingested decreases to about 40% by the age of six to eight years [6].

The following tests can be used for establishing the diagnosis of disaccharidase deficiency:

demonstration of reducing compounds and measurement of pH in the stools;

chromatography of faecal carbohydrates;
oral carbohydrate loading;
measuring hydrogen concentration of expired air;
radioscopy after ingestion of a mixture of barium sulphate and lactose;
determination of disaccharidase activity in the jejunal mucosa.

The results of most of these tests are greatly influenced by other factors such as intestinal motility. Activity of the enzymes can be measured directly in homogenized tissue samples obtained by jejunal biopsy. This paper deals with experience gathered with the last-mentioned method.

## Materials and Methods

Jejunal biopsy was carried out in 30 children admitted because of symptoms pointing to malabsorption. In addition to histological examination, activity of lactase, saccharase and maltase was determined. Mean age of the patients was 2.4 years with a range from eight months to ten years. In 23 the diagnosis of coeliac disease has been confirmed, the remaining 7 are being followed up. In other words, a third biopsy, definitely confirming the diagnosis, has not yet been done. The symptoms reported at admission by the parents are listed in Table I.

Table I

Symptoms before admission to hospital of patients with established or suspected coeliac disease

| Symptom | No. | Per cent |
|---|---|---|
| Impaired growth | 30 | 100 |
| Diarrhoea | 13 | 43 |
| Bulky maldigested stools | 13 | 43 |
| Meteorism | 12 | 40 |
| Loss of appetite | 9 | 3 |
| Vomiting | 6 | 2 |
| Abdominal pain | 1 | 3.3 |
| Oedema | 1 | 3.3 |
| Good appetite | 1 | 3.3 |

Determination of the enzymes was carried out by the method of Dahlquist [5]. The tissue sample immediately after removal was homogenized at 0 °C and deep-frozen. The measurements were carried out within two weeks after obtaining the sample. The results were expressed in international units (1 IU = 1 $\mu$mol substrate/g wet tissue/min). For comparison, the data of Burgess [3] obtained from 112 children with a normal jejunal mucosa were used. These were 2–16 IU for lactase, 3–20 IU for saccharase, and 15–77 IU for maltase. Sampling of the tissue was performed by a Watson-capsule from a section between the duodenojejunal junction and 10 cm distally from this. The enzyme activities were compared with the degree of villous atrophy of the jejunum. Classification of the atrophy was done using the principle of Oehlert [12]. The following distribution was found according to the degree of villous atrophy: partial villous atrophy (PVA), stage II or III: 4 cases; subtotal or total villous atrophy (SVA respectively TVA): 26 cases.

## Results

For each enzyme the results are grouped according to the degree of villous atrophy and the clinical diagnosis. In Figure 1 it can be seen that lactase activity was below the normal limit in all cases but one exhibiting SVA or TVA (96%); in fact, it was absent in 69% of such cases. Among the four cases affected by PVA one had no lactase activity whatever, in two the value was within the normal limits.

Saccharase activity was determined in all but two of the 26 patients

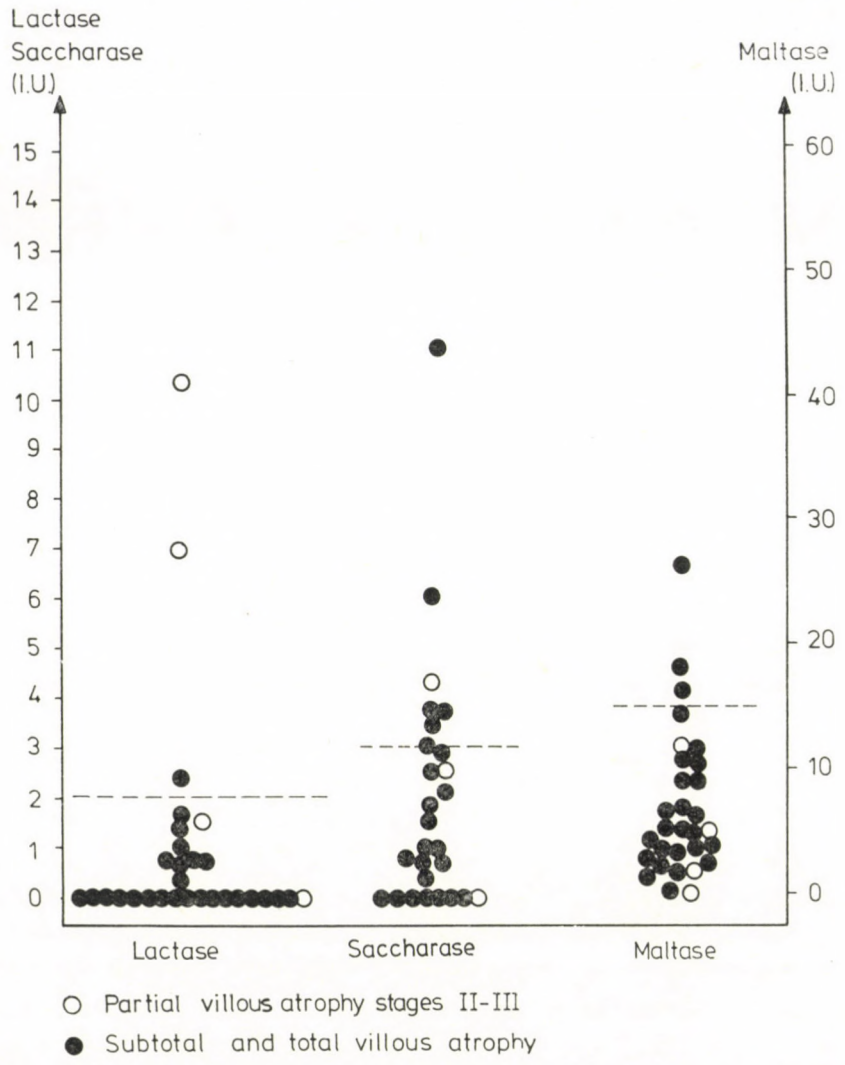



FIG. 1.

affected by subtotal or total villous atrophy. Absence of activity was demonstrated in 29%, an activity below the lower normal limit in 79% of cases (Fig. 1). Thus, saccharase is less sensitive to damaging factors than lactase. An abnormally low activity of saccharase was found in two cases out of the three with PVA.

Among patients with SVA or TVA all but three (88%) had a maltase value falling below the normal limit. Total absence of maltase, however, could only be demonstrated in a single patient (4%), i.e. maltase proved to be a resistant enzyme. In the patient with partial villous atrophy and manifest coeliac disease the deficiency in

maltose cleaving led to clinical symptoms, therefore a diet poor in maltose had to be prescribed during the initial phase of treatment.

Comparison of the figures shows that lactase is the most valuable and maltase the least vulnerable enzyme. In spite of the fact that all three enzyme activities were depressed or absent in the majority of patients affected by subtotal or total villous atrophy, no close correlation existed between the histological findings obtained by light microscopy and the enzyme activities, since decreased or absent activity could be observed even in cases with partial villous atrophy. Similarly, no age dependence could be observed in the groups with various degrees of villous atrophy.

## Discussion

The disaccharidases are sited in the vicinity of the microvillous structure of epithelial cells lining the mucosal surface of the small bowel [10]. This adjacent situation makes them vulnerable to various damaging factors. In infancy and early childhood there is a marked proneness to mucosal abnormalities and secondary disaccharidase, chiefly lactase, deficiency after enteritis. Differentiation between mucosal damage due to enteritis and gluten sensitive enteropathy is not easy. In doubtful cases a diet containing no disaccharides and gluten may be indicated [1]. In case of lactase deficiency the ingested lactose cannot be split, it thus passes to lower sections of the small bowel, the unsplit sugar exerts its osmotic effect on the intestinal wall; the hypertonic solution in itself causes cellular damage and a decrease of disaccharidase activity [13]. The undigested sugar is then fermented by bacteria in the colon.

Christopher et al [4] investigated the pathomechanism of diarrhoea in 5 patients affected by lactase deficiency: after lactose ingestion they found the ileal fluid to have an osmolality of 300 mosm/l, and in the stools this value was 379 mosm/l. In their opinion, the diarrhoea was due to altered ileal secretion and colonic absorption. Bacterial fermentation of the unsplit lactose explains the higher osmolality in the stools and the fermentation products may inhibit the absorption of water in the colon.

Disaccharidase activity can be demonstrated all along the normal small intestine [2], the activity being lower in the distal sections. The damaging factors rarely cause mucosal damage all along the small bowel, in most cases there is only a reduction in sugar splitting capacity.

In coeliac disease, the villous damage is most pronounced in the upper part of the small intestine, the ileum is usually normal. Since biopsy is usually performed in the upper, damaged section, an abnormally low enzyme activity found here does not necessarily lead to clinical manifestation of disaccharide maldigestion and thus to diarrhoea. This was reflected also in our material: diarrhoea was mentioned in the history of only 13

cases (43%) out of 30 children with established or suspected coeliac disease.

In our experience, the mere demonstration of a decreased or absent disaccharidase activity in the jejunal biopsy specimen is no indication for a lactose-free diet. Elimination of lactose is only necessary at initiation gluten-free or the diet if diarrhoea has occurred in the history. Walker–Smith et al prescribe a lactose-free diet in coeliac disease only if diarrhoea appears immediately after an oral load of lactose [14]. In coeliac patients, biochemical deficiency of saccharase or maltase rarely leads to clinical manifestations.

Lactose malabsorption does not necessarily lead to diarrhoea. Conversely, it may be a frequent cause of abdominal pain. Liebman [cit. 9] performed lactose loading in 38 children with recurrent abdominal pain and in 11 of them he found a pathological curve. Four weeks of lactose-free diet resulted in disappearance of the complaints and so it was concluded that lactose intolerance may be a major factor in causing recurrent abdominal pain in children.

In older children, adult type hypolactasia or late onset lactase deficiency must be taken into consideration. In such cases the initially normal lactase activity of infancy decreases with age. The condition is common in certain races. In Japan, for instance, lactase deficiency was revealed in 30% of three year old children and in 89% of adults by the $H_2$ breath test based on the observation that bacterial fermentation of lactose in the colon produces molecular hydrogen [11]. In this condition the lactase deficiency exists in the presence of a normal histology of the jejunal mucosa.

Congenital lactase deficiency has to be distinguished from lactose intolerance with lactosuria, a condition characterized by specific clinical symptoms appearing after lactose ingestion. The latter condition is not due to deficient enzyme activity but to the mucosal leakage of lactose.

A comparison of the light microscopic findings with the enzyme activities obtained from the same sample allowed the conclusion that with increasing villous atrophy the activity of the disaccharide-splitting enzymes decreases. The most vulnerable was lactase, in accordance with data obtained by others, but no explanation of the phenomenon can be offered. It can, however, be seen from Table I that the correlation between histology and enzyme activity is unclear since moderate villous atrophy may occur with total deficiency of the enzymes and, conversely, normal activity is compatible with severe atrophy of the villi.

Electron microscopy of the microvillous structure will perhaps be able to establish some relationship between morphology and function [7]. For the diagnosis of coeliac disease, jejunal biopsy before and after gluten withdrawal and the estimation of faecal fat excretion are fully sufficient; thus, routine disaccharidase assays are not necessary for the purpose.

## References


1. Anderson CM, Gravey M, Burke V: Coeliac disease. Some still controversial aspects. Arch Dis Child 47:292, 1972
2. Antonowitz J: Development and distribution of lysosomal enzymes and disaccharidases in human fetal intestine. Gastroenterology 67:51, 1974
3. Burgess EA: Techniques of investigation. In: Diseases of the Small Intestine in Childhood, ed. Walker-Smith JA, Pitman Medical Publications. London 1979, p. 82
4. Christopher NL, Bayless TM: Role of the bowel and colon in lactose induced diarrhea. Gastroenterology 60:845, 1971
5. Dahlquist A: Method for assay of intestinal disaccharidases. Anal Biochem 7:18, 1964
6. Gray GM: Carbohydrate digestion and absorption. Role of the small intestine. N Engl J Med 292:1225, 1975
7. Harrison M, Walker-Smith JA: Reinvestigation of lactose intolerant children: lack of correlation between continuing lactose intolerance and small intestinal morphology, disaccharidase activity and lactose tolerance test. Gut 18:48, 1977
8. Holzel A, Schwarz V, Sutcliffe KV: Defective lactose absorption causing malnutrition in infancy. Lancet 1:1126, 1959
9. Liebman WM: Recurrent abdominal pain in children: Lactose and sucrose intolerance, a prospective study. Pediatrics 64:43, 1979
10. Miller D, Crane RK: The digestive function of the epithelium of the small intestine I. An intracellular locus of disaccharide and sugar phosphate ester hydrolysis. Biochim Biophys Acta 52: 281, 1961
11. Nose O, Iida Y, Kai T: Breath hydrogen test for detecting lactose malabsorption in infants and children. Prevalence of lactose malabsorption in Japanese children and adults. Arch Dis Child 54:436, 1979
12. Oehlert W: Pathologie des Magen-Darm-Traktes. Schattauer Verlag, Stuttgart-New York 1978, p. 326
13. Teichberg S, Lifshitz F, Pergolizzi R, Wapnir RA: Response of rat intestine to a hyperosmotic feeding. Pediatr Res 12:720, 1978
14. Walker-Smith JA: Sugar malabsorption. In: Diseases of the Small Intestine in Childhood, ed. Walker-Smith JA, Pitman Medical Publishers, London 1979, pp. 250–278
15. Weijers HA, Van de Kamer JH, Mossel DRA, Dicke WK: Diarrhoea caused by deficiency of sugar-splitting enzymes. Lancet 2:296, 1960


*Received August 3, 1982*

K Horváth MD
Tűzoltó u. 7
H-1091 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (2), pp. 137–142 (1983)*

# Effect of lithium carbonate on the peripheral leukocyte count in children suffering from haematological malignancies

S Molnár and P Kajtár

Department of Paediatrics, University Medical School, Pécs

Effects of lithium carbonate on peripheral white blood cell and granulocyte counts were investigated in children treated for acute lymphoblastic leukaemia and non-Hodgkin malignant lymphoma. $Li_2CO_3$ given orally for two weeks in a single daily dose of 700 mg/m² caused a significant and lasting increase in the peripheral WBC and granulocyte counts and increased the granulocyte ratio during induction of remission and maintenance cytotoxic therapy. Haematologic actions and the long-term effect of lithium carbonate are discussed.

Leukocytosis and neutrophil granulocytosis was reported to develop in patients treated with $Li_2CO_3$ for manic-depressive psychosis [12, 20]. Later lithium has been found effective in reducing the degree and duration of neutropenia in adults receiving chemotherapy for small-cell carcinoma of the lung [11], carcinoma of the prostate [3], Hodgkin and non-Hodgkin malignant lymphoma [2], acute myeloid leukaemia [17], and in children with solid tumours [19].

Since the effects of lithium carbonate in adults suffering from lymphoblastic leukaemia are contradictory [1, 2] and no examinations were performed in children, the present study was designed to explore the effects of lithium carbonate as supportive treatment in children suffering from acute lymphoblastic leukaemia.

## Materials and Methods

Twenty-one children, 16 boys and 5 girls, were treated with $Li_2CO_3$; 15 patients suffered from acute lymphoblastic leukaemia (ALL) and 6 patients from highly malignant non-Hodgkin lymphoma (T-lymphoblastoma, nHml). All were in remission, and were investigated during maintenance cytotoxic chemotherapy, either according to the therapeutic protocol of the Hungarian Leukaemia Study Group for Children, which is highly similar to the BFM protocol developed by Riehm et al [13], or according to the protocol of Wollner et al [21]. Another 4 patients were treated during the last two weeks of induction of remission of ALL. $Li_2CO_3$ was given in a single daily dose of 700 mg/m² orally for two weeks and the cytotoxic therapy was not interrupted. During maintenance therapy prednisone pulse treatment had been terminated at least two weeks before $Li_2CO_3$ was given. During induction of remission prednisone treatment was continued.

Quantitative and qualitative changes in peripheral white blood cells (WBC) and serum lithium levels were measured. Five hundred leukocytes were counted for the differentials. Serum lithium levels were determined by atomic absorption method.

The results were compared either with baseline data, measured at the beginning of the lithium treatment or with controls. Controls receiving identical cytotoxic treatment were collected in a randomized fashion. Results were compared with another lithium study where 400 mg/m² of $Li_2CO_3$ was given. Since WBC counts and differentials in patients with ALL and nHml were not statistically different, the two groups were combined for evaluation.

Statistical analysis was done with Student's $t$ test.

## Results

Serum lithium concentrations of our patients (0.72 ± 0.07 mmol/l and 0.56 ± 0.06 mmol/l in the 1st and 2nd weeks respectively) reached therapeutic levels (>0.55 mmol/l) [18], but remained below the toxic concentration (>1.5 mmol/l) [18, 19]. When only 400 mg/m² of lithium carbonate was given, the therapeutic range could hardly be reached. As it can be seen in Fig. 1, in both groups there was a considerable decline of the serum lithium level within a week.

Lithium carbonate, given during the last two weeks of remission induction therapy, caused a significant increase in the number of peripheral WBC; a rise in the absolute number and ratio of the circulating granulocytes at the end of the lithium therapy was also observed (Fig. 2).

During maintenance chemotherapy, 700 mg/m² of lithium carbonate caused a significant and lasting increase in the number of peripheral WBC (Fig. 3). The differences were significant at the end of the 1st and 2nd weeks in comparison to controls and baseline data.

Investigation of the peripheral WBC and absolute granulocyte counts showed that the increase and duration of granulocytosis was as high and lasting as that of the WBC (Fig. 4). The changes of the granulocyte ratio showed that the granulocytosis induced by lithium may have been responsible for the leukocytosis.

Four patients suffered from viral infection and were compared to con-

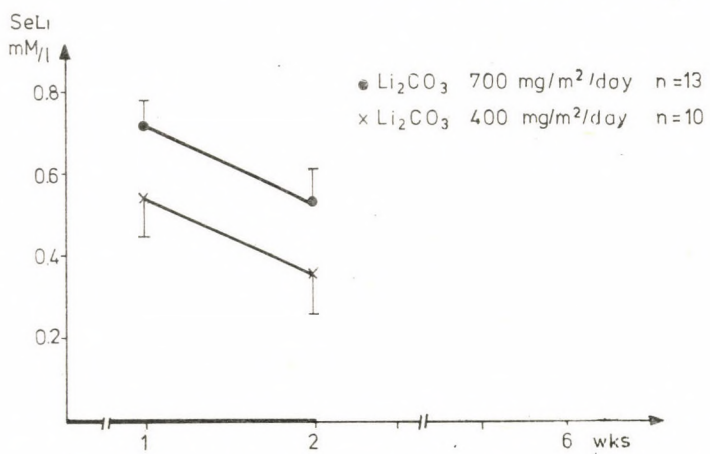



Fig. 1. Serum lithium level ($\bar{x}$ ± SE) in patients treated with $Li_2CO_3$ for two weeks (full line)

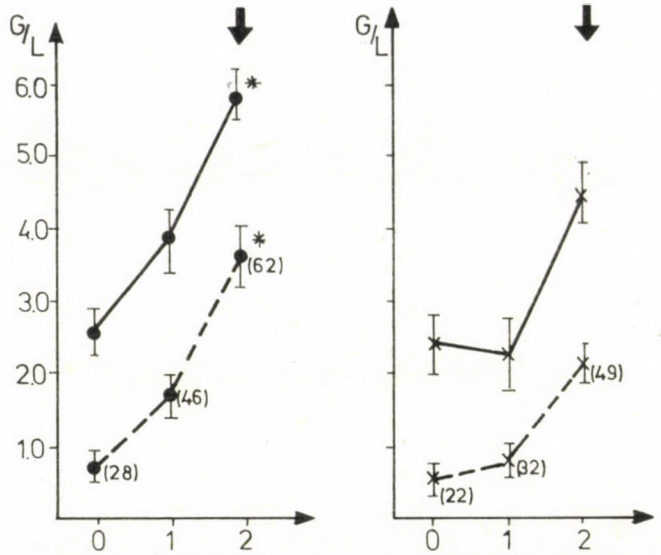



FIG. 2. Effect of $Li_2CO_3$ treatment (thick line) on WBC (full line) and granulocyte (broken line) counts in the last two weeks of induction of remission of ALL ($\bar{x} \pm SE$); dots, patients treated with $Li_2CO_3$; crosses, controls; arrow, bone marrow biopsy; * $p < 0.05$ in comparison to controls and to baseline data. Number in brackets represents the granulocyte ratio in per cent

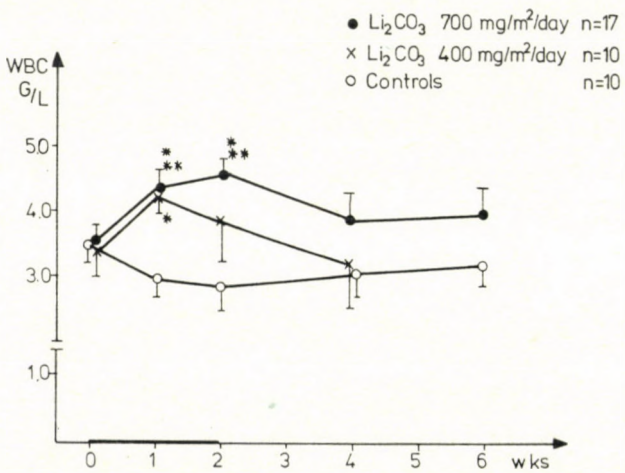



FIG. 3. Effect of $Li_2CO_3$ treatment (full line) on WBC count ($\bar{x} \pm SE$). * $p < 0.05$ in comparison to controls; ** $p < 0.05$ in comparison to baseline data

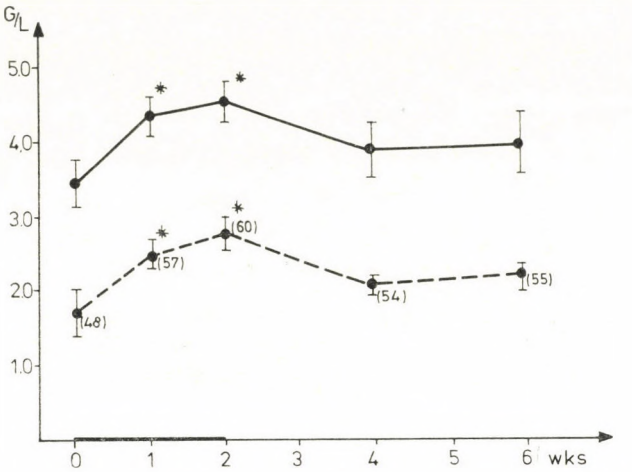



FIG. 4. Effect of $Li_2CO_3$ treatment (thick line) on WBC (full line) and granulocyte counts (broken line) ($\bar{x} \pm SE$). * $p < 0.05$ in comparison to baseline data. Number in brackets represents the granulocyte ratio in per cent

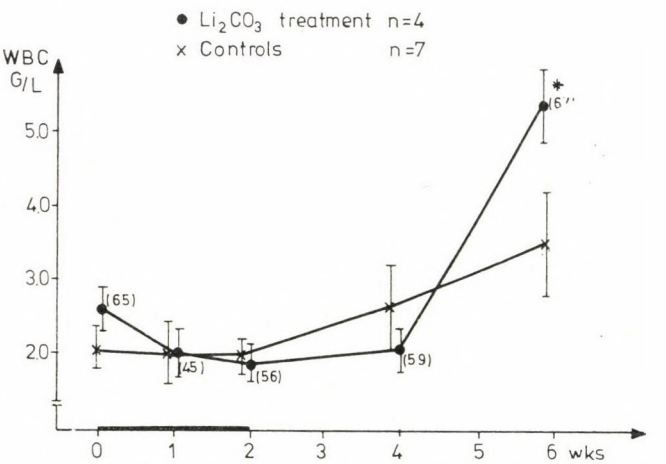



FIG. 5. Effect of $Li_2CO_3$ treatment (full line) on WBC counts during infection ($\bar{x} \pm SD$). * $p < 0.05$ in comparison to controls and to previous data. Number in brackets represents the granulocyte ratio in per cent

trols with similar symptoms. The cytotoxic treatment remained unchanged in both groups. Lithium treatment did not cause an early response, but after the 4th week there was a significant increase in the number of WBC in the group treated with lithium (Fig. 5). The changes in the granulocyte ratio seemed to be similar.

## DISCUSSION

In the present study lithium induced a significant degree of leukocytosis and granulocytosis at the end of treatment during induction of remission. The increase in the proportion of granulocytes was particularly evident. This was in agreement with the ob-

servations of Bandini et al [1] who showed that in adults lithium may shorten the duration and mitigate the severity of neutropenia during induction of remission of ALL. Casirola et al [2] however, could not confirm these observations.

Lithium carbonate in a daily dose of 700 mg/m$^2$ produced a significant leukocytosis in the 1st and 2nd weeks with a lasting cell production during maintenance cytotoxic therapy. Various doses of lithium carbonate resulted in different serum lithium levels as well as in different degrees of leukocytosis. Stein et al [18] found that a significant degree of leukocytosis could be produced only when the serum lithium concentration exceeded 0.55 mmol/l. Such a serum lithium concentration could only be produced when a lithium carbonate dose of 700 mg/m$^2$/day had been administered. In children with solid tumours 400—600 mg/m$^2$/day was followed by therapeutic lithium levels and a definite increase of the WBC count [19]. The differences may be explained by the lasting suppression of the bone marrow of patients with haematologic malignancies. The correlation between the administered dose of lithium carbonate, the serum lithium level and granulocyte production is not linear [14, 18] but may be close to it. It has been shown that the higher the serum lithium level, the longer the elimination half-time, and the greater the effect (Minsker et al cit. 7). This relationship has been supported by experiments performed in mice [6].

The administered dose of lithium carbonate appears to be important [6, 18]. If the serum lithium concentration exceeds 1.5 mmol/l, in addition to a rebound leukopenia, one has to reckon with an increased risk of lithium toxicity. It has been suggested that the reduced mature leukocyte reserve in the bone marrow resulting from the release of leukocytes facilitates the toxic effect of lithium carbonate on the bone marrow [6].

During lithium treatment the absolute granulocyte count increased significantly in the 1st and 2nd weeks. The increase of the granulocyte ratio in the differentials was lasting and considerable. As to the mechanism of these responses to lithium carbonate, a direct stimulation of granulocyte colonies, enhanced colony stimulating activity (CSA), proliferation of the granulocyte progenic cells and the pluripotential stem cells are the most reasonable alternatives [4, 5, 8, 9, 10, 14].

The changes in the serum lithium levels and the long-term effect of lithium carbonate could be explained by its turnover within the organism, and by the dynamics of its elimination. The drug is distributed in the whole body water, but crosses cell membranes at a slow rate. This accounts for the delayed (6–10 days) therapeutic response, and the slow (2 3 weeks) elimination rate [7, 15]. Cytotoxic therapy by affecting cellular metabolism may alter the distribution and excretion rate of lithium.

It should be emphasized that lithium therapy is ineffective in infections, but after its elimination a re-

bound leukocytosis develops. This is probably due to the facilitatory effect of lithium on the deliberation reaction [16] of the bone marrow after repression.

In conclusion it can be said that in children treated for ALL or non-Hodgkin malignant lymphoma lithium carbonate in a daily dose of 700 mg/m$^2$ administered for two weeks is capable to induce a lasting and significant leukocytosis and granulocytosis during remission induction and maintenance cytotoxic chemotherapy.

## References


1. Bandini G, Ricci P, Visani G, Tura S: Lithium carbonate in haematology. Lancet 2:926, 1980
2. Casirola G, Invernizzi R, Ippoliti G, Pavia G, Bottoni A: $Li_2CO_3$ effects on primitive and secondary neutropenia. Haematologica (Pavia) 65:746, 1980
3. Catane R, Kaufman J, Mittelman A, Murphy GP: Attenuation of myelosuppression with lithium. N Engl J Med 197:452, 1977
4. Fernandez LA, MacSween JM: Lithium and T cell colonies. Scand J Haematol 25:382, 1980
5. Friedenberg WR, Marx JJ: The effect of lithium carbonate on lymphocyte, granulocyte and platelet function. Cancer 45:91, 1980
6. Gallicchio VS, Chen MG: Modulation of murine pluripotential stem cell proliferation in vivo by lithium carbonate. Blood 56:1150, 1980
7. Goodnick PJ, Fieve RR, Meltzer HL, Dunner DL: Lithium elimination half-life and duration of therapy. Clin Pharmacol Ther 29:47, 1981
8. Harker WG, Rothstein G, Clarkson DR, Athens JW, Macfarlane JL: Enhancement of colony stimulating activity production by lithium. Blood 49: 263, 1977
9. Lancet editorial. Lithium in haematology. Lancet 2:626, 1980
10. Lewitt LJ, Quesenberry PJ: The effect of lithium on murine hematopoiesis in a liquid culture system. N Engl J Med 302:713, 1980
11. Lyman GH, Williams CC, Preston D: The use of lithium carbonate to reduce infection and leukopenia during systemic chemotherapy. N Engl J Med 302:257, 1980
12. Radomski JL, Fuyat HN, Nelson AA, Smith PK: The toxic effects, excretion and distribution of lithium chloride. J Pharmacol Exp Ther 100:429, 1950
13. Riehm H, Gadner RH, Welte K: Die West-Berliner Studie zur Behandlung der akuten lymphoblastischen Leukämie des Kindes. Erfahrungsbericht nach 6 Jahren. Klin Paediatr 189:89, 1977
14. Rothstein G, Clarkson DR, Larsen W, Grosser BI, Athens JW: Effect of lithium on neutrophil mass and production. N Engl J Med 298:178, 1978
15. Singer I, Rotenberg D: Mechanism of lithium action. N Engl J Med 289:254, 1973
16. Spiers ASD: Blood abnormalities during leukaemia treatment. Lancet 1:674, 1974
17. Stein RS, Flexner JM, Graber SE: Lithium and granulocytopenia during induction therapy of acute myelogenous leukemia. Blood 54:636, 1979
18. Stein RS, Howard CA, Brennan M, Czorniak M: Lithium carbonate and granulocyte production. Cancer 48: 2696, 1981
19. Steinherz PG, Rosen G, Ghavini F, Wang Y, Miller DR: The effect of lithium carbonate on leukopenia after chemotherapy. J Pediatr 96:923, 1980
20. Tisman G, Herbert V, Rosenblatt S: Evidence that lithium induces human granulocyte proliferation, elevated serum vitamin $B_{12}$ binding capacity in vivo and granulocyte proliferation in vitro. Br J Haematol 24:767, 1973
21. Wollner NP, Burchenal JH, Lieberman PH, Exelby PR, D'Angio GJ, Murphy ML: Non-Hodgkin's lymphoma in children. Cancer 37:123, 1976


*Received August 5, 1982*

S Molnár MD
József A. 7
H-7623 Pécs, Hungary

*Acta Paediatrica Hungarica, 24 (2), pp. 143–148 (1983)*

# Fetal alcohol syndrome: amino acid pattern

R TICHÁ,[1] J SANTAVY,[2] and Z MATLOCHA[3]

Infants' Institute OUNZ[1], Department of Human Genetics[2], and Second Department of Internal Medicine[3] Palacký University, Olomouc, Czechoslovakia

A study of the serum amino acid concentrations in 6 children with the fetal alcohol syndrome revealed significant changes in their pattern, i.e. a decrease in hydroxyproline and proline (indicating disorders in skeletal development) and an increase especially in the alanine, leucine, isoleucine and tyrosine levels (indicating probably a damage to CNS development).

It is well established that alcohol is a teratogenic factor and that its abuse by mothers during gestation may lead to delivery of a defective child. Confirmatory evidence in that respect has been provided by detailed clinical and experimental studies published in many countries during the past 10 years, ever since a correct description of the fetal alcohol syndrome (FAS) had been given [3, 4].

The result of the intrauterine effect of alcohol is a defective somatic and mental development. The mental retardation is ascribed to structural changes in the brain produced during embryogenesis. Clarren et al. [1] demonstrated disorders in migration of neuronal and glial elements in the brain at autopsy of 4 children born to chronic alcoholic mothers. During the late fetal period alcohol is said to cause changes in the biochemism of the brain which result in behavioural disorders of the child during the postnatal period [7, 8]. Ellis and Krsiak [2] found in young rats fed with alcohol a low serotonin concentration in the brain. These young rats showed behavioural disorders manifesting with increased aggressivity, increased locomotor activity and decreased learning ability. Véghelyi et al [9] studied the question why some heavy drinkers give birth to healthy offspring while others who drink much less give birth to children with FAS. These authors could show that an involvement of the human fetus occurs in those women in whom after the intake of alcohol the level of acetaldehyde rises above 40 $\mu$mol [9, 10]. The mechanism of development of mental disorders in children with FAS is still obscure.

Involvement of the child's organism in FAS is of a general nature. Not only development of the brain is affected but also the growth and development of the skeleton, and this may justify the conclusion that in FAS a disturbance of the whole metabolism occurs. In the present study an attempt has been made to clarify these disorders by determination of the amino acid spectrum in the blood serum of children with FAS.

## Reports of Cases

Of a total of 24 children with FAS, born to 12 alcoholic mothers and followed-up since 1978, and in 6 children 12 to 36 months of age, the serum amino acids have been studied by chromatography on ion exchangers (automatic amino acid analyser AAA8881 Mikrotechna, Prague).

Psychological examination was repeatedly carried out in all the children, up to 3 years of age by the method of Brunet–Lezine (DQ), and above 3 years of age by the method of Terman–Merill (IQ). The electrolyte household and liver function tests showed normal values and chromosomal examinations revealed a normal karyotype in every child. The investigated children showed the following manifestations of FAS.

*Patient 1.* B. Z., a girl born in 1976 was the first child of a 23-year-old mother who since more than 3 years and throughout the entire course of the pregnancy consumed a daily mean of 150 g of absolute alcohol. The child was born without complications, with a birth-weight of 1500 g, length 42 cm. Apgar score 10. She showed since birth an increased irritability, tremor of the extremities, and weak sucking. At the age of 3 years her weight was only 9500 g and her height, 90 cm. Both values were under the 3rd percentile and the head circumference was 46 cm (-1 SD). She had generalized hypotonia, hypertelorism, indistinct philtrum, gothic palate; fine light hair, hypoplastic slowly growing nails, slight arachnodactyly on the hands, hypoplastic labia maiora with a moderate mental retardation (IQ = 80) and conspicuous hyperactivity. The blood amino acid spectrum showed changes (Table I).

At 5 years of age, growth was below the 10th percentile, the peculiar appearance of the face persisted. The girl is mentally retarded, unconcentrated, jittery, especially failing in manual skills.

In 1979, the mother at 40 weeks gestation gave birth to a second child. The birth weight was 2100 g, the length 48 cm. At 3 years of age, the girl had cranio-facial dysmorphism with microcephaly (head circumference 44 cm = −3 SD). The growth values were under the 3rd percentile, the IQ was repeatedly around 50.

*Patient 2.* The male patient Ch. M. was born in 1976 as the eleventh child of a 36-year-old chronic alcoholic mother with 6 years history of alcohol abuse. During her last gestation she consumed a daily mean of 180 g, of absolute alcohol. The child was delivered without complications, with 2250 g weight and 44 cm length. The gestational time was not known. The 1 and 5 min Apgar score was 7 and 9, respectively. There were signs of immaturity.

On admission, at 5 months of age, the weight was 3330 g, the length 47 cm, psychomotor development was retarded, the developmental quotient DQ = 50. The child had an anomalous appearance, antimongoloid slant

of palpebral fissures, ptosis of right eyelid, strabismus, hypoplastic philtrum, thin upper vermilion border, gothic palate, strikingly low-set ears, fine light hair, spoonlike deformation of toe-nails, clinodactyly of both fifth fingers, hypospadias and fovea coccygea. X-rays showed a considerably retarded ossification, microphalangia of the toes on both feet.

Growth was always under the 3rd percentile, at 12 months of age the weight was 5000 g, at 24 months 6000 g, with 74 cm length, at 4 years of age it was 10 kg with 87 cm length. Psychomotor development was retarded, at 4 years of age the IQ was 50. The amino acid levels at 3 years of age are given in Table I.

On examining the family in 1978, we found that it consisted of two different groups of children. The first 8 siblings were born at term with a birth weight above 3000 g, they had dark hair and developed well both somatically and mentally. The three younger siblings born between 1973 and 1976 were small-for-dates, had light hair, delayed psychomotor development and growth deficiency. These three children were diagnosed as having FAS.

*Patient 3.* P. V. a girl, was born in 1979 as the second child of a 23-year-old mother with a 5 year history of alcoholism. She consumed a daily mean of 120 g of absolute alcohol. Delivery was without complications, birth-weight 2130 g, length 43 cm, estimated gestational age was 33 weeks. At 6 months the baby had severe psychomotor retardation, hypotonicity, cranio-facial dysmorphism, nail hypoplasia, growth retardation. At 6 months she weighed 4500 g, at 12 months 7100 g, at 18 months 8200 g, with 71 cm length and a head circumference of 44 cm (−1 SD), values under the 3rd percentile.

The amino acids at 18 months are given in Table I. At 2 years of age the child was severely underdeveloped, jittery, could not yet walk, her verbalization was unintelligible.

The first sibling, a girl born in 1977 with 2300 g and 46 cm length was raised by the grandparents. According to their information the child is severely underdeveloped, somewhat jittery, with retarded psychomotor development.

*Patient 4.* L. M., a boy born in 1978 was the third child of a 30-year-old mother with an 8 year history of alcohol abuse who up to the 4th month of gestation drank a daily mean of 150 g of absolute alcohol. After the gravidity had been confirmed she restricted somewhat her alcohol intake. Delivery at 38 weeks gestation, birthweight 2600 g, length 47 cm, Apgar score 10. At 8 months of age, the child had marked muscle hypotonia, his weight was 7900 g, length 70 cm, head circumference 43 cm. The facial characteristics were a hypoplastic nasal bridge, anteverted nostrils, short palpebral fissures, low-set ears. He had a ventricular septal defect. At 12 months the weight was 8300 g, the length 68 cm, corresponding to the 3rd percentile. He began to stand up

TABLE I

Serum amino acid concentrations (μmol/l)

| | Cys OH | Tau | Asp | Hyp | Thr | Asn | Glu | Gln | Pro | Gly | Ala | Cit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Normal | 0–20 | 14–215 | 0–17 | 32 | 114–335 | 45 | 20–106 | 537–888 | 106–277 | 223–509 | 235–409 | 0–28 |
| B. Z. | 0 | 163 | 10 | *0* | 186 | 2 | 85 | 385 | *73* | 195 | **617** | 0 |
| Ch. M. | 0 | 26 | 0 | *0* | 113 | 0 | **201** | **934** | *14* | 274 | **690** | 0 |
| P. V. | 0 | 71 | **34** | *2* | 201 | 13 | 72 | 541 | *11* | **511** | **703** | 4 |
| L. M. | 0 | **286** | **21** | *0* | 158 | 33 | 101 | 856 | *0* | 304 | 102 | 0 |
| D. S. | 14 | 209 | 2 | *0* | 171 | 41 | **651** | 639 | *42* | 353 | **762** | 0 |
| H. M. | 0 | 201 | **53** | *0* | 207 | 33 | **122** | 358 | *16* | 241 | **770** | 0 |
| Mean values | 2 | 159 | **20** | *0* | 173 | 20 | **205** | 619 | *26* | 313 | **607** | 0 |

Italics: decreased value
Bold face: increased value

at 2 years of age. X-rays revealed kyphosis, thoracic asymmetry, and other changes. For the blood amino acid values see Table I.

The first sibling, a girl born in 1967 with 2900 g and 48 cm length, is healthy with a normal appearance and intelligence. The second sibling, a boy born in 1976 has already the typical characteristics of FAS: a birth weight of 2100 g, length 44 cm, marked craniofacial dysmorphism with low-set ears, a heart defect, pigeon breast, clinodactyly of the fifth finger, camptodactyly on right hand, a cavernous haemangioma, fovea coccygea, etc. At 5 years of age his growth remains below the 3rd percentile, mental debility and hyperactivity. Throughout this pregnancy, the mother drank a daily mean of 180 g of absolute alcohol.

*Patient 5.* D. S., a boy was born in 1978 as the fourth child of a 37-year-old mother with an 8 year history of alcoholism. During this pregnancy she consumed a daily mean of 150 g of absolute alcohol. Delivery from breech presentation, birth-weight 1850 g, length 47 cm. At birth, the infant showed slight signs of immaturity, the Apgar score was 10. He had short palpebral fissures, a large nasal bridge, a long, flat philtrum, a thin vermilion border, low-set ears, nail hypoplasia, retention of testicles, scrotal hernia, generalized hypotonia and deformed lower extremities.

At 12 months of age the weight was 6300 g, at 2 years 8800 g with 77 cm length, values below the 3rd percentile. Defective psychomotor development, DQ = 60–70. The serum amino acids showed abnormal values (see Table I).

The first two siblings are normal and healthy. The third sibling, a girl, was born at term in 1972 from an uncomplicated gestation, with a birth-

in children with FAS

| Val | 1/2 Cys | Met | Ile | Leu | Tyr | Phe | β-Ala | Orn | Lys | His | Arg | Ser |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 80–245 | 70–168 | 9–41 | 26–52 | 47–109 | 41–99 | 41–110 | 0–14 | 49–151 | 114–268 | 48–114 | 21–87 | 94–242 |
| **443** | 70 | **63** | **113** | 6 | 92 | 94 | 0 | 34 | 100 | 41 | 11 | 195 |
| **301** | 91 | **50** | **125** | **147** | 59 | 8 | 0 | 11 | 256 | 54 | 15 | 20 |
| **453** | 100 | **54** | **78** | **204** | **159** | 20 | 0 | 23 | **285** | 16 | 20 | 193 |
| 109 | 20 | **71** | **107** | **121** | **101** | 51 | 0 | 8 | 103 | 88 | **101** | 201 |
| **356** | 21 | **77** | **63** | **225** | **128** | 87 | 0 | 91 | **283** | 48 | **125** | 224 |
| **428** | 42 | **68** | **153** | **258** | **191** | 9 | 0 | 143 | **285** | **115** | **105** | **254** |
| **348** | 57 | **64** | **90** | **160** | **122** | 45 | 0 | 52 | 219 | 60 | 63 | 181 |

weight of 2400 g and 45 cm length. At 7 years of age, she was mentally backward, she had mutism, encopresis and enuresis. Her growth persisted under the 3rd percentile.

In 1980 a fifth child was born, with 1600 g birth-weight and 41 cm length and the characteristics of FAS with the same cranio-facial dysmorphims as his older brother D. S., and some other changes. His growth persists under the 3rd percentile, he is hyperactive and mentally deficient with a DQ of 50.

*Patient 6.* H. M., a boy born in 1978 was the second child of a 33-year-old chronic alcoholic mother. Since 6 years and also during her pregnancy she consumed a daily mean of 240 g of absolute alcohol. The baby's birth weight was 3250 g, his length, 50 cm. Since birth the infant has shown increased irritability and disorders in food intake. To unusual situations he reacted with increased tremor up to convulsions of the upper extremities. He has a conspicuous epicanthus, strabismus, hypoplastic philtrum, gothic palate, heart defect, umbilical hernia, and generalized hypotonia. He has a slight cerebellar dysfunction and began to walk at 2 years of age. For the amino acid values see Table I. At 4 years of age, growth was at the 10th percentile, the IQ was 55 with severe psychomotor instability.

The first child, born in 1971, is somatically healthy and mentally well-developed.

## Results

Table I shows the values for the individual amino acids. The first line contains the levels obtained in matched controls to facilitate comparison with those of the affected children.

From Table I it is evident that abnormal levels occurred in every examined child. Proline and hydroxyproline were considerably decreased to approximately 1/10 of the normal while the levels of alanine, valine, methionine and isoleucine were increased. The concentration of leucine was increased in 5 children, that of tyrosine in 4 children, both by 50–100%. It was not possible to find a relationship between these values and the clinical symptoms.

## Discussion

Decreased hydroxyproline and proline values are usually associated with disturbances of growth and development of the supporting apparatus. This might be due to a disturbance of collagen and elastin metabolism. Still, the cause of the alteration is not clear and some disturbance in liver metabolism induced by alcohol might be assumed. Also, the increased concentration of tyrosine, leucine and isoleucine has a negative effect on development of the central nervous system and this damage together with the morphological changes, may elicit the neuropsychic symptoms in children with FAS. Further studies are, however, required to clarify the meaning of the affected amino acid pattern and also its eventual use in diagnostics.

## References

1. Clarren SK, Alvord EC, Sumi SM, Streissguth AP, Smith DW: Brain malformations related to prenatal exposure to ethanol. J Pediatr 92:64, 1978
2. Ellis J, Kršiak M, Pöschlová N: Effect of alcohol given at different periods of gestation on brain serotonin in offspring. Activ Nerv Sup 20:287, 1978
3. Jones KL, Smith DW, Ulleland C, Streissguth AP: Pattern of malformation in offspring of chronic alcoholic mothers. Lancet 2:1267, 1973
4. Jones KL, Smith DW: Recognition of the fetal alcohol syndrome in early infancy. Lancet 2:999, 1973
5. Mamunes P, Prince PE, Thornton NH, Hunt PA, Hitchcock ES: Intellectual deficits after transient tyrosinemia in the term neonate. Pediatrics 57:675, 1976
6. Menkes JH, Welcher DW, Levi HS, Dallas J, Gretsky NE: Relationship of elevated blood tyrosine to the ultimate intellectual performance of premature infants. Pediatrics 49:218, 1972
7. Rosett LH, Snyder P, Sander LW, Lee A, Cook P, Weiner L, Gould J: Effects of maternal drinking on neonate state regulation. Dev Med Child Neurol 21:464, 1979
8. Streissguth AP, Landesman-Dwyer S, Martin JC, Smith DW: Teratogenic effects of alcohol in human and laboratory animals. Science 209:353, 1980
9. Véghelyi P, Osztovics M, Kardos G, Leisztner L, Szaszovszky E, Igali S, Imrei J: The fetal alcohol syndrome: symptoms and pathogenesis. Acta paediatr Acad Sci Hung 19:171, 1978
10. Véghelyi PV, Osztovics M: The alcohol syndromes: The recombigenic effect of acetaldehyde. Experientia 34:195, 1978

*Received September 5, 1982*

MUDr. R Tichá
Dr. Heyrovského 23
775 00 Olomouc, Czechoslovakia

*Acta Paediatrica Hungarica, 24 (2), pp. 149–157 (1983)*

# Isolation and physicochemical properties of an adenosine-rich gluten fraction

M Szabolcs, S Csorba[1] and M Hauck[2]

Central Research Laboratory, [1]Department of Paediatrics and [2]Institute of Biochemistry
University Medical School, Debrecen

Gluten proteins were isolated from the 0.01 mol acetic acid extract of bread. It was observed that precipitation of gluten provoked by 200 mM NaCl could partly be inhibited by adenosine. Based on this finding a method for isolation of the gluten fraction resisting saline precipitation in the presence of adenosine was elaborated. This fraction termed by us gluten-A-S, was found to have a lower glutamine + glutaminic acid and a higher proline and phenylalanine content than gluten. By sodium dodecylsulphate polyacrylamide gel electrophoresis gluten-A-S was shown to contain components of 58 000 and 34 000 dalton molecular weight after mercaptoethanol treatment while without the latter it contained a component of 74 000 dalton. The absorption maximum of the compound is at 260 nm; $E^{280nm}/E^{260nm} = 0.5$. In accordance with previous findings, gluten-A-S was found to contain 50–100 nmol adenosine per mg protein in a strong binding.

It seems that in addition to the small amount of tightly bound adenosine, gluten-A-S contains a larger quantity of adenosine loosely bound to the protein.

The physiological effects of dissociable adenosine bound to gluten and its possible role in the pathomechanism of gluten sensitive enteropathy is discussed in detail.

In previous studies it was shown that certain fractions of gluten proteins (gliadine, glutenine) fail to precipitate under the effect of 200 mM NaCl if various purine derivatives (caffeine, adenosine, adenosine triphosphate, etc.) are added [11], in other words the gluten proteins become partly soluble probably as a result of interaction between them and the purine derivative.

Adenosine isolated from gluten extracts has been incriminated for the inhibitory effect of gluten proteins on intestinal peristalsis [8]. Since gluten preparations were found to contain purine or pyrimidine derivatives [10] it seemed logical that protein-bound purine or pyrimidine derivatives liberated in the intestine might slow down bowel movements by inhibiting acetylcholine production, i.e. they might play some role in the pathomechanism of coeliac disease.

For this reason we examined the nature of gluten protein — adenosine bonds by measuring some physicochemical properties (molecular weight, absorption spectrum, amino-acid composition, etc.) of the gluten fraction resisting precipitation by 200 mmol/l NaCl in the presence of adenosine. In this paper the results of that study are described.

## Materials and Methods

Gluten was used in the experiments as in a previous study [11] the highest quantities of protein were found in the supernatant after precipitation by 200 mmol/l NaCl in the presence of adenosine, if non-fractionated gluten was used.

*Preparation of gluten from bread.* Slices of 200 g wheat bread were extracted by 1000 ml of a solution containing 10 mmol/l acetic acid and 0.8 mmol/l sodium azide at room temperature under continuous stirring for four hours. The mixture was then kept at 4 °C for 14–16 h, thereafter centrifuged at 2000 *g* at 4 °C, for 60 min. The precipitate was discarded, the volume of the supernatant was measured, and under continuous stirring solid sodium chloride was added to a final concentration of 200 mmol/l. The mixture was kept at 0 °C for 4–5 h, thereafter centrifuged at 2000 *g* for 60 min. The supernatant containing mainly starch and saline soluble proteins was discarded, the precipitate was redissolved in about 100 ml of the extraction solution, then solid NaCl was added up to a final concentration of 200 mmol/l. After standing for some hours, centrifugation, discarding the supernatant, redissolution of the precipitate in acetic acid plus sodium azide, addition of salt, and centrifugation were repeated. The last precipitate was dissolved in the extraction fluid in a quantity to obtain a protein concentration of 3–5 mg/ml. In order to remove the undissolved proteins the mixture was centrifuged at 40 000 *g* for 40 min (Beckman L3-50 preparation centrifugue, Ti 60 rotor). The precipitate was discarded and the clear supernatant containing the gluten protein was kept at −20 °C until used.

*Adenosine treatment of gluten protein.* To 36 ml solution containing 0.6–0.7 mg protein/ml, 310 mg adenosine was added. To promote solution of the latter, the mixture was continuously stirred at 37 °C, the final concentration of adenosine was thus 30 mmol/l. The solution was kept at room temperature for 30 min, 36 ml 400 mmol/l NaCl was added, the mixture was kept in ice-water for 2–4 h and then centrifuged at 40 000 *g* at 0 °C for 40 min. The precipitate was redissolved in a solution containing 10 mmol/l acetic acid and 0.8 mmol/l sodium azide and dialysed against the same fluid in order to remove the excess adenosine. The precipitated protein was termed gluten-A-P, the supernatant protein gluten-A-S. To remove the remaining adenosine, the mixture was dialysed 8 times against 2 l of ion-free water which was changed first after 4 h, then after each twelve hours.

*Demonstration of adenosine in gluten-A-S* was carried out by paper chromatography using isopropanol-ammonia-water, 7 : 2 : 1. After chromatography the paper was dried, the spot of adenosine clearly separated from protein was localised under UV-light, cut out and eluted in 0.1 N HCl. The concentration of adenosine was determined by measuring optical density at 259 nm, and the adenosine content in nmol of 1 mg gluten-A-S was calculated.

*Amino acid analysis.* The amino acid composition of all preparations was determined by help of a Lys (Chinoin) amino acid analyser as described previously [10].

*Sodium dodecylsulphate polyacrylamide gel electrophoresis at pH 7.* Samples containing 50–100 mg protein were mixed in a ratio of 1 : 1 or 1 : 2 with incubation solution containing 0.01 M sodium phosphate pH 7, 5% sodium dodecylsulphate, 1% mercaptoethanol ("+MCE") or without this latter compound ("−MCE"), 0.005% bromophenol blue and 40% glycerol; these were incubated at 100 °C for 5 minutes, quantitatively transferred under electrode buffer onto the top of the gel columns. Electrophoresis, staining and removal of excess stain were carried out according to Weber and Osborn [13]. The reference proteins used as standards were, bovine serum albumin (molecular weight: 68 000 dalton), IgG ("+MCE"): 50 000 resp. 23 000, "−MCE": 160 000 dalton), and ovalbumin (molecular weight: 42 000 dalton) as described in detail elsewhere [10].

*Determination of absorption spectra and protein content.* The absorption spectrum of proteins was examined in an Opton PM 2 DL spectrophotometer. The protein content was measured by the method of Lowry et al [6]. The calibration curve was constructed by the use of known quantities of bovine serum albumin. All determinations were carried out in 4–5 parallel samples. The results were nearly identical, in the Table and Figures one typical experiment each is shown.

All reagents were of analytical purity produced by Reanal (Budapest), with the exception of adenosine which was a product of Serva (Heidelberg).

## Results

In the first series of experiments the effect of various adenosine μmol/protein mg ratios on the precipita-

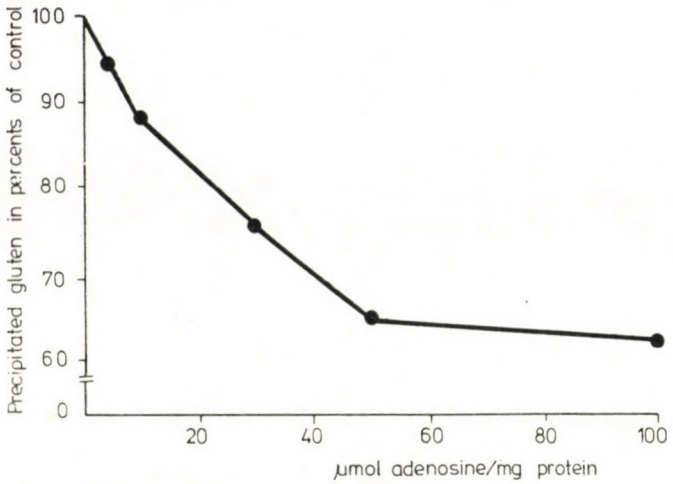



FIG. 1. Precipitation of gluten by 200 mM NaCl in the presence of various μmol adenosine/mg protein ratios. See text for details

tion of gluten in 200 mmol/l NaCl was investigated. Samples containing gluten, sodium chloride and various amounts of adenosine were centrifuged at 2000 *g* for 60 minutes and the protein content of the precipitate was determined [6]. As can be seen from Fig. 1, precipitation of gluten by 200 mmol/l NaCl decreased with the increase of the adenosine/protein ratio from 0 to 50 μmol/mg. Over 50 μmol/mg there was no further change, so that in subsequent experiments a ratio of 45–50 μmol/mg protein was applied.

Table I shows the results of amino acid analysis. The composition of gluten-A-P is similar to that of non-fractionated gluten and this explains the fact that like gluten-gluten-A-P is soluble only in acetic acid. Gluten-A-S greatly differs from both gluten-A-P and gluten in this respect. In gluten-A-S there is less glutaminic acid + glutamine, while its proline content exceeds 1.4 times and its phenylalanine content nearly twice the corresponding values of gluten. The gluten–A–S preparation too has

TABLE I

Amino acid composition of gluten, gluten-A-P and gluten-A-S

| Amino acid | Gluten | Gluten-A-P | Gluten-A-S |
|---|---|---|---|
| | mol per cent | | |
| Lys | 2.30 | 2.6 | 0.73 |
| His | 1.10 | 1.1 | 1.36 |
| Arg | 1.60 | 1.7 | 0.94 |
| Asp+Asn | 2.00 | 1.5 | 4.38 |
| Thr | 1.80 | 1.7 | 2.76 |
| Ser | 4.80 | 4.8 | 6.81 |
| Glu+Gln | 42.10 | 40.0 | 34.3 |
| Pro | 17.90 | 19.7 | 24.3 |
| Gly | 2.90 | 3.8 | 2.89 |
| Ala | 2.40 | 2.4 | 1.1 |
| Val | 3.00 | 2.3 | 1.3 |
| Met | 0.90 | 0.8 | 0.87 |
| Ile | 3.60 | 3.8 | 2.78 |
| Leu | 5.90 | 5.4 | 4.42 |
| Tyr | 2.70 | 1.8 | 1.1 |
| Phe | 5.00 | 5.7 | 9.7 |

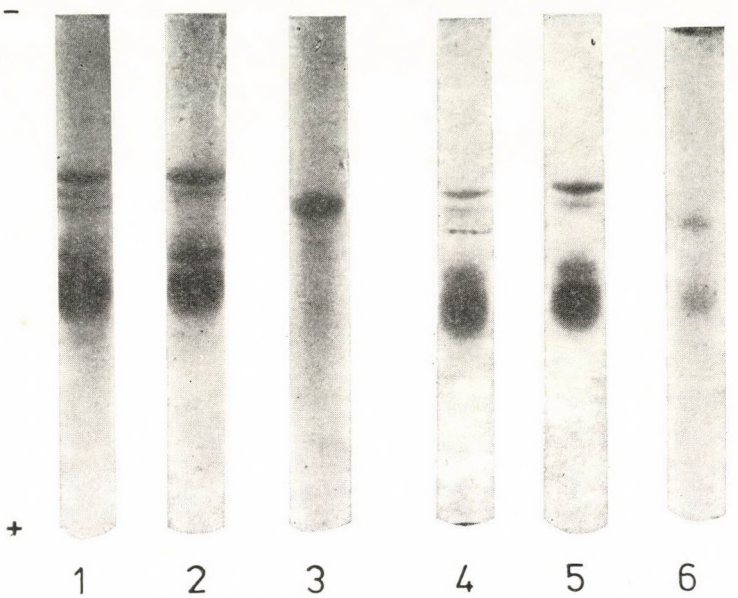



FIG. 2. Stained preparations of gluten (1,4), gluten-A-P (2,5) and gluten—A-S (3,6) after sodium dodecylsulphate polyacrylamide gel electrophoresis. Pictures 4, 5 and 6 represent preparations pretreated with heat (100 °C) and mercaptoethanol for 5 minutes. With preparations 1—3 no mercaptoethanol was applied

a different solubility: it is soluble in water and saline.

The preparations were tested for homogeneity by sodium dodecylsulphate polyacrylamide gel electrophoresis. The first three sections of Fig. 2 show the composition of preparations heat treated in an incubation fluid not containing mercaptoethanol ("—MCE"); the second three sections

TABLE II

Molecular weight of components obtained by sodium dodecylsulphate polyacrylamide gel electrophoresis of gluten, gluten-A-P and gluten-A-S

| Preparation | Incubation fluid | Component | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | Molecular weight, $10^3$ dalton | | | | | | |
| Gluten | −MCE | 97 | 83 | 74 | 56 | 49 | 40 | 34.5 |
| | +MCE | 74 | 66 | 60 | 49 | 43 | 38 | 32.5 |
| Glu-A-P | −MCE | 97 | 82 | — | 56 | 48 | 39 | 34.5 |
| | +MCE | 73 | 65 | — | 47 | 43 | 36 | 32.5 |
| Glu-A-S | −MCE | — | — | 74 | — | — | — | — |
| | +MCE | — | — | 58 | — | — | 34* | 31* |

* traces

show the corresponding pictures obtained in "+MCE" experiments; here the eventual disulphide bonds have been subjected to reduction. The results of both types of pretreatment are summarized in Table II. This shows the following facts. On electrophoresis gluten separated into seven components different in molecular weight. Pretreatment with mercaptoethanol did not increase their number, but changes occurred in their molecular weight. This points to changes in molecular shape induced by disulphide bond reduction within the polypeptide chain, resulting in a decrease of molecular weight, as it has already been assumed [1, 12]. The third fraction counted from the top of the gel column of non-fractionated gluten, which originally had a molecular weight of about 74,000 dalton and 5800 respectively 38,000 dalton after mercaptoethanol reduction, appeared in the supernatant (gluten-A-S) and was thus missing from gluten-A-P.

Polyacrylamide gel electrophoresis without SDS treatment by the method of Davis [3] described in detail earlier [2] revealed that the gluten-A-S protein (Fig. 3, 3) mainly consists of gluten fraction I (Fig. 3, 1) sited next the cathode. Correspondingly, gluten-A-P (Fig. 3, 2) contains comparatively small amounts of fraction I while fractions II and III dominate in it.

The absorption spectrum of gluten-A-S and gluten-A-P was examined and compared with that of non-fractionated gluten (Fig. 4). The maxi-

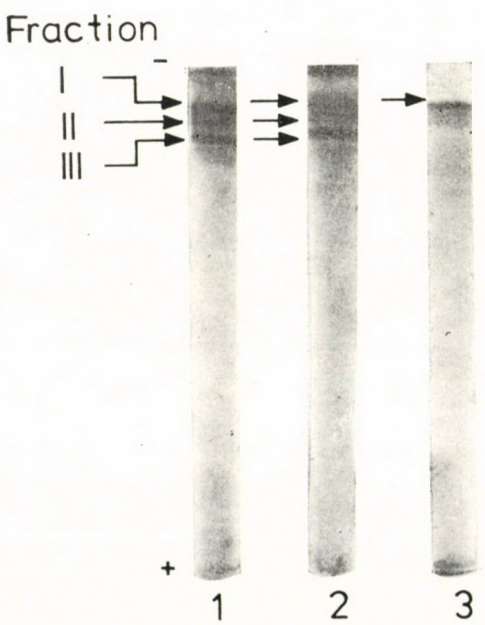



FIG. 3. Testing for homogeneity of gluten (1), gluten-A-P (2) and gluten-A-S (3) by polyacrylamide gel electrophoresis without sodium dodecylsulphate, according to the method of Davis (3)

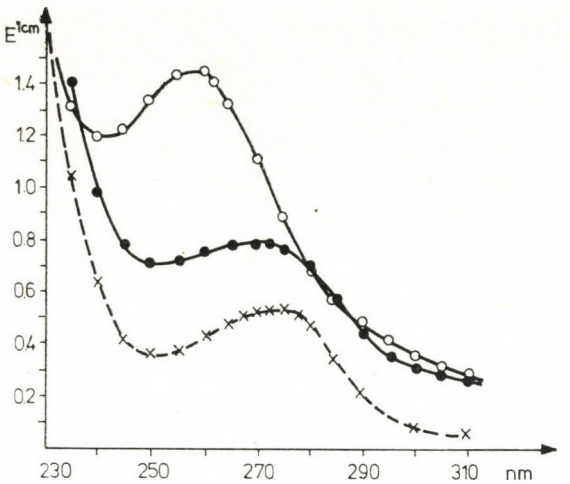



FIG. 4. Absorption spectra of gluten (crosses), gluten-A-P (dots) and gluten-A-S (circles)

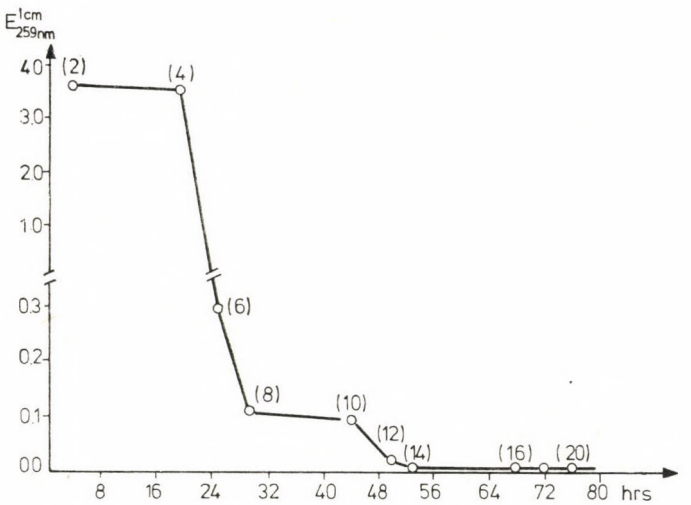



FIG. 5. Extinction values measured at 259 nm in the dialysing water of gluten-A-S, plotted against time and volume of dialysing fluid. The numbers in brackets next the points representing the individual extinction values indicate the cumulative volume of dialysing fluid

mum of gluten and gluten-A-P lies at 275 nm while with gluten-A-S the highest extinction was found at 260 nm. This suggests that the adenosine binding component is in the supernatant. As described in the methodological section, 1 mg gluten-A-S contains 50–100 nmol adenosine.

When dialysis was performed in order to remove adenosine, about 70–72 ml of the supernatant was dialysed against 2 l cold ion-free water

first for four hours, then seven more times for 12 hours each. The optical density of each 2 liter dialysis fraction was measured at 259 nm in order to determine its adenosine content. Fig. 5 shows the results; here the extinction values are plotted against time, the numbers in bracket represent the cumulative volume of the dialysing water. It can be seen that the adenosine concentration did not decrease gradually between the 4th (8) and 5th (10) fractions and adenosine was not practically removed from the gluten-A-S, while between the 5th (10) and 6th (12) fractions the adenosine concentration decreased nearly to zero. From this it was concluded that gluten-A-S contains adenosine combining sites different in strength.

## Discussion

It has been shown [10] that gluten protein preparations contain purine or pyrimidine derivatives (nucleic acids, nucleotides, nucleosides or bases). Robinson et al [8] isolated adenosine from gluten extract by chromatography and electrophoresis and showed that it was the factor responsible for the inhibitory effect of gluten proteins on intestinal peristalsis. It may thus be anticipated that purine or pyrimidine derivatives bound to gluten proteins and liberated in the bowel are capable of inhibiting acetylcholine production and in this way intestinal motility may play some intermediary role in the pathomechanism of coeliac disease.

Salt precipitability of gluten proteins decreases when adenosine is added to the medium (Fig. 1). This led us to the idea that a protein component containing adenosine and soluble in saline could be isolated. Such a fraction may be useful in immunological and inhibition experiments where solubility at various pH values is an important requisite.

We succeeded in isolating a gluten fraction soluble in saline at various pH values by salt fractionation of gluten in the presence of adenosine. This fraction, gluten-A-S, differs from gluten and gluten-A-P by its amino acid pattern: it contains less glutamine and glutaminic acid and more proline and phenylalanine (Table I). Also, the sum of apolar amino acid (Pro, Gly, Ala, Val, Met, Ile, Leu, Phe) concentrations is higher in gluten-A-S (47.7%) than in gluten (41.6%) or gluten-A-P (43.9%). In spite of the higher participation of apolar amino acids, gluten-A-S has a better solubility in water or saline.

Sodium dodecylsulphate polyacrylamide gel electrophoresis revealed the presence of a component with a molecular weight of 74,000 dalton and, after pretreatment with mercaptoethanol, two fractions weighing 58,000 and 34,000 dalton, respectively, were obtained.

The absorption maximum of gluten and gluten-A-P is at 275 nm, that of gluten-A-S at 260 nm. The latter may be due to the adenosine bound to gluten-A-S, or to a high participation of phenylalanine in the protein structure. The second possibility can be

excluded since a high phenylalanine content leads to four maxima, at 253, 259, 265 and 269 nm [4]. Since the gluten-A-S preparation has a single maximum at 260 nm and the presence of adenosine in a quantity of 50 nmol/mg protein can be demonstrated, it may be regarded as proven that gluten-A-S (with a ratio $E^{280nm}/E^{260nm} = 0.5$) does in fact contain adenosine.

In some preliminary experiments the eventual inhibitory effect of gluten-A-S was tested; it exerted no or hardly any effect on the acetylcholinesterase of the fragmented sarcoplasmic reticulum isolated from the muscle tissue of the fish Amiurus nebulosus (this preparation has a very high enzyme activity: 1–2 μmol acetylcholine per mg protein/minute) [9], nor on the adenosine-triphosphatase activity of actomyosin isolated from rabbit muscle by the method of Portzehl et al [7]. It is also probable that the adenosine content of the gluten-A-S fraction, which is released from its binding in the intestinal lumen, is not sufficient to interfere with acetylcholine production and, consequently, with intestinal peristalsis. We suppose that much more adenosine would be needed for such an effect. However, in addition to the non-dialysable adenosine, gluten-A-S probably contains a fairly large amount of adenosine which is easily liberated from the protein molecule, as can be judged from Figure 5. This rapidly released adenosine may exert an inhibitory effect on acetylcholine production and intestinal motility.

Our finding concerning a large quantity of adenosine loosely bound to gluten-A-S and its possible effect on peristalsis needs experimental confirmation by studies on the adenosine binding sites of gluten, their number, quality and binding constants.

## Acknowledgement

We are indebted to Mrs I. Korom and to the medical student Emese Kiss for help in carrying out the experiments.

## References

1. Beckwith AC, Wall JS, Jordan RW: Reversible reduction and reoxidation of the disulfide bonds in wheat gliadin. Arch Biochem 112:16, 1965
2. Csorba S, Szabolcs M, Kávai M, Jezerniczky J, Szabó B: Über die Antigenität des Gliadins und die Antikörper gegen Gliadin. Acta Paediatr Acad Sci Hung 16:249, 1975
3. Davis JB: Disc electrophoresis II. Method and application to human serum proteins. Ann NY Acad Sci 121: 404, 1964
4. Drabikowski W, Dabrowska R, Barlyko B: Separation and characterization of the constituens of troponin. Febs Lett 12:148, 1971
5. Frazer AC: The present state of knowledge on celiac syndrome. J Pediatr 57:262, 1960
6. Lowry OH, Rosebrough NJ, Farr AR, Randall RJ: Protein measurement with the Folin phenol reagent. J Biol Chem 193:265, 1951
7. Portzehl H, Schramm G, Weber H: Aktomyosin und seine Komponenten. Z Naturforsch 5b:61, 1950
8. Robinson GB, Schneider R, Frazer AC: A substance from wheat gluten, which inhibits the intestinal peristaltic reflex. Biochim Biophys Acta 93:143, 1964
9. Szabolcs M, Kövér A, Kovács L, Rácz M: Some properties of the sarcoplasmatic reticular fraction of fish (Amiurus nebulosus) muscle. Acta Biochim Biophys Acad Sci Hung 1:233, 1966
10. Szabolcs M, Csorba S, Kávai M, Francia I Szabó B: Eigenschaften des

Gliadins und der Antikörper gegen Gliadin bei Zöliakie. Acta Paediatr Acad Sci Hung 18:155, 1977
11. Szabolcs M, Csorba S, Hauck M: Physikochemische und funktionelle Eigenschaften des aus Brot isolierten Gliadins und seiner verschiedenen Fraktionen. Acta Paediatr Acad Sci Hung 22: 165, 1981
12. Taylor NW, Cluskey JE: Wheat gluten and its glutenin component: Viscosity, diffusion and sedimentation studies. Arch Biochem Biophys 97:399, 1962
13. Weber K, Osborn M: The reliability of molecular-weight determinations by dodecyl sulfate acrylamide gel electrophoresis. J Biol Chem 244:4406, 1969

*Received September 20, 1982*

M Szabolcs Ph D
P.O. Box 3
H-4012 Debrecen, Hungary

*Acta Paediatrica Hungarica, 24 (2), pp. 159–168 (1983)*

# Primary aortitis in childhood

G JÓJÁRT, B ZÁBORSZKY, E SZONDY, M HORVÁTH and I HEGEDÜS

Municipal Hospital, Cegléd; National Institute of Cardiology; Arteriosclerosis Working Group of the Ministry of Health; Third Department of Medicine, Semmelweis University Medical School; and Pest County Hospital, Budapest

The case of a 5-year-old boy affected by autoimmune aortitis is reported. The onset was acute, the progression rapid. Hypertension, absence of right radial pulse, elevated ESRand immune globulin levels, cellular and humoral immunity against blood vessel wall were observed. The tests suggested an autoimmune origin of the aortitis. On immunosuppressive treatment the signs of activity disappeared and the condition improved and after captopril treatment the blood pressure decreased.

During the last thirty years an increasing body of reports has been published on obstructive panarteritis of the aorta and the great arteries. The disorder is rare in Europe, especially in children. We describe here a case in whom immunological studies relevant to the aetiology of the disease have been carried out.

## REPORT OF A CASE

The five years old boy was first admitted on 25 September, 1979. He had fever, experienced thickening of his fingertips and pain in the extremities and the chest one month before admission. At admission we saw a normally developed boy with dyspnoea, pale skin and clubbed fingers. A marked jugular and epigastrial pulsation could be observed. No pulse was palpable on his right arm and above the right subclavian artery. Pronounced pulsation was present in his left extremities while a reduced pulse was observed in the right lower extremity. No difference could be demonstrated in the circumference of the extremities. Oscillation was hardly measurable on his right arm, it was reduced on the right leg. No blood pressure could be measured on the right arm, the value was 180/120 mmHg on the left arm. The flush method gave a blood pressure of 105 on the right arm, 150 on the left arm, 120 on the right and 155 mmHg on the left leg. Above the abdominal aorta a systolic murmur was heard. The liver was enlarged by 2 cm. The eyegrounds were normal.

Chest X-rays revealed an enlarged heart with a dilated left ventricle and markedly dilated aorta. The ECG showed signs of left ventricular hypertrophy. Intravenous pyelography gave normal findings.

Laboratory findings: ESR: 40 mm/h; WBC: 10.5 G/l; haemoglobin: 1.44 mmol/l (9.3 g/dl). Blood smears urinalysis, platelet count, serum iron, total lipid, cholesterol, creatinine, glu-

cose, urinary vanylmandelic acid, liver function tests, LE cell tests, VDRL were normal. The Mantoux test showed a normergic reaction. Serum total protein was 69 g/l; albumin: 0.39; alpha$_1$: 0 07; alpha$_2$: 0.14; beta: 0.18; gamma globulin: 0.22. Plasma sodium and chloride, were normal, plasma potassium 3.6 mmol/l.

Vasodilator treatment resulted a drop of the blood pressure measured on the left arm to a value of 135/90 mmHg.

As the parents refused the recommended aortography, the child was discharged after prescription of antihypertensive treatment.

He was readmitted on 2 March 1980, in an unconscious state and having clonic convulsions. His blood pressure was 240/130 mmHg on the left arm. Anticonvulsive, antihypertensive and dehydrating treatment resulted in regain of consciousness. The eyeground arteries showed constriction, the Gunn sign was positive. This time the laboratory findings were ESR: 60 mm/h; WBC: 11.4 G/l; plasma potassium: 4.1 mmol/l; serum total protein: 78 g/l; gamma globulin: 0.28; IgG: 20.5 g/l; IgM: 2.80 g/l; IgA: 3.20 g/l; CRP: 50 mg/l; alpha$_1$-antitrypsin: 6.1 g/l; alpha$_1$ acid glycoprotein: 2.54 g/l; haptoglobin: 4.25 g/l; $C_3$ 0.90; $C_4$, 0.48 g/l; no antinuclear factor was found in the serum.

The following blood pressure values were obtained by the ultrasound method: right brachial artery: 120, left brachial artery: 170, arteria dorsalis pedis, right: 140, left: 175; arteria tibialis posterior, right: 142, left: 190 mmHg.

This time the parents consented to the aortography. The hepatic and lienal arteries showed normal filling, the distal section of the aorta showed unevenness and multiple constrictions. The initial section of the left renal artery was narrow, the right renal artery could not be distinguished (Fig. 1). The left iliac artery showed two constricted sections shortly after the bifurcation of the aorta, on the right side the common iliac artery showed a complete obstruction over a two cm long segment adjacent to the bifurcation. The external and internal iliac artery was intensively filled up through collateral vessels (Fig. 2).

As an autoimmune process against the blood vessel wall was suspected, immunological studies were carried out. Human aorta affected by lipid plaques and normal vena cava intima were used as antigens. The antigens were applied as an extract prepared with calcium chloride — tris — citrate buffer [46]. Since it was supposed that the specifically reacting fraction of the blood vessel antigen is a low density lipoprotein, LDL antigen prepared by gradient ultracentrifugation was used for testing the cell-mediated immunity. The tests performed were a modified leucocyte migration test [45] for cellular immunity (normal value MI = 0.8 to 1.2), passive haemagglutination [4] for humoral immune responses (normal value below 1 : 32), for circulating

immune complexes a modified method of complement consumption and Clq solubility [9] (normal values below 15% and 0.28, respectively) and a method utilizing polyethyleneglycol (PEG) precipitation [13] (normal value below 0.04).

The following results were obtained.

Cellular immune response: MI = = 0.32 in the presence of aorta antigen, 0.39 with venous antigen, 0.31 with LDL antigen. The MI value was 0.55 in the presence of aorta antigen plus autologous serum, 0.32 with LDL plus adresone, 0.43 with LDL plus azathioprine, 0.30 with LDL plus clofibrate. Humoral immune reponse: 1 : 256 with aorta antigen, 1 : 2048 against venous intima. Circulating immune complexes: negative result with complement consumption test, 0.35 with Clq solubility test, 0.02 with PEG precipitation.

The inhibition of leucocyte migration in the presence of aorta and vein wall antigen or LDL pointed to cellular sensitization and, at the same time, elevated levels of humoral antibodies against blood vessel wall antigens were demonstrated. It was therefore decided to apply immunosuppressive treatment with dexamethasone and chlorambucil and, in addition, vasodilatory, sympathicolytic and diuretic therapy.

As a result, blood pressure stabilized at 200/120 mmHg. The steroid was administered in a gradually

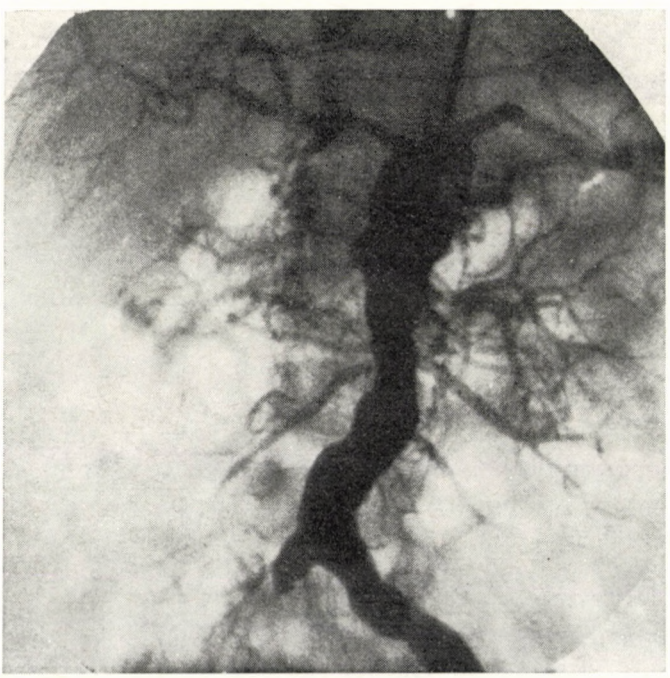


FIG. 1 Lumbar aortography. The aorta has roughly uneven contours with multiple constrictions. The left renal artery is constricted near the aorta, no right renal artery can be distinguished

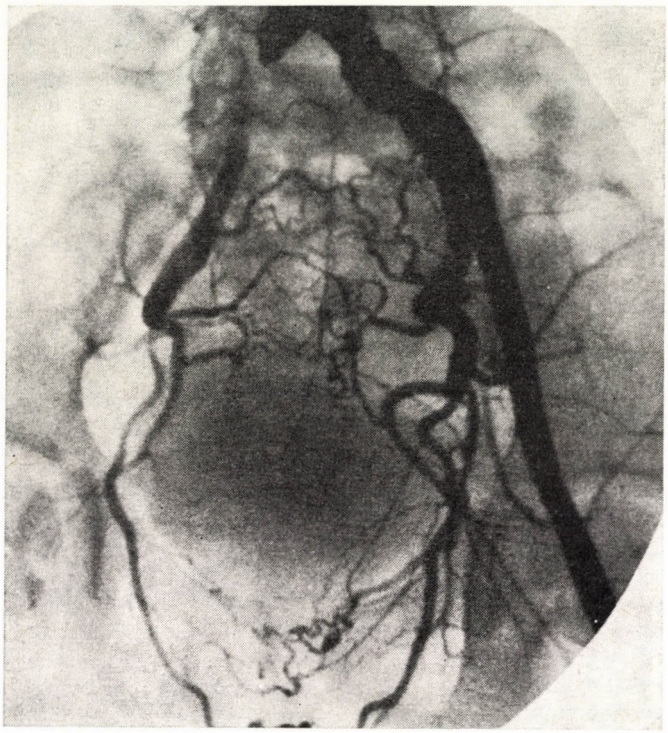


FIG. 2 The left common iliac artery shows two narrow segments after the bifurcation. The right common iliac artery displays a two cm long completely obliterated segment. The right external and internal iliac arteries fill through the extensive collateral network

decreasing dose over 4 months, chlorambucil for 5 months. The boy's condition improved, he became free of complaints, the laboratory findings normalized. The circumference of the right arm showed a reduction by 1.5 cm in comparison to that of the left arm. and a 1 cm difference developed between the femoral circumference values. By January, 1981, blood pressure became 150/110 mm Hg on the right arm, the right radial pulse became palpable. By this time the ESR again increased to a value of 45 mm/h, the previously normal gamma globulin value was again elevated to 0.25, and IgG was 12.8 g/l, with normal values for all other immune globulins. Renin activity in blood plasma gave a basal value of 33 ng/ml/24 h, after 2 hours of walking it was 40 ng/ml/24 h (with our method the normal basal value lies between 5 to 16 ng/ml/24 h).

Histological examination of a specimen removed from the pectoralis major muscle showed normal arterioles. In the specimen, by immunofluorescent methods no IgA, IgE, IgG, IgM, C' or fibrin could be found. The studies involving immunity against blood vessel wall antigens were again carried out, with the following results: MI: 0.79 in the pres-

ence of aorta antigen, 0.68 with venous antigen. Humoral immune response against aorta antigen: 1 : 1024, against venous wall antigen: 1 : 128. Circulating immunocomplexes: negative with complement consumption test, 0.46 with the Clq solubility test, 0.03 with PEG precipitation.

The relapse of the autoimmune process has made us to reintroduce dexamethasone and chlorambucil treatment. Chlorambucil was applied for 4 months and in October, 1981, the steroid is still taken. On captopril with diuretic treatment the blood pressure decreased to 125/80 mmHg. The patient's condition now is satisfactory and the laboratory findings are normal.

## Discussion

Primary aortitis attacks the great vessels rich in elastic fibres. The inflammatory process begins in the adventitia near to the media, with round cell infiltration. As the disorder proceeds, panarteritis and periarteritis develop, with destruction of the elastic fibres [6, 17, 18, 21, 22, 23, 30, 41]. Weakening of the blood vessel wall can lead to development of saccular aneurysms, proliferation of the intima may narrow the lumen which then may completely be obstructed by thrombi formed in the constricted segments. In most cases the aortic disorder is segmental, alternation of diseased and uninjured segments results in an irregular lumen. The great arteries are usually attacked at their arisal from the aorta. The blood vessels are obstructed gradually, leaving time for development of a collateral circulation. The disorder may also involve the pulmonary artery [19, 22, 26, 30, 31].

Any segment of the aorta may be involved, the symptoms may thus be variable. The various forms of localization were regarded as separate disorders, therefore the condition has many synonymous descriptions: aortic arch syndrome, pulseless disease, young women's arteritis, (obliterative) brachiocephalic aortitis, atypic coarctation, "inverse" coarctation, middle aorta syndrome, panaortitis syndrome, epiaortic arteritis, Takayasu's disease, Takayasu's syndrome, Takayasu's aortitis, etc.

The disease proceeds in two phases. In the first, systemic symptoms are characteristic: fatigue, loss of weight, headache, pain in the chest and extremities, anaemia, oedema, fever, dyspnoea, tachycardia, clubbing of fingers, exanthem, pericarditis, iridocyclitis [8, 19, 23, 29, 35, 52]. This stage is followed by the obliterative phase in weeks or months, the symptoms greatly depend on the localization of obliteration. In our patient the occlusive symptoms developed about one month after the general complaints such as fever, chest and extremity pain, clubbing of fingers etc. had presented themselves.

If the aortic arch and the arteries arising from it are involved in the process, the term aortic arch syndrome is justified. The pulse is weak or unpalpable, blood pressure is unmea-

surable and oscillations are sharply reduced in the affected extremity. The extremity is weaker, colder and thinner than its counterpart. In our patient at the first admission the most striking finding was the unmeasurable blood pressure, the unpalpable pulse on the right arm with arterial hypertension on the left arm. When the carotid arteries are involved, symptoms of internal carotid occlusion may appear, and trophic disturbances such as loss of hair, necrosis of the nasal septum, fatigue of the masticatory muscles (so-called masticatory claudication) and hypoxic eye symptoms with transitory impairment of vision (visual claudication), iritis, iridocyclitis, cataract, microaneurysms of the eyeground arterioles, *de novo* formation of retinal blood vessels, ocular hypertension. Involvement of the lower extremities as seen in our patient, is rather unusual. Among the cases occurring in childhood, involvement of the abdominal aorta is frequent, most child patients have therefore hypertension [7, 12, 18, 23, 35, 52]. This in turn causes cardiomegaly, heart failure and eyeground symptoms in most patients.

The diagnosis can be confirmed by aortography.

In our patient blood pressure was elevated on the left arm from the beginning. This then became more pronounced and led to encephalopathy. Initially the eyeground was normal, but later the signs of arterial hypertension developed.

Primary aortitis is more frequent in Eastern countries. Nasu [31] collected 1844 cases from Japanese hospitals. Of the patients, 85 to 90% were women and only 3—4% were children, 17 were younger than 10 years and 151 were between 10 and 20 years at onset of the first symptoms. Child cases were reported from Japan, Korea, Thailand, India, Singapore, Mexico, Chile, USA, Australia, Africa, the Soviet Union and Germany [7, 10, 12, 17, 18, 22, 23, 25, 26, 30, 32, 33, 35, 37, 40, 41, 42, 43, 47, 51, 52, 53]. Among the children, 85—90% were girls. The youngest patient was 9 months old [53].

The aetiology of the disease is a a matter of controversy. The tuberculous and the autoimmune origin has the highest number of believers. Many patients had had tuberculosis in their history, in some cases the tuberculous process was still active at the time of the onset of aortitis. On the other hand the tuberculous origin of the disease cannot be accepted since the diseased arteries show no sign of tuberculosis and in the vascular wall no acid fast bacteria can be demonstrated (this happened only once, in the case cited in reference 22). In the countries with a high incidence of aortitis tuberculosis is rather frequent their coexistence may thus be a coincidence. If tuberculosis has any role in the pathogenesis it is exerted by some allergic mechanism [21, 22, 26, 52]. Others think that primary aortitis is an autoimmune disease independent of tuberculosis [16, 20, 23, 27, 29, 36, 50, 55].

In patients affected by aortitis the laboratory findings point to an auto-

immune origin: the erythrocyte sedimentation rate is accelerated in the active phase of the disease, the level of alpha$_2$ and gamma globulin, of IgG and IgM is usually elevated, mild anaemia is frequent and a moderate increase of the leucocyte count is the rule [2, 5, 14, 19, 23, 29, 36, 44, 52].

Primary aortitis may be associated with other autoimmune disorders like rheumatoid arthritis [15, 24, 25, 38], polymyositis [28], glomerulonephritis [54], ulcerative colitis [5], terminal ileitis [3], ankylosing spondylitis [34], and systemic lupus erythematosus [24].

Immunity against the vascular wall has been investigated by several authors with various results. Many [2, 14, 39, 44] were unable to demonstrate antibodies against the wall of aorta or large arteries in the serum of their patients. Others [16, 20, 27, 29, 48, 50, 55] succeeded in finding such antibodies. In addition to differences in the methods, it may be anticipated that the patients were in different stages of the disease. It may also be supposed that the aetiology of the disorder is not quite homogeneous.

At the first admission of our patient, ESR, and the serum levels of alpha$_2$ and gamma globulin were elevated. During the most active phase of autoimmune processes, markedly increased IgG, moderately increased IgM and IgA, increased levels of acute phase proteins in the presence of normal complement levels, were encountered. Studies of immune reactivity against vascular wall performed in this stage showed an exaggerated immune response to aortic and venous wall antigens, both cellular and humoral. The level of circulating immune complexes was slightly increased.

Treatment led to some improvement but then a relapse ensued. In this period the IgG level was a multiple of the normal, the acute phase proteins, however, gave a normal value. The cellular reaction to the vascular wall could not be demonstrated while the humoral response to aortic wall was markedly augmented and the level of circulating immune complexes showed an increase over the previous values. The immunological findings therefore suggested an autoimmune origin.

The therapy of primary aortitis is an unresolved problem. Some think that steroid treatment is ineffective [5, 23, 26, 41], others reported on good results with corticosteroids [1, 8, 14, 20, 29, 32, 50]. Antimetabolite treatment has been thought to be effective but experience with it is scarce [11, 54]. A good effect can be expected in the early phase of the disease thus an early diagnosis is of importance [19 44].

In our case the disease showed rapid progress as long as no treatment was given. Corticosteroid and antimetabolite therapy resulted in improvement, the laboratory parameters improved, the aortitis became inactive. The previously impalpable pulse on the right arm reappeared but this had to be ascribed to an improvement of the collateral circulation since the right subclavian artery showed no

pulsation. Three months after termination of the first course of treatment there was a relapse as expressed by the increased ESR and gamma globulin level. A second course of immunosuppressive treatment led to disappearance of the signs of activity without decreasing the blood pressure. This then decreased on captopril treatment.

Severe arterial occlusions may be treated surgically, but the results are questionable and this kind of treatment does not resolve the underlying disease; progression of the latter may abolish the beneficial effect of surgery. Therefore, surgery is indicated only if there occur severe functional disturbances [8, 20, 26], especially in connection with stenosis of the aorta or the renal arteries. After unilateral constriction of the renal artery, nephrectomy may abolish hypertension but later the other renal artery may become involved and the hypertension will return [7]. Since in our case the abdominal aorta was involved together with both renal arteries, there is no chance for reconstructive surgery.

The prognosis of primary aortitis cannot be predicted exactly. Out of the 1844 patients of Nasu [31] 100 died, but only one out of the 17 patients under 10 years. The prognosis seems to be independent of age, laboratory findings or localization; it is said to be favourable if there is no complication or only one of mild degree (retinopathy, hypertension, aortic regurgitation or aneurysm [9]. With severe or multiple complications, 30% of the patients die within 5 years.

## Acknowledgements

We are indebted to Dr. I. Kolonics (Department of Angiology, National Institute of Cardiology) for advices, to Dr. S. Sonkodi (First Department of Medicine, University Medical School, Szeged) for renin determination, to Professor Edit Beregi and Dr. O. Régiusz (Centre of Gerontology, Semmelweis University Medical School, Budapest) for histological and immune fluorescence examinations.

## References

1. Ask Upmark E: On the "Pulseless disease" outside of Japan. Acta Med Scand 149:161, 1954
2. Asherson RA, Asherson GL, Schrire V: Immunological studies in arteritis of the aorta and great vessels. Br Med J 3:589, 1968
3. Bigot R, Cateau P, Chermet J, Doyon D, Monnier JP: Iléite terminale et maladie de Takayasu. Ann Radiol (Paris) 16:767, 1973
4. Boyden SV: The adsorption of proteins on erythrocytes treated with tannic acid and subsequent hemagglutination by antiprotein sera. J Exp Med 93:107, 1951
5. Chapman R, Dawe C, Whorwell PJ, Wright R: Ulcerative colitis in association with Takayasu's disease. J Am Dig Dis 23:660, 1978
6. Cheitlin MMD, Carter CPB: Takayasu's disease. Unusual manifestations. Arch Intern Med 116:283, 1965
7. Danaraj TJ, Wong HO, Thomas MA: Primary arteritis of aorta causing renal artery stenosis and hypertension. Brit Heart J 25:153, 1963
8. Fraga A, Mintz G, Valle L, Flores Izquierdo G: Takayasu's arteritis: Frequency of systemic manifestations (study of 22 patients) and favorable response to maintenance steroid therapy with adrenocorticosteroids (12 patients). Arthritis Rheum 15:617, 1972
9. Füst G, Szondy É, Székely J, Nánai I, Gerő S: Studies on the occurrence of circulating immune complexes in vascular diseases. Atherosclerosis 29:181, 1978
10. Gelfand M: Case reports: Giant cell arteritis with aneurismal formation in an infant. Br Heart J 17:264, 1959

11. Gilligan BS: Brachiocephalic arteritis in a young female (Takayasu's disease). Clin Exp Neurol 14:100, 1977
12. González-Cerna JL, Villavicencio L, Molina B, Bessudo L: Nonspecific obliterative aortitis in children. Ann Thorac Surg 4:193, 1967
13. Hasková V, Kaslik J, Riha I, Matl I, Rovensky J: Simple method of circulating immune complex detection in human sera by polyethylene glycol precipitation. Z Immunitaetsforsch 154:399, 1978
14. Hirsch MS, Aikat BK, Basu AK: Takayasu's arteritis. Report of five cases with immunological studies. Bull Johns Hopkins Hosp 115:29, 1964
15. Hope-Ross P, Bien EJ, Palladino VS, Graham G: Rheumatoid arthritis. Report of an unusual case. Ann Int Med 52:682, 1960
16. Ikeda M: Takayasu's disease. Immunological studies. Jpn Circ J 30:87 1966
17. Isaacson C, Klachko DM, Wayburne S, Simson JW: Aortitis in children. Lancet 2:542, 1959
18. Isaacson C: An idiopathic aortitis in young Africans. J Pathol 81:69, 1961
19. Ishikawa K: Natural history and classification of occlusive thromboaortopathy (Takayasu's disease). Circulation 57:27, 1978
20. Ito I: Aortitis syndrome with reference to detection of anti-aorta antibody from patients' sera. Jpn Circ J 30:75, 1966
21. Jellinek H, Littmann I, Süle É, Földi M, Máthé Z: Takayasu's disease and tuberculosis. Acta Med Acad Sci Hung 16:5, 1960
22. Kinare SC: Nonspecific aortitis (Takayasu's disease). Autopsy study of 35 cases. Path Microbiol 43:134, 1975
23. Lee K, Sohn K, Hong C, Kang S, Berg K: Primary arteritis (Pulseless disease) in Korean children. Acta Paediatr Scand 56:526, 1967
24. Lesoff MH, Glynn LE: The pulseless syndrome. Lancet 1:799, 1959
25. Lomas RW, Bolande RP, Gibson WM: Primary arteritis of the aorta in a child. Am J Dis Child 97:87, 1959
26. Lupi-Herrera E, Sánches-Torres G, Marcushamer J, Mispireta J, Horwitz S, Vela JE: Takayasu's arteritis. Clinical study of 107 cases. Am Heart J 93:94, 1977
27. Maekawa M, Ishikawa K: Immunological studies of aortitis syndrome. Jpn Circ J 30:79, 1966
28. Miller GAH, Thomas ML, Medd WE: Aortic arch syndrome and polymyositis with LE cell in peripheral blood. Br Med J 1:771, 1962
29. Nakao K, Ikeda M, Kimata S, Niitami H, Miyakora M, Ishimi Z, Hoshiba K, Takeda Y, Ozawa T, Matsushita S, Kuramochi M: Takayasu's arteritis. Clinical report of eighty four cases and immunological studies of seven cases. Circulation 35:1141, 1967
30. Nasu T: Pathology of pulseless disease. A systemic study and critical reviews of 21 autopsy cases reported in Japan. Angiology 14:225, 1963
31. Nasu T: Takayasu's truncoarteritis in Japan. A statistical observation of 76 autopsy cases. Path Microbiol 43:140, 1975
32. Numano F, Isohisa I, Kishi U, Arita M, Maezawa H: Takayasu's disease of twin sisters. Possible genetic factors. Circulation 58:173, 1978
33. Okumi M, Iijima MD, Kobayashi N, Saity I: Primary arteritis in children: Report of three cases. Paediatr Univ Tokio 7:32, 1962
34. Paloheimo JA, Julkunen H, Siltanen P, Kajander A: Takayasu's arteritis and ankylosing spondylitis. Acta Med Scand 179:77, 1966
35. Paton BC, Chartikavanij K, Buri P, Prachuabmoh K, Jumbala MRB: Obliterative aortic disease in children in the tropics. Circulation 31:(Suppl I) 197, 1965
36. Riehl JL, Brown JB: Takayasu's arteritis. An autoimmune disease. Arch Neurol 12:92, 1965
37. Roberts WC, Wibbin EA: Idiopathic panaortitis, supra-aortic arteritis, granulomatous myocarditis and pericarditis. Am J Med 41:453, 1966
38. Sandring H, Welin G: Aortic arch syndrome with special reference to rheumatoid arthritis. Acta Med Scand 170:1, 1961
39. Sano K, Saito I: Immunological studies of pulseless disease. Neurol Med Chir (Tokyo) 8:28, 1966
40. Saveleva LA, Sivkova A: Pulseless disease in childhood. Pediatrija 42:67, 1963
41. Sen PK, Kinare SG, Kulkarni TP, Parulkar GB: Stenosing aortitis of unknown etiology. Surgery 51:317, 1962
42. Sen PK, Kinare SG, Engineer SD, Parulkar GB: The middle aortic syndrome. Br Heart J 25:610 1963
43. Steeger A, Vargas L: Enfermedad de Takayasu. Rev Chil Pediatr 31:377, 1960
44. Strachan RW, Wigzell FW, Anderson JR: Locomotor manifestations and serum studies in Takayasu's arteriopathy. Am J Med 40:560, 1966

45. Szabó G, Szegedi Gy, Fekete B, Petrányi Gy: The investigation of cellular immune reactivity by leukocyte migration test. Orv Hetil 113:134, 1972
46. Szondy É, Jobbágy A, Link E, Gerő S: Immunological studies with aortic and venous tissue antigens I. The antigen structure of vascular tissues. Arterial Wall 3:81, 1975
47. Ueda H, Ito I, Saito Y: Studies on arteritis, with special reference to pulseless disease and its diagnosis. Naika (Japan) 15:239, 1965
48. Ueda H, Saito Y, Ito I, Yamaguchi H, Sugiura M, Morooka S: Immunological studies of aortitis syndrome. Jpn Heart J 8:4, 1967
49. Ueda H, Saito Y, Morooka S, Ito I, Yamaguchi H, Sugiura M: Immunological studies of aortitis syndrome. Jpn Heart J 9:73, 1968
50. Ueda H, Saito Y, Yamaguchi H, Takeda T, Morooka S, Ito I: Further immunological studies of aortitis syndrome. Jpn Heart J 12:1, 1971
51. Wagenvoort CA, Harris LE, Brown AL, Veeneklaas GMH: Giant cell arteritis with aneurism formation in children. Pediatrics 32:861 1963
52. Warshaw JB, Spach MS: Takayasu's disease (primary aortitis) in childhood. Case report with review of literature. Pediatrics 35:620, 1965
53. Westphal J, Löbbecke F, Mietens C: Arteritis der von Aorta abgehenden großen Gefäße (Takayasu-arteritis) im Säuglingsalter. Klin Paediatr 188:570, 1976
54. Zillulero GE, Ferrer P, Garcia OL, Moore M, Pardo V, Strauss J: Takayasu's arteritis associated with glomerulonephritis. A case report. Am J Dis Child 132:1009, 1978
55. Yoshitoshi Y, Seki K, Susuki H, Masuyama K, Yamana Y, Koida K, Eto S: Immunological studies in Takayasu's disease. Jpn J Intern Med 22:1450, 1968

*Received October 29, 1981*

G Jójárt MD
Városi Kórház
H-2701 Cegléd, Hungary

*Acta Paediatrica Hungarica, 24 (2), pp. 169—174 (1983)*

# The importance of cow's milk protein intolerance in chronic diarrhoea of children

Ágnes VÁRKONYI, Márta BODA and Ida SZABÓ

Department of Paediatrics, University Medical School, Szeged

A survey is given of the cases diagnosed as cow's milk protein intolerance in the last 5 years. The diagnosis was established on the basis of the regression of clinical symptoms after elimination from the diet of cow's milk and their recurrence after milk challenge. In more than half of the cases intestinal biopsy was carried out; three patients were rebiopsied after milk challenge.

Intestinal biopsy is indicated solely in cases when the exclusion of coeliac disease is necessary for the correct diagnosis.

Cow's milk protein intolerance denotes a condition where the immunological reaction elicited by the consumption of cow's milk is accompanied by clinical symptoms[12].

The existence of intolerance to cow's milk was first described at the beginning of this century [1] but even in the forties the condition was considered to be rare, probably because only the most serious cases could be diagnosed [9]. Then the criteria established by Goldman et al [5] and the relationship between cow's milk protein intolerance and the morphological changes of the jejunal mucosa discovered by Lamy et al [8] have facilitated the diagnosis. In spite of this, there is still no general agreement on its criteria [9, 10, 12, 15].

## Patients and Methods

A total of 35 patients, 16 boys and 19 girls, were studied. The diagnosis of cow's milk protein intolerance was based on the remission of symptoms after the elimination of cow's milk from the diet and the relapse that follows a milk challenge. Milk challenge was usually done twice with 5–10 ml/kg of pasteurized cow's milk. If there was no reaction after the first exposure, the challenge was repeated 24 h later. Intestinal biopsy was carried out in 28 patients. To exclude giardiasis, an impression smear was prepared from the biopsy material and stereomicroscopic observation was followed by histological examination with the light microscope and later by scanning electron microscopy.

## Results and Discussion

Figure 1 shows the average time of introduction of cow's milk in the diet, the presentation of clinical symptoms, the end of the illness and the beginning of the gluten containing diet. The clinical course can be seen in Fig. 2. Case 35 has been left out of consideration.

The time of introduction of cow's milk into the diet was at $2.8 \pm 1.8$ months of age. The shortest lactation time was one week, the longest 6 months. The time of the onset of symptoms was at $4.1 \pm 2.2$ months.

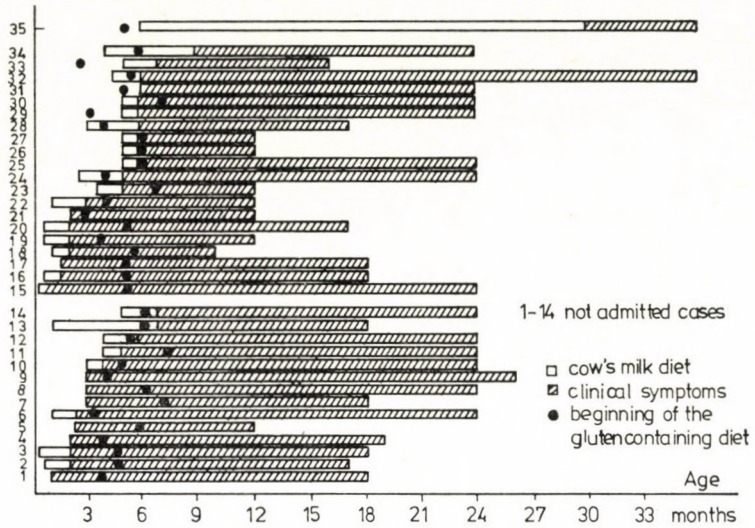



FIG. 1. Appearance of clinical symptoms of cow's milk protein intolerance

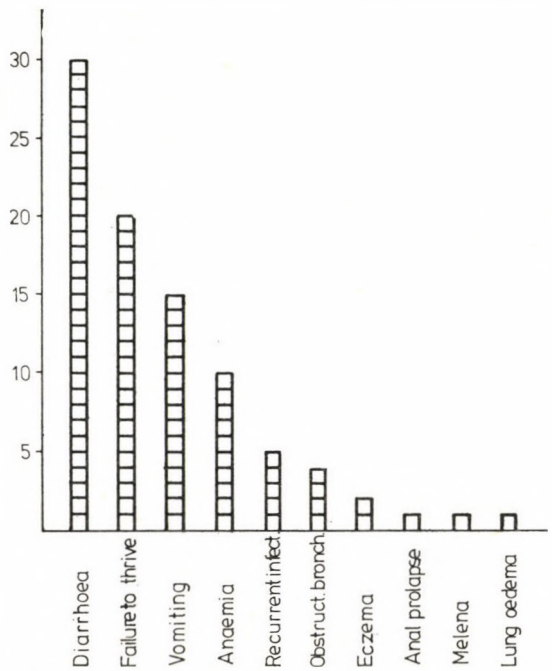



FIG. 2. Leading clinical symptoms at the beginning of cow's milk protein intolerance

TABLE I

Appearance of clinical symptoms of cow's milk protein intolerance

| | Age, months | | | |
|---|---|---|---|---|
| | At beginning of cow's milk diet | At onset of the disease | At beginning of gluten containing diet | At cessation of symptoms |
| X | 2.8 | 4.1 | 5.0 | 19.5 |
| SD | 1.8 | 2.2 | 1.2 | 5.6 |

This was in contrast with the observations that in 90% of the cases the symptoms would develop before the 3rd month of life [4, 5]. Kuitunen et al [7] even mention 2 months for presentation of the disease. [Table I].

In our patients the symptoms of cow's milk intolerance disappeared at $19.5 \pm 5.6$ months of age. In two cases the disease terminated only at the end of the third year of life. In one of them the symptoms presented after a serious viral infection at the age of 30 months, and cow's milk could be reintroduced into the diet at the age of 36 months. The other patient suffered from temporary IgA deficiency and had a recurrent giardiasis before the manifestation of cow's milk intolerance. In Case 34 the illness was preceded by an E. coli enteritis.

Introduction of a gluten containing diet was done at $5 \pm 1.2$ months of age. In two cases the gluten containing diet was started just after the symptoms of cow's milk intolerance had appeared. In every case when gluten was introduced earlier than a month before the appearance of symptoms of cow's milk intolerance, intestinal biopsy was performed right at the beginning to exclude coeliac disease.

Figure 2 shows the most frequent clinical symptoms of our patients with cow's milk intolerance. Corresponding to data in the literature the leading symptoms in our patients

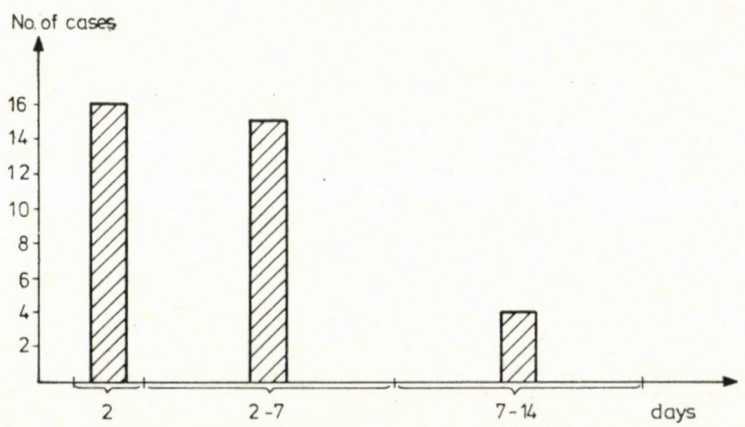



FIG. 3. Recurrence of symptoms after the first cow's milk challenge following a cow's milk free diet

were diarrhoea, failure to thrive and vomiting. Eczema was observed in two cases only; in one of these anal prolapse, in the other serious pulmonary oedema were the main complications. The degree of failure to thrive corresponded to about 10 percentile, while that of body height was generally between 25–50 percentile. In contrast with coeliac patients, the children with cow's milk intolerance usually had a well proportioned, slender constitution and they did seem to be seriously ill.

During the disease, a temporary lactose malabsorption was observed in 19% of the patients. In these cases milk challenge was delayed until lactose absorption had normalized.

Figure 3 shows the onset of symptoms after the first milk challenge. As it can be seen, they appeared within 48 h in 47% of the cases. In 11% we observed a coeliac disease-like reaction, where the symptoms only presented between the 7th and 14th day. These forms were difficult to diagnose. In the other cases the time between the milk challenge and the appearance of symptoms was between 2 and 7 days, in agreement with the fact that in cow's milk intolerance the change of digestive function is related to the damage to the intestinal mucosa [2, 3, 7, 8, 10, 13, 14].

In 7 children kept on cow's milk, intestinal biopsy revealed in two cases slightly increased cellular infiltration, in 4 patients partial villous atrophy (Fig. 4) and in one case a subtotal villous atrophy (Fig. 5). This latter

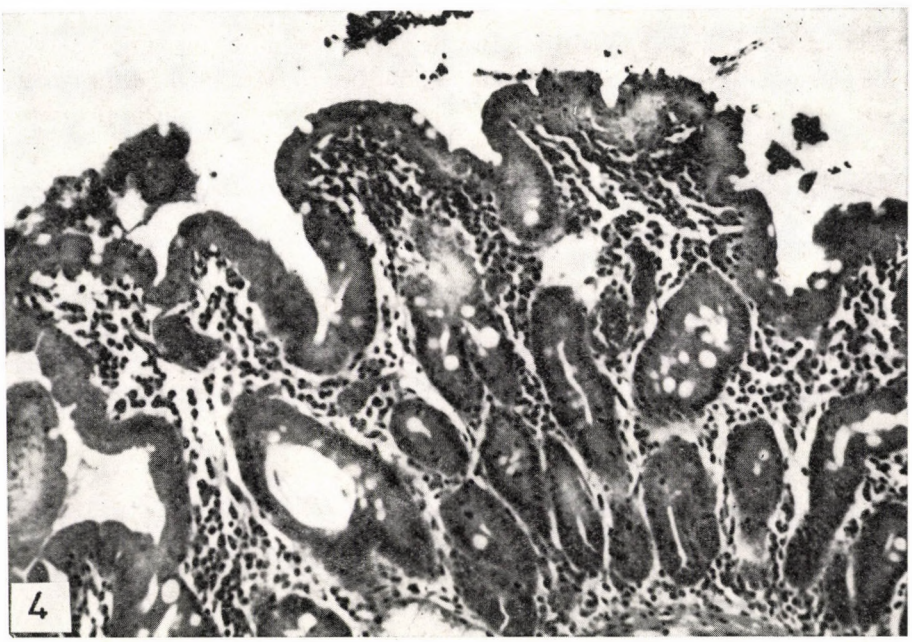



FIG. 4. Partial villous atrophy (haematoxylin eosin, × 40)

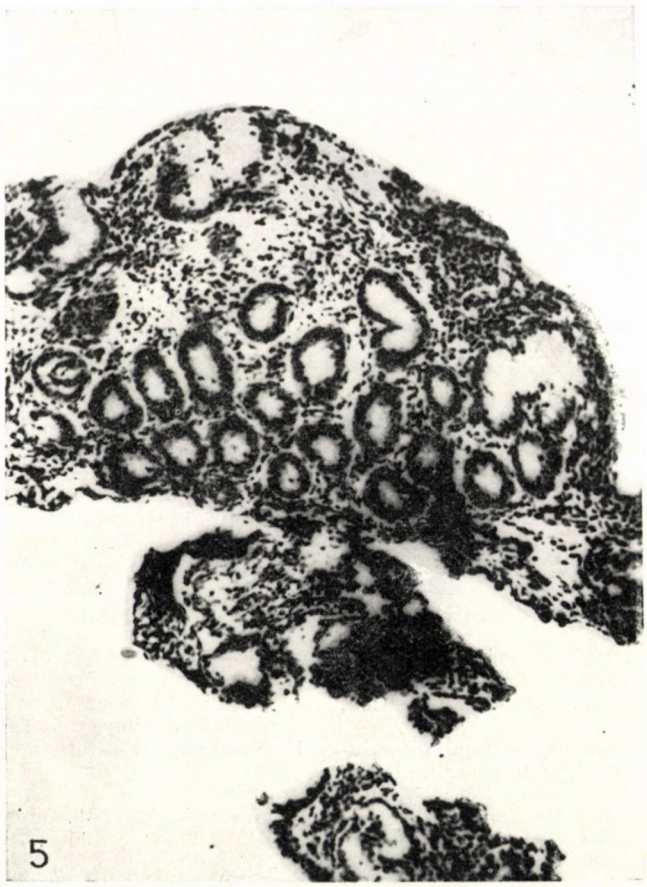



FIG. 5. Subtotal villous atrophy (haematoxylin eosin, × 40)

case subsequently developed into a typical coeliac disease.

In three cases the biopsy was performed before and following milk challenge which lead to partial villous atrophy in two of them. In the third case the light microscopical picture did not show any significant change, but scanning electronmicroscopy disclosed cellular oedema and microvillus destruction.

Three patients had already been on a cow's milk free gluten containing diet for a longer time when the intestinal biopsy was performed. Coeliac disease was clearly excluded by the biopsy. In one case *Giardia lamblia* was detected.

The elimination diet consisted of human milk, meat and vegetables. Changes in the diet always caused some difficulty because the infants had taken a liking to the one they had been given.

To conclude, cow's milk protein intolerance is a transitory illness limited to a certain age. Its diagnosis is an everyday problem which rests on the

history, the clinical symptoms and on the response to a cow's milk challenge after a cow's milk free diet given for a certain period. Intestinal biopsy is justifiable only if exclusion of coeliac disease is necessary for the correct diagnosis.

## Acknowledgements

We thank Dr. Gizella Karácsony from the First Department of Medicine of the University Medical School of Szeged for histologic evaluation of intestinal biopsy material.

## References

1. Finkelstein H: Kuhmilch als Ursache akuter Ernährungsstörungen bei Säuglingen. Monatschr Kinderheilkd 4:65, 1905
2. Fontaine JL, Navarro J: Small intestinal biopsy in cow's milk protein allergy in infancy. Arch Dis Child 50:357, 1975
3. Freier S, Kletter B: Clinical and immunological aspects of milk protein intolerance. Aust Paediatr J 8:140, 1972
4. Gerrard JW, McKenzie JWA, Goluboft N, Garson JZ, Maningas CS: Cow's milk allergy: Prevalence and manifestations in an unselected series of newborns. Acta Paediatr Scand [Suppl] 234:1, 1973
5. Goldman AS, Anderson DW, Sellers WA, Saperstein S, Kniker WT, Halpern SR: Milk allergy I. Oral challenge with milk proteins in allergic children. Pediatrics 32:425, 1963
6. Kuitunen P, Visakorpi JK, Hallman N: Histopathology of duodenal mucosa in malabsorption syndrome induced by cow's milk. Ann Paediatr 205:54, 1965
7. Kuitunen P, Rapola J, Savilahti E, Visakorpi JK: Response of the jejunal mucosa to cow's milk in the malabsorption syndrome with cow's milk intolerance. A light and electron-microscopic study. Acta Paediatr Scand 62:585, 1973
8. Lamy M, Nezelof C, Jos J, Frézal J, Rey J: La biopsie de la muqueuse intestinale chez l'enfant; premiers resultats d'une étude des syndromes de malabsorption. Presse Méd 71:1267, 1963
9. Lebenthal E: Textbook of Gastroenterology and Nutrition in Infancy. Raven Press, New York 1981, p. 689
10. Shiner M, Ballard J, Brook CGD: Intestinal biopsy in the diagnosis of cow's milk protein intolerance without acute symptoms. Lancet 2:1060, 1975
11. Verkasalo M, Kuitunen P, Savilahti E, Tiilikainen, A: Changing pattern of cow's milk intolerance. Acta Paediatr Sand 70:289, 1981
12. Visakorpi JK: Nahrungsmittelintoleranz im Säuglingsalter. Monatschr Kinderheilkd 128:166, 1980
13. Visakorpi JK, Immonen P: Intolerance to cow's milk and wheat gluten in the primary malabsorption syndrome in infancy. Acta Paediatr Scand 56:49, 1967
14. Walker-Smith JA: Cow's milk protein intolerance: transient food intolerance of infancy. Arch Dis Child 50:347, 1975
15. Walker-Smith JA, Harrison M, Kilby A, Phillips A, France N: Cow's milk-sensitive enteropathy. Arch Dis Child 53:375, 1978
16. WHO Committee Report: Contemporary patterns of breast-feeding. World Health Organization, Geneva 1981

*Received August 24, 1982*

Ágnes Várkonyi MD
P.O. Box 471
H-6725 Szeged, Hungary

*Acta Paediatrica Hungarica, 24 (2), pp. 175–187 (1983)*

# Six years mortality statistics in a Libyan paediatric hospital

R Singh and A Abudejaja

Department of Family and Community Medicine, Faculty of Medicine, University of Garyounis, Benghazi, Libya

During the six year period from 1975 to 1980, at Al-Fateh Paediatric Hospital 35,488 sick children under 12 years of age were admitted for in-patient treatment; 3 009 had a fatal outcome. The mortality rate per 1000 admissions and discharges respectively, was 54.9 and 52.1 in 1975; and 135.6 and 119.4 in 1980. The age specific mortality rate per thousand discharges was 219.4 for infants, 32.8 for 1 to 4 years, 21.7 for 5 to 9 years, 25.7 for 10 to 12 years of age. Although the overall mortality rate was almost equal for boys and girls, it was higher for boys below 1 year or over 10 years, and higher for girls between 1 to 9 years of age. The proportion of deaths and admissions was more during winter the season from September to January and during the summer season from May to July. More than 80% of those who recovered were admitted with acute respiratory infection, gastroenteritis, meningitis, diseases of urinary system, acute poisoning and symptoms or ill-defined conditions; whereas, more than 70% of expired cases were admitted with prematurity, gastroenteritis, septicaemia, acute respiratory diseases and congenital malformations. The case fatality in 1980 was 84.5% for septicaemia, 55.5% for prematurity, 41.7% for congenital malformations, 18.9% for malnutrition and 16.1% for diseases of nervous system.

## Introduction

For centuries mortality had been the primary determinant of population trends; it still remained so in many developing countries and formed the major challenge to the medical profession. It was the prevention of early deaths especially among infants and children that formed the primary objective of public health and social welfare departments. The mortality statistics were still an indispensable part of "informed decision" although in research fields there was growing concern for other phenomena such as fertility, morbidity, positive health, and provision for and use of health services [6, 7, 13, 17, 19].

Infant and childhood mortality is high in the developing countries. In some of these countries particularly in rural areas nearly one-half of all deaths occurred in infants and children under five years. It was calculated that 97% of all deaths below 5 years of age took place in less developed parts of the world [4, 5, 16, 20].

In the Eastern Mediterranean Region, of the approximately 11 million children born each year, about 1.5 million died in infancy and a further half million before the age of 5 years, constituting a 20% loss of liveborn babies [14]. A large number was due to preventable conditions; about half of them to diarrhoeal disease (often with malnutrition), respiratory dis-

TABLE I

Admitted, discharged

| Year | Admissions Total | Discharges | | | Deaths | | |
|---|---|---|---|---|---|---|---|
| | | Male | Female | Total | Male | Female | Total |
| 1975 | 6 566 | 3 516 | 3 068 | 6 604 | 203 | 160 | 363 |
| 1976 | 7 341 | 3 770 | 3 126 | 6 896 | 251 | 217 | 468 |
| 1977 | 5 951 | 3 113 | 2 475 | 5 588 | 246 | 194 | 440 |
| 1978 | 5 636 | 2 828 | 2 202 | 5 030 | 287 | 232 | 519 |
| 1979 | 4 920 | 2 413 | 1 933 | 4 346 | 346 | 278 | 624 |
| 1980 | 5 054 | 2 434 | 1 951 | 4 385 | 329 | 266 | 595 |
| Total | 35 488 | 18 074 | 14 775 | 32 849 | 1 662 | 1 347 | 3 009 |

eases, immunizable infections and diseases of early neonatal and early childhood periods. The mortality among infants and children occupied a prominent place in the region and appeared to outweigh all other problems.

High child mortality figures, however, dropped quite steeply in the near past. One such drop occurred 20 to 30 years ago when infant mortality rate in Europe and North America dropped from 120 to 26 per 1000 live-births, in many instances despite of economic recession and unemployment [4]. A dramatic decline occurred more recently in general mortality, infant and childhood mortality in Libya along with some other Arab, Asian and South American countries [2]. High childhood mortality is not simply dependent on economic status but is affected by the specific health programmes particularly when the former become ineffective.

Therefore, the problem of infant and childhood mortality has been studied at the Al-Fateh Paediatric Hospital, Benghazi, where annually more than five thousand children utilized the indoor treatment facilities and more than four hundred of them died. Benghazi had a total of 433 301 inhabitants in 1980; from 1972 to 1979, the birth rate fluctuated between 46.1 to 50.6 per 1000 live births and the crude death rate varied from 6.0 to 11.1 per 1000 population [8].

The present study included collection of information from the records of all the sick children aged 12 years or less who were admitted from 1975 to 1980. The conditions were classified according to the international classification of diseases or injuries (1965) and for tabulation included the underlying cause or disease process. The findings were compared with previous reports when available.

## Materials and Methods

The hospital at present affords 200 in-patient beds distributed among medical, neonatal, and isolation wards. The staff on

and dead patients, 1975—1980

| Discharges and deaths | | | Mortality rate per 1000 discharges and deaths | | | Mortality rate per 1000 admissions |
|---|---|---|---|---|---|---|
| Male | Female | Total | Male | Female | Total | |
| 3 719 | 3 248 | 6 967 | 54.5 | 49.2 | 52.1 | 54.9 |
| 4 021 | 3 343 | 7 364 | 62.4 | 64.9 | 63.5 | 67.8 |
| 3 359 | 2 669 | 6 028 | 73.2 | 72.6 | 72.9 | 78.7 |
| 3 115 | 2 434 | 5 549 | 92.1 | 95.3 | 93.5 | 103.1 |
| 2 759 | 2 211 | 4 970 | 125.4 | 125.7 | 125.5 | 143.5 |
| 2 763 | 2 217 | 4 980 | 119.0 | 119.9 | 119.4 | 135.6 |
| 19 736 | 16 122 | 35 858 | 84.4 | 83.4 | 84.0 | 91.6 |

July 1st, 1981, included 464 members as follows: 9 university teaching staff, 15 registrars and senior registrars, 28 senior house officers, 120 nurses, 50 nursing aids, 39 laboratory specialists and technicians, and 203 administrative and other supportive staff. On the average 10 to 12 interns at a time were posted for paediatric training throughout the year.

## Results and Discussion

### *Year and season*

There were 35,488 admissions, 32,849 discharges and 2009 deaths at Al-Fateh Paediatric Hospital during the period from 1975 to 1980 (Table I). The average number of admissions and deaths over the period were: 5914 and 501 per year, 493 and 42 per month, and 16 and 1.4 per day respectively. During the period under review the number of admissions decreased from 6566 in 1975 to 5054 in 1980, but the number of deaths increased from 363 in 1975 to 595 in 1980. The mortality rate between 1975 and 1980 increased from 54.9 to 135.6 per 1000 adminissions and from 52.1 to 125.5 per 1000 discharges (Table I). Thus the mortality rate per unit of admissions or discharges more than doubled in the six year period. However, the general mortality rate and crude birth rate in Benghazi showed no upward trend with only slight fluctuations from year to year [8]. The annual death rate per thousand discharges increased steadily year after year which was documented to be 52.1 in 1975, 63.5 in 1976, 72.9 in 1977, 93.5 in 1978, 125.5 in 1979 and 119.4 in 1980 (Table I).

Monthwise, a higher proportion of deaths were recorded from September to January though more admissions were recorded from May to July. The cumulative average mortality rate ranged from 90 to 106.3 in November, December and January, and 68.2 to 74.2 in May, June and July. The mortality trends were similar whether the denominator was per 1000 admissions or discharges. The mortality rate per 1000 discharges in 1980 also doubled

TABLE II

Mortality rate per 1000 discharges including deaths by month, 1975—80

| | Mortality rate per 1000 discharges including deaths | | | | | |
|---|---|---|---|---|---|---|
| | 1975 | 1976 | 1977 | 1978 | 1979 | 1980 |
| January | 74.4 | 90.5 | 70.2 | 101.4 | 115.1 | 98.9 |
| February | 75.9 | 77.4 | 81.3 | 93.7 | 79.6 | 137.8 |
| March | 84.7 | 54.9 | 70.2 | 80.4 | 91.8 | 161.3 |
| April | 52.0 | 48.5 | 72.7 | 121.5 | 128.8 | 121.2 |
| May | 46.9 | 43.3 | 27.8 | 85.2 | 138.8 | 148.6 |
| June | 63.5 | 67.1 | 61.3 | 78.3 | 84.7 | 105.2 |
| July | 28.3 | 46.4 | 61.4 | 86.8 | 115.0 | 106.0 |
| August | 33.7 | 50.8 | 110.6 | 86.9 | 130.2 | 105.2 |
| September | 39.0 | 57.8 | 82.4 | 92.5 | 162.6 | 104.4 |
| October | 41.2 | 72.4 | 69.0 | 91.9 | 138.8 | 109.8 |
| November | 48.5 | 80.4 | 89.5 | 78.1 | 156.1 | 116.1 |
| December | 54.8 | 96.0 | 90.7 | 127.8 | 126.1 | 137.7 |
| Total | 52.1 | 63.5 | 72.9 | 93.5 | 125.5 | 119.4 |

for individual months compared to their own rates in 1975 except for the month of January which had only a moderate increase of about 30% during the period (Table II).

*Duration of Hospitalization*

In 1980, of all dead patients 40.0% died within 48 h, 27.6% between 2–6 days, 15.1% between 7–13 days and 17.6% in 14 or more days. Mean hospitalization before death was 7.3 days with a usual range from a few hours to 64 days. There was a premature baby who stayed for 161 days in the hospital before he died. In 1979, 24.6% and 33.4% of all deaths were reported within 24 and 48 hours, respectively. Many of these children were brought to hospital in extreme conditions of shock and ill-health. Some parents are unwilling to bring their children to the hospital unless it is absolutely necessary and hence caused a delay in examination. Women often wait for their husbands before they transport their sick children to the doctor and often husbands will bring the child to hospital unaccompanied by the mother resulting in inaccurate clinical histories and a delay in treatment. To save the potentially avoidable deaths, the children would have to be brought or referred earlier for hospital admission.

*Age*

The proportion of dead and discharged cases during 1980 was 90.6% and 56.0% respectively under 1 year, 6.4% and 26.4% between 1–4, 3.0% and 17.6% over 5 years of age (Table

TABLE III

Mortality rate by age and sex, 1980

| Age | Discharges | | | | Deaths | | | | Mortality rate per 1000 discharges | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | | Male | Female | Total | | Male | Female | Total |
| 0—27 days | 235 | 245 | 480 | | 181 | 127 | 308 | | 770.2 | 518.3 | 641.6 |
| 28—365 days | 1 082 | 894 | 1 976 | | 127 | 104 | 231 | | 117.3 | 116.3 | 116.9 |
| Under 1 year | 1 317 | 1 139 | 2 456 | (56.0) | 308 | 231 | 539 | (90.6) | 233.8 | 202.8 | 219.4 |
| Under 1—4 year | 752 | 405 | 1 157 | (26.4) | 15 | 23 | 38 | (6.4) | 19.9 | 56.7 | 32.8 |
| Under 5—9 year | 263 | 198 | 461 | (10.5) | 3 | 7 | 10 | (1.7) | 11.4 | 35.4 | 21.7 |
| Under 10—12 year | 104 | 207 | 311 | (7.1) | 3 | 5 | 8 | (1.3) | 28.8 | 24.1 | 25.7 |
| Total 0—12 year | 2 437 | 1 948 | 4 385 | (100) | 329 | 266 | 595 | (100) | 135.0 | 132.4 | 136.5 |

In brackets: percentages

TABLE IV

Distribution of deaths by age group in Al-Fateh Paediatric Hospital, Benghazi, and Inter-American investigation of mortality in childhood

| Age group | Inter-American project, 1973* | | Al-Fateh Paediatric, Hospital, 1980 | |
|---|---|---|---|---|
| | No. | Per cent | No. | Per cent |
| Under 5 years | 35 095 | 100.0 | 577 | 100.0 |
| Under 1 year | 27 602 | 78.6 | 539 | 93.4 |
| Neonate (less than 4 weeks) | 12 674 | 36.1 | 308 | 53.3 |
| Postneonate (4 to 52 weeks) | 14 928 | 42.5 | 231 | 40.0 |
| 1—4 years | 7 493 | 21.4 | 38 | 6.5 |

* From Puffer, RR and Serrono, CV: Pattern of Mortality in Childhood. Report of Inter-American Investigation of Mortality in Childhood. Pan American Health Organization, Washington, D.C. 1973

III). The population distribution of children of 12 years or less in Benghazi as well as the whole of Libya was composed of 10% infants, 34.6% under 5 years and 54.4% between 5 to 12 years [9, 11]. Thus the proportion of admissions and deaths was 5 to 9 times higher for infants, almost equal for 1 to 4 years and 3 times less for 5—12 years of age than their respective representation in the population.

As to the deaths under 5 years of age, out of 577 (96.9% of the total), 53.3% were among neonates, 40.0% among postneonates; 93.4% for infants and 6.5% for 1–4 years in comparison to 36.1%, 42.5%, 78.6% and 21.4% respectively reported from the Inter-American Project (Table IV).

In 1980, the number of deaths per 1000 discharges was 641.6 for neonates (0–27 days), 116.9 for postneonates (28–365 days), 219.4 for infants (neonates and postneonates together), 32.8 for 1–4 years, 21.7 for 5–9 and 25.7 for 10–12 years of age (Table III). The age specific mortality per 1000 population in the whole of Libya was 78.5 under 1 year (per 1000 livebirths) 10.2 for 1–4 years, 1.8 for 5–9 years, and 1.1 for 10 to 12 years [12]. The age specific mortality rates in 1970–75 for more developed regions of the world ranged from 8.3 to 40.3 for infants and 0.4 to 2.0 for 1–4 years old [17]. Such rates in less developed regions varied from 85 to 130 for infants and 6 to 30 for 1–4 years of age [17]. Thus mortality rates in Libya though lower than the mortality rates of many developing countries were still 2 to 9 times higher for infants and 5 to 25 times higher for the 1–4 years age group in comparison to those reported from most of the developed countries [17, 20].

Within the country the mortality rate was 71 times higher for infants, 9 times for 1–4, 1.6 times higher for 5–9 years of age than that for 10–14 years, the lowest among the Libyan population [12]. The age specific mortality rate per thousand discharges in the present study during 1980 was

30 times higher for neonates, 5 times for postneonates, 1.6 times for 1 to 4 years and 1.2 times for 10 to 12 years of age in comparison to the lowest rate for 5 to 9 years [12, 16]. The risk of death both in developing and developed countries was universally lowest for the 5 to 14 years age group though the highest mortality rates were observed among the elderly in developed countries and among infants in developing countries [12].

*Sex*

Male children (under 12 years) formed 54.3 of admissions, 56.4% of deaths in the study whereas they form about 48% of the total population in Benghazi. The mortality rate per thousand discharges for boys and girls were 770.2 and 518.3 among neonates, 117.3 and 116.3 among postneonates, 233.8 and 202.8 among infants and 35.4 among the 5–9 years old and 28.8, and 24.1 among those aged 10 years or more (Table III). Although there were no significant difference in overall mortality rate by sex, the risk of death among boys was significantly higher during infancy and later childhood (10–12 years) thang among girls except between 1–9 years of age where, the reverse trend was observed. In comparison to the opposite sex the relative risk of death for boys was 1.15 times higher during infancy and over 10 years and 3 times lower between 1 to 9 years. The rates of infant and perinatal mortality at Benghazi have earlier been reported to be higher for males as also reported in most countries of the world except Czechoslovakia, Afghanistan, India and Nepal [1, 2, 3, 4, 9, 11]. In fact, over the last 30 years there was a rising trend in the male sex mortality rates over the female in all age groups; the increase, however, was not uniform. The lower mortality rates for females during infancy showed their constitutional superiority, high rates during 1–9 years indicated a possible inadequacy of care or attention due to male sex preference and the decrease after 10 years might be due to the victory over adverse social conditions and the influence of pubertal hormones.

Child loss in Libya has been observed to be 1.6 per every married woman and 1.2 per woman in the reproductive age group, a substantial loss to the mothers, families and the country [3].

*Leading causes of childhood mortality*

Out of 595 deaths, 141 (23.7%) were due to prematurity, 85 (14.4%) to diarrhoeal diseases (mostly gastroenteritis), 65 (10.9%) to respiratory infections (mostly pneumonia), 71 (11.9%) to septicaemia, 66 (11.1%) to congenital malformations, 44 (7.4%) to nervous system diseases (mostly meningitis), 30 (5.0%) to birth trauma, birth anoxia or hypoxia, 18 (3.0%) to malnutrition and anaemia, 27 (4.5%) to ill-defined conditions, and 13–15 (2.5%) each to haemolytic disease of the newborn and other specified diseases (Table V). A small number of deaths occurred due to renal disease

TABLE V

Causes of death in different age groups, 1980

| Medical causes or disease condition | Neonate (0—27 days) | | Postneonate (28 - 365 days) | | Infant (0—365 days) | | Under five (0—4 years) | | 0 - 9 years | 12 years or less | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | per cent | No. | per cent | No. | per cent | No. | per cent | No. | No. | per cent |
| Prematurity (unspecified) | 125 | 40.6 | 15 | 6.5 | 140 | 25.9 | 141 | 24.4 | 141 | 141 | 23.7 |
| Diarrhoeal diseases | 9 | 2.9 | 74 | 32.0 | 83 | 15.4 | 85 | 14.7 | 86 | 86 | 14.4 |
| Septicaemia | 28 | 9.1 | 32 | 13.8 | 60 | 11.1 | 70 | 12.1 | 70 | 71 | 11.9 |
| Acute respiratory disease | 21 | 6.8 | 36 | 15.6 | 57 | 10.6 | 64 | 11.1 | 64 | 65 | 10.9 |
| Congenital malformations | 37 | 12.0 | 22 | 9.5 | 59 | 10.9 | 63 | 10.9 | 65 | 66 | 11.1 |
| Diseases of nervous system | 19 | 6.2 | 18 | 7.8 | 37 | 6.8 | 39 | 6.6 | 42 | 44 | 7.4 |
| Birth trauma and birth anoxia | 28 | 9.1 | 2 | 0.8 | 30 | 5.6 | 30 | 5.2 | 30 | 30 | 5.0 |
| Ill-defined conditions | 20 | 6.5 | 6 | 2.6 | 30 | 4.8 | 27 | 4.7 | 27 | 27 | 4.5 |
| Malnutrition, anaemia, rickets, etc. | 1 | 0.3 | 12 | 5.2 | 13 | 2.4 | 17 | 2.9 | 18 | 18 | 3.0 |
| Haemolytic disease of newborn | 11 | 3.6 | 2 | 0.8 | 13 | 2.4 | 13 | 2.3 | 13 | 13 | 2.2 |
| Diseases of urinary system | 1 | 0.3 | 5 | 2.2 | 6 | 1.1 | 9 | 1.6 | 10 | 10 | 1.7 |
| Infectious hepatitis | 0 | — | 3 | 1.3 | 3 | 0.6 | 5 | 0.8 | 5 | 5 | 0.8 |
| Leukaemia and lymphoma | — | — | 1 | 0.4 | 1 | 0.2 | 1 | 0.2 | 2 | 4 | 0.6 |
| Other diseases | 8 | 2.6 | 3 | 1.3 | 11 | 2.0 | 13 | 2.3 | 14 | 15 | 2.52 |
| Total | 308 | 100.0 | 231 | 100.0 | 539 | 100.0 | 577 | 100.0 | 587 | 595 | 100.0 |

TABLE VI

The cause and age specific mortality rate (case fatality rate per 100 cases) in 1980

| Conditions | Total cases discharged, or dead | | | Dead | | | Case fatality rate | | |
|---|---|---|---|---|---|---|---|---|---|
| | Under 1 year | 1—12 years | Total | Under 1 year | 1—12 years | Total | Under 1 year | 1—12 years | Total |
| Respiratory diseases | 847 | 573 | 1 420 | 57 | 8 | 65 | 6.72 | 1.39 | 4.57 |
| Diarrhoeal diseases | 986 | 203 | 1 189 | 83 | 3 | 86 | 8.41 | 1.47 | 7.23 |
| Ill-defined conditions | 293 | 341 | 634 | 26 | 1 | 27 | 8.87 | 0.41 | 4.25 |
| Dieases of nervous system | 141 | 132 | 273 | 37 | 7 | 44 | 26.24 | 5.30 | 16.11 |
| Disease of urinary system | 34 | 134 | 168 | 6 | 4 | 10 | 17.64 | 2.49 | 5.95 |
| Acute poisoning | 19 | 133 | 152 | — | 1 | 1 | — | 0.75 | 0.65 |
| Other diseases (specified) | 20 | 115 | 135 | 11 | 2 | 13 | 55.00 | 1.73 | 9.62 |
| Prematurity (unspecified) | 253 | 1 | 254 | 140 | 1 | 141 | 55.33 | — | 55.51 |
| Haemolytic disease of newborn | 126 | — | 126 | 13 | — | 13 | 11.50 | — | 11.50 |
| Congenital anomalies | 97 | 61 | 158 | 59 | 7 | 66 | 60.82 | 11.4 | 41.77 |
| Malnutrition anaemia | 13 | 82 | 95 | 13 | 6 | 18 | 100.00 | 7.31 | 18.94 |
| Rheumatic fever/rheumatic heart disease | 19 | 48 | 67 | — | 1 | 1 | — | 2.08 | 1.49 |
| Surgical conditions | 10 | 46 | 56 | — | — | — | — | — | — |
| Infectious diseases | 3 | 57 | 60 | 3 | 2 | 5 | 100.00 | 3.50 | 8.33 |
| Malignancy | 1 | 40 | 41 | 1 | 3 | 4 | 100.00 | 7.50 | 9.75 |
| Birth trauma/birth anoxia | 68 | — | 68 | 30 | — | 30 | 44.11 | — | 44.11 |
| Septicaemia | 70 | 14 | 84 | 60 | 11 | 71 | 85.75 | 78.57 | 84.52 |
| Total | 2 995 | 1 980 | 4 980 | 539 | 56 | 595 | 17.99 | 2.82 | 11.95 |

Frequencies are based on 10% randomized sample of discharges plus total deaths.

(10 cases), infectious hepatitis (5 cases), malignancy (4 cases), and 1 each to kerosene poisoning and rheumatic heart disease. Among the discharged cases more than 80% were due to respiratory infections (1420 cases), diarrhoeal disease (1189 cases), ill-defined conditions (634 cases), diseases of the nervous system (273 cases), and of the urinary system (168 cases), and acute poisonings (152 cases). The majority of admissions was due to respiratory infections, gastroenteritis, pneumonia, septicaemia and congenital malformations.

The case fatality was 11.95% for all diseases among all age groups, 17.99% under 1 year and 2.82% for 1–12 years of age (Table VI). The risk of death from all diseases together was nearly 7 times higher among infants than those over 1 year of age. The case fatality rate was 84.5% for septicaemia, 55.5% for prematurity, 44.1% for birth trauma and birth anoxia, 41.7% for congenital malformations, 18.9% for malnutrition and anaemia, 16.1% for meningitis, and 11.5% for haemolytic disease of the newborn (Table VI). The case fatality rate for diseases like respiratory infections, diarrhoeal diseases, renal disease, malignancy, rheumatic heart disease and ill-defined conditions varied between 1.4 to 9.7%. Children with acute poisoning had a case fatality of 0.65% which was the lowest among all causes. The common agents of poisoning necessitating admission in the order of frequency were kerosene, drugs (barbiturates, salicylates) and insecticides (Flit, Baygon, etc.).

The 66 deaths due to congenital anomalies included 24 cases of congenital heart disease, 21 of unspecified congenital malformations, 7 each of multiple congenital anomalies and congenital malformations of the nervous system including 1 spina bifida, 3 of Down syndrome and one of congenital malformation of the kidney. The other specified conditions comprised hepatic failure (3 cases), mental retardation (2 cases), coagulation defect (2 cases) and one case each of scarlet fever, pneumothorax, head injury, Reye's syndrome, aplastic anaemia and 2 others.

The case fatality rate among infants for all the diseases was 2 to 30 times higher than in the older age groups (1–12 years), except for prematurity and other conditions confined to infants. The protection provided by breast feeding against infections and death in young childhood has been confirmed both for the underdeveloped and the industrialized countries [20, 21]. Hospital admissions for diarrhoeal diseases were more common in weaned infants and the case fatality was significantly higher among weaned children, particularly for measles, diarrhoeal diseases and acute lower respiratory tract infections [21]. Differences in infant and childhood mortality between developing and developed countries exist not only in the level of mortality but also in the leading causes of death [5, 6, 7, 14, 15, 16, 18, 19]. Those of our hospital and also community based studies [1, 2] showed the preponderance of prematurity, diarrhoeal dis-

TABLE VII

Leading causes of child deaths at Al-Fateh Paediatric Hospital, Benghazi in 1980, compared with developing countries and developed countries*

| Age group | Infants | 1–4 years |
|---|---|---|
| Benghazi (Al-Fateh Paediatric Hospital) | Prematurity (unspecified), diarrhoeal diseases, septicaemia, acute respiratory infections, congenital malformation, meningitis, birth injuries | Septicaemia, acute respiratory infections, congenital anomalies, malnutrition, renal diseases, infectious hepatitis, diarrhoeal diseases |
| Developing countries | Diarrhoeal diseases, acute respiratory infections, etc., whooping cough | Diarrhoeal diseases, acute respiratory infections, etc., measles |
| Developed countries | Birth injuries, congenital anomalies, influenza, pneumonia, diarrhoeal diseases | Accidents, congenital anomalies, malignant neoplasm, acute respiratory infections |

* Summarized from WHO Technical Report Series No. 600, 1976.

eases, septicaemia, acute respiratory infections, congenital anomalies, meningitis and birth trauma among the leading causes of infant deaths; and septicaemia, acute respiratory infections, congenital anomalies, malnutrition and renal diseases among the 1–4 year old fatalities (Table VII). The most common causes of infant mortality were diarrhoeal diseases and acute respiratory infections in developing regions; and birth injuries, congenital anomalies and to some extent respiratory infections and diarrhoeal diseases in developed countries [12, 16, 17]. In developing countries the real frequency of congenital anomalies and birth injuries was concealed due to overshadowing by other infective and parasitic diseases. The main causes of childhood mortality in developing nations were indeed the continuation of conditions operating during infancy with addition of measles or malaria; whereas in developed countries accidents and malignancy occupy important positions in childhood mortality [5, 16, 17, 20].

## CONCLUSIONS

In our hospital, during 1975 to 1980 the mortality rate varied between 52.1 (1975) to 125.5 (1978) per 1000 discharges and progressively increased by years. The higher proportion of deaths was observed from September to January though a higher proportion of admissions occurred from May to July. The highest documented mortality rate of 106.8 was for the month of December and the lowest of 68.2 was observed for the month of May. The death rates had doubled for almost all months between 1975 to 1980 which pointed to the necessity of more detailed investigations of the factors responsible for such changes. The death rates were higher for males

during infancy most probably due to the constitutional superiority of females, and higher for females during early childhood (1–9 years) possibly due to neglected care or poor attention to girls, and higher among males thereafter which could be due to the superior constitution along with the benevolent influence of pubertal hormones among girls. The mortality rates were inversely proportional to age. The mortality rate of 641.6 per 1000 discharges among neonates was reduced to 116.3 (1/4) by the post-neonatal period, 32.8 (1/20) by 1–4 years, 21.7 (1/29) by 5 to 9 years and 25.7 (1/25) by 10 to 12 years of age. The risk of death was inversely proportional to age and was observed to fall dramatically with the increase in age.

Prematurity, septicaemia, congenital anomalies, and birth trauma or birth anoxia contributed to approximately 50% of all deaths; whereas these formed only 11.3% of total admissions. A need was felt to further analyse the above mentioned four causes by refining the diagnosis and predisposing factors. The future reduction of mortality among children in homes and at the hospital in particular was obviously linked to the prevention and early efficient management of such conditions.

## References

1. Abudejaja A, Gupta BS, Singh R, Khan AU, Legain M: Perinatal Mortality at Benghazi in 1977. Garyounis Med J 4(2):15, 1981
2. Abudejaja A, Singh R, Khan MA: Trends and factors of infant mortality in Benghazi and Libyan Jamahiriya. Garyounis Med J 5(1):37, 1982
3. Abudejaja A, Singh R, Khan MA, Legain M: Pregnancy wastage, child losses and reproductive profile of Libyan Women. International Conference: The Child and Arabic Medicine. Faculty of Medicine, University of Al-Fateh, Tripoli, S.P.L.A.J., March 1982
4. Harfouche JK: Health care problems of the young child in a developing ecological context. Bull WHO 57(3):387, 1979
5. Puffer RR, Serrano CV: Patterns of mortality in childhood; PAHO, PASIB, Regional Office of World Health Organization, Scientific Publication No 262, Pan American Organization, Washington pp. 1–38, 1963
6. Rayan M: Aspects of male mortality. Br Med 284:181, 1981
7. Rui-Zhu Ling: A brief account of 30 years' mortality of Chinese population. World Health Stat Q 34(2):127, 1981
8. Secretariat of Census and Statistical Department: Municipal Office, Benghazi, 1981
9. Secretariat of Census and Statistical Department: Population Census Summary Data 1973, Tripoli 1977
10. Secretariat of Census and Statistical Department: Statistical Abstract of Libya 1978, Tripoli 1980
11. Secretariat of Census and Statistical Department: Vital Statistics of the Socialist People's Libyan Arab Jamahiriya 1978. Tripoli 1980
12. United Nations: Demographic Year Book, United Nations, New York, 1978 and 1979
13. WHO: Manual of Mortality Analysis. Division of Health Statistics, World Health Organization, Geneva 1977
14. WHO: The present state of child health in the region EM/RC 28/Tech.Disc. 1. Regional Office for the Eastern Mediterranean, World Health Organization, Geneva 1978
15. WHO: Infant and Early Childhood Mortality in Relation to Fertility Patterns: Report on AD-Hoc Survey in Greater Kabul Afghanistan 1972–1975. World Health Organization Regional Office for the Eastern Mediterranean, EM/ST/120; E/AFG/DHS/002/FP, 1978
16. WHO: World Health Statistical Annual: Vital Statistics and Causes of Death. World Health Organization, Geneva 1979
17. WHO: The world's main problems. World Health Forum, 2:264, 1981

18. WHO: Clinical management of acute respiratory infections in children. Bull. WHO 59(5):707, 1981
19. WHO: Mortality in Asia. WHO Chron 35:163, 1981
20. WHO Interaction of Nutrition and Infection, World Health Organization, Geneva 1968
21. Walsh JA, Warren KS: Selective primary health care: An interim strategy for disease control in developing countries. N Engl J Med 301:967, 1979

*Received September 20, 1982*

R Singh M D
P. O. Box 7578
Birka Post Office
Benghazi, Libya

*Acta Paediatrica Hungarica, 24 (2), pp. 189–194 (1983)*

# Positive skin prick tests of immediate type in non-allergic children

E Cserháti, Annemarie Gegesi Kiss, Györgyi Mezei, J Kelemen and Julianna Puskás

First Department of Paediatrics, Semmelweis University Medical School, Budapest

Prick tests with twenty different Bencard antigens were performed in 300 children aged 2–16 years, all having a negative individual and familial history for allergic disease. At least one positive result was obtained in 64% of the children and among the 6000 tests a total of 727 were positive. Of the positive tests 93% were + or ++, 7% were +++ or ++++. No relationship was found between age and the incidence of positive skin tests. Mild reactions against more than one antigen in the same individual were quite frequent, pronounced reactions (+++ or ++++) against more than one antigen were exceptional. The incidence of mild reactions was found to be independent of the gender; strong reactions occurred in girls twice as often as in boys. The highest incidence of positive reactions was observed with house-dust mite, pollens, hay and straw dust, and canine and feline hairs. The diagnostic value of mild positivity is slight but pronounced positivity, especially against more than one antigen, must carefully be considered and in any case followed by a bronchial provocation test.

Airway allergy plays a prominent role among diseases of allergic origin. Identification of the precipitating antigen is important in diagnosis and therapy alike, specific causal treatment being based on such a knowledge. The history, prick tests, RAST determinations and airway provocation tests are the most widely used tools in identification of the allergen(s). These methods are of various reliability. Reliability is satisfactory if (*i*) the method gives no negative result with the causative antigen and (*ii*) no false positive result occurs in healthy individuals. Immediate type skin reactions fulfil these expectations to a certain degree. Only to a certain degree since positive reactions may also be encountered among healthy persons.

In this study we have attempted to determine the incidence of positive prick tests among healthy Hungarian children.

## Materials and Methods

Three-hundred children, 146 boys and 154 girls ranging in age from 2 to 16 years, were selected for the study. The history revealed no allergic disorder in the children and in their first-degree relatives. The list of the twenty Bencard allergens used in the study can be seen in Fig. 3. The prick test was performed according to the recommendation of the makers: a drop of the solution containing the antigen is placed onto the flexor surface of the forearm, the prick is carried out by a lancet through the drop of antigen solution. The result is read after 15–20 min. A prick using the control solution supplied with the antigens is carried out in each case; this solution contains except the antigen itself all solvents and preservatives used throughout the procedure of production.

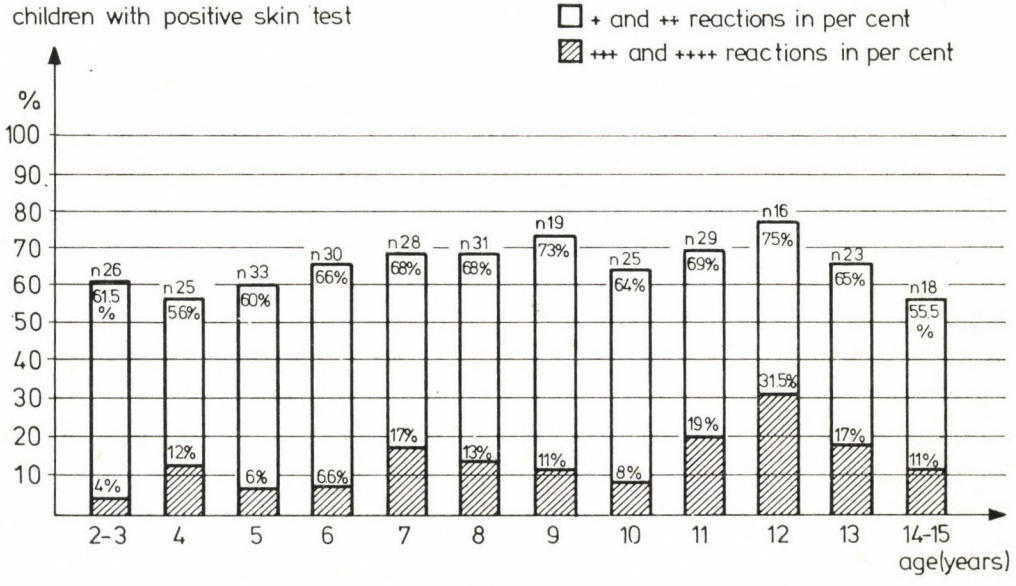

children with positive skin test
+ and ++ reactions in per cent
+++ and ++++ reactions in per cent
%
100
90
80
70
60
50
40
30
20
10
n 26
61.5 %
4%
n 25
56%
12%
n 33
60%
6%
n 30
66%
66%
n 28
68%
17%
n 31
68%
13%
n 19
73%
11%
n 25
64%
8%
n 29
69%
19%
n 16
75%
31.5%
n 23
65%
17%
n 18
55.5 %
11%
2-3
4
5
6
7
8
9
10
11
12
13
14-15
age(years)

FIG. 1

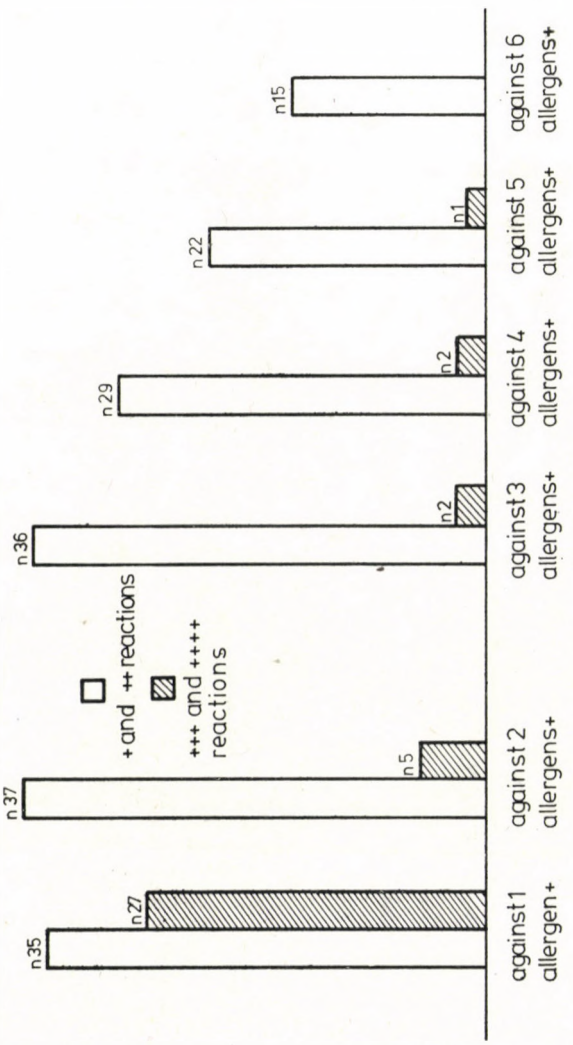

n35
n27
n37
n5
n36
n2
n29
n2
n22
n1
n15
+ and ++ reactions
+++ and ++++ reactions
against 1 allergen+
against 2 allergens+
against 3 allergens+
against 4 allergens+
against 5 allergens+
against 6 allergens+

FIG. 2

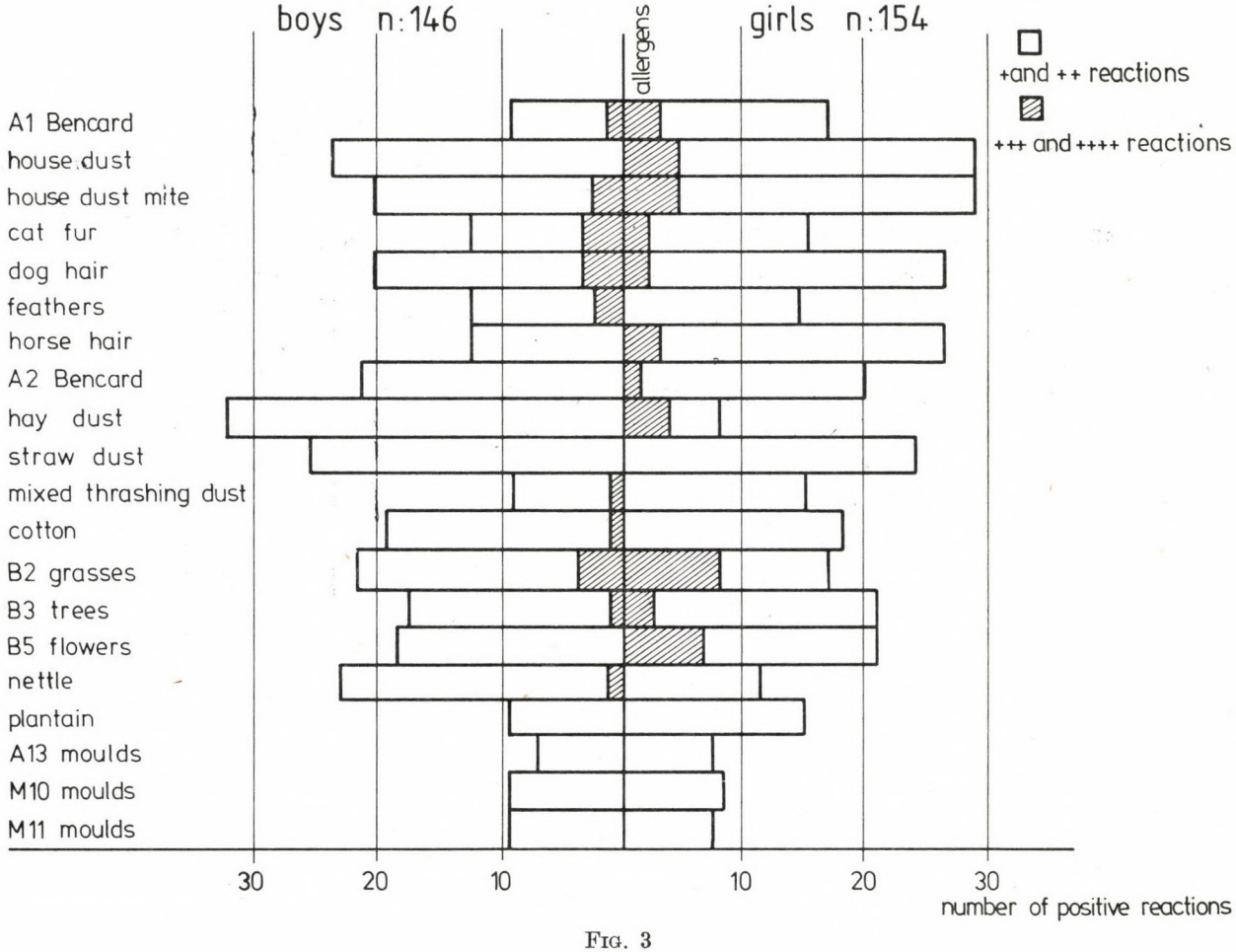

boys n:146
girls n:154
allergens
+and ++ reactions
+++ and++++ reactions
A1 Bencard
house dust
house dust mite
cat fur
dog hair
feathers
horse hair
A2 Bencard
hay dust
straw dust
mixed thrashing dust
cotton
B2 grasses
B3 trees
B5 flowers
nettle
plantain
A13 moulds
M10 moulds
M11 moulds
30
20
10
10
20
30
number of positive reactions

FIG. 3

In evaluation the following scoring was used

+ no urtica, erythema smaller than 3 mm in diameter;
++ urtica up to 3 mm in diameter, pronounced erythema;
+++ urtica 3–5 mm in diameter plus erythema;
++++ urtica exceeding 5 mm in diameter usually with pseudopodium formation, marked erythema.

## Results

Among the 6 000 tests, each 20 in 300 children, 727 were positive and 5 273 were negative. 93% of all positive results (95% in boys and 91% in girls) were of grade + or ++, while grades +++ or ++++ made up only 7% of all positive reactions (5% in boys, 9% in girls). 192 out of the 300 children had a positive reaction against at least one antigen; i.e. 64% for both sexes, 66% for boys and 62% for girls. In girls, the incidence of severe positivity (+++ or ++++) was twice as high as in boys. Unexpectedly, the incidence of positive skin reactions was not higher in school children than in children between 2 and 4 years of age; thus age did not seem to have any effect on this incidence (Fig. 1).

Mild, + or ++, reactions against a high number of antigens were seen quite frequently. Strong reactions, rating +++ or ++++, against more than one antigen were exceptional (Fig. 2).

Figure 3 demonstrates that mild reactions occurred with the same frequency in boys and girls; the more severe degrees of positivity are more frequent in girls.

The following antigens provoked positive reactions at an appreciable rate: house-dust, house-dust mite, hay and straw dust, pollens, canine and feline hairs (Fig. 2).

## Discussion

Positive skin reactions to various antigens are a common finding in healthy adults [3, 4, 6, 11, 12]. Halonen et al [6] found a higher incidence in young adults. In the accessible literature we found no data for healthy children. According to the present results, two-thirds of healthy Hungarian children aged 2 to 16 years, with no history of allergy, gave a + or ++ positive reaction against one or more of twenty Bencard allergens.

In agreement with data in the literature, we feel that the diagnostic and clinical importance of such positivity is very restricted. Our finding concerning strong +++ or ++++ positivity in a small but definite percentage of healthy children seems to be unique. This higher incidence of a strong positive result in girls (9%) compared to boys (5%) can be related to the observation that freedom from symptoms in the presence of an increased IgE level occurs more frequently in girls than in boys.

We have thus drawn the conclusion that + and ++ positivity is of questionable importance, and also that +++ or ++++ reactions cannot be regarded a dependable indication of allergy. Our findings corroborate the opinion [1, 2, 7, 8, 9, 10] that a strong positive result of a prick

test performed correctly is an indication for a bronchial provocation test, as even in the presence of a positive history and a positive prick test only 30—80% of the cases exhibit a positive reaction to the same allergen when used in a bronchial provocation test. According to these findings, immunotherapy protracted over years means to the patient a considerable load not without risks and is superfluous in 20—70% of the cases if indication for this form of treatment is based only on the result of the skin test. The closest relationship was found by all authors between the result of bronchial provocation and a ++++ positive skin test.

For evaluation of +++ or ++++ results we refer here to the findings of Hagy et al [5]; these authors performed skin tests in 903 healthy young persons and followed them during seven subsequent years. Allergic disease supervened with a significantly higher frequency in those exhibiting a strong positive reaction at the beginning of the study. Atopy in family members further increased the risk. Still, we feel that a positive reaction of +++ or ++++ intensity cannot simply be regarded as a normal scatter of the method.

*Received October 9, 1982*

E. Cserháti MD
Bókay J. u. 53
1083 Budapest, Hungary

## References

1. Aas K: Allergic asthma in childhood. Arch Dis Child 44:1, 1969
2. Bryant DM, Burns MW, Lazarus L: The correlation between skin tests, bronchial provocation tests and the serum level of IgE specific for common allergens in patients with asthma. Clinical Allergy 5:145, 1975
3. Davis JB: Asthma and wheezy bronchitis in children. Clin Allergy 6:329, 1976
4. Deamer WC: Pediatric allergy: some impressions gained over a 37 year period. Pediatrics 48:930, 1971
5. Hagy GW, Settipane GA: Risk factors for developing asthma and allergic rhinitis. A 7-year follow-up study of college students. J Allergy Clin Immunol 58:330, 1976
6. Halonen M, Barbee RA, Labowitz MD, Burrows B: An epidemiologic study of the interrelationship of total serum immunoglobulin E, allergy skin-test reactivity, and eosinophilia. J Allergy Clin Immunol 69:221, 1982
7. Hardt H von der, Meiser W: Allergentestungen beim kindlichen Asthma bronchiale. Monatschr Kinderheilkd 123:577, 1975
8. Hardt H von der: Allergologische Diagnostik und Behandlung der Bronchialerkrankungen beim Kinde. Monatschr Kinderheilkd 124:216, 1976
9. Jarisch R, Kummer F, Oppolzer R: Das "Asthmaprogramm". Wien Klin Wochenschr 87:740, 1975
10. Stemmann EA, Völker P, Both A, Schachoff R, Bayer J, Wilsing L: Diagnostische Differenzierung asthmatischer Syndrome zur Verbesserung therapeutischer Resultate. Monatschr Kinderheilkd 124:260, 1976
11. Tan WC, Teoh PC: An analysis of skin prick test reactions in asthmatics in Singapore. Ann Allergy 43:44, 1979
12. Whitcomb, N: Incidence of positive skin tests among medical students. Ann Allergy 29:67, 1971

*Acta Paediatrica Hungarica, 24 (2), pp. 195–199 (1983)*

# Prevention of adult cardiovascular disease in obese children

A Czinner, Mária Tichy and L Barta

First Department of Paediatrics, Semmelweis University Medical School, Budapest

An investigation was carried out to establish the risk factors of cardiovascular disease among obese children. Among 173 obese children 38% were endangered in respect of cardiovascular disease. The frequency of hyperlipoproteinaemia was near to 20%. It is considered necessary to separate these children from the group of obese children and to treat them according to the outlined aspects.

Nowadays, the aetiology of cardiovascular diseases, in other words, the risk factors which could lead to such disorders, are mostly known. And still we have to face difficulties when planning examination programmes in order to throw light on the risk factors in childhood.

Large screening programmes are known which take into consideration the whole child population, especially as regards lipid parameters. Others again propose only the screening of the risk-population, e.g. of children of parents recovered from juvenile heart infarction, considering that metabolic disturbances of lipoprotein are hereditary and even the way of life within one and the same family is alike [1].

Among the risk factors the importance of obesity is widely known. The decrease of physical working capacity goes together with obesity. The relationship between the latter and the high density lipoprotein-cholesterol level (HDL-C), which is a protective agent for the vessel walls, is also known. It seemed thus obvious to regard as a risk population the obese children free from endocrine changes and to start among them an investigation.

## Materials and Methods

From our out-patients we have selected 173 obese children, 90 girls and 83 boys without any disturbance of endocrine origin. Their mean age was $12.6 \pm 1.93$ years. In all children we measured on the right side of their body 5 skinfolds (biceps, triceps, subscapular, suprailiac, calf) with Holtain caliper and estimated the per cent of body fat according to Parizkova and Roth [10]. On the basis of anthropometrical data the body fat per cent of all boys was over 25% while that of the girls was over 30%.

A detailed family history was taken and after 12 hours fasting native and heparinized red blood cell samples were obtained from the children. Cholesterol and HDL-C were determined enzymatically, triglyceride according to Laurell, lipoid by agargel electrophoresis according to Noble. From the above data the frequency of hyperlipoproteinaemia was established.

After 5 minutes in lying position, blood pressure was repeatedly measured on all extremities.

The data obtained were elaborated and scored according to the system of Nora [9] as modified by us.

*Questions concerning family history*

1. Has a first-degree relative (parent or sibling) had a heart attack or coronary disease and/or a stroke with onset before age 45?
2. Has a first-degree relative had a heart attack, coronary disease and/or a stroke with onset before age 65?
3. Has a second-degree relative had a heart attack, coronary disease and/or a stroke with onset before age 65?
4. Does the child or a first-degree relative have juvenile onset diabetes?

*Questions concerning lipid and lipoproteinaemias*

5. Has the cholesterol level repeatedly been higher than 5.17 mmol/l?
6. Has the serum cholesterol level been repeatedly higher than 5.70 mmol/l?
7. Has the triglyceride level been repeatedly higher than 1.95 mmol/l?
8. Has the HDL-C level repeatedly been lower than 0.77 mmol/l?

*Questions concerning blood pressure, weight, smoking, physical working capacity*

9. Has the blood pressure repeatedly been higher than 140/90 mmHg?
10. Is the body fat per cent in boys higher than 25%, in girls higher than 30%?
11. Does the child perform vigorous exercise daily?
12. Does the child smoke?

*Counting of risk indexes*

| | Score |
|---|---|
| *Family history* (the single maximum score is 3) | |
| Coronary disease in first-degree relative before age 45 | 3 |
| Coronary disease in first-degree relative before age 65 | 2.5 |
| Coronary disease in second-degree relative before age 65 | 1 |
| Stroke in first-degree relative before age 45 | 1 |
| Stroke in second-degree relative before age 65 | 0.5 |
| *Lipids, lipoproteins* (add value to a maximum score of 2) | |
| Cholesterol higher than 5.70 mmol/l | |
| HDL-C under 0.77 mmol/l | 2 |
| Cholesterol higher than 5.17 mmol/l | 1 |
| HDL-C under 0.77 mmol/l (normal HDL-C, no point) | 1 |
| Triglyceride level higher than 1.95 mmol/l | 0.5 |
| *Blood pressure, weight, smoking, physical exercise* (add to all values) | |
| Smoking regularly | 1.5 |
| Juvenile diabetes in patient or first-degree relative | 1 |
| Lack of regular physical activity | 0.5 |
| Blood pressure higher than 140/90 mm Hg | 1 |
| Body fat per cent over 25% or 30% respectively | 0.5 |

## Results

We have processed the data of 173 out-patients according to the above aspects. Detailed results are given in Table I. On the basis of the family history (cardiac infarction, stroke) 7.5% of obese children obtained scores. If juvenile diabetes was included 17.9% of the children had a positive family history.

Considering the serum lipids and lipoprotein parameters, we have met

Table I

Frequency of risk factors in obese children (n: 173)

| | No. of cases | Per cent |
|---|---|---|
| *Family history* | | |
| Early onset coronary disease in first-degree relatives | 3 | 2 |
| Stroke in first-degree relatives | 5 | 3 |
| Coronary disease in first-degree relatives before age 65 | — | — |
| Coronary disease and stroke in second-degree relatives before age 65 | 5 | 3 |
| Diabetes (juvenile onset) in first-degree relatives | 18 | 10 |
| *Hyperlipoproteinaemia (Fredrickson)* | | |
| Type II/a | 16 | 9 |
| Type II/b | 6 | 3 |
| Type IV | 14 | 8 |
| Regular smoking | 6 | 3 |
| High blood pressure — 140/90 mmHg | 56 | 32 |
| Lack of physical activity | 147 | 85 |
| High body fat per cent | 173 | 100 |

Frederickson types II/a (9.2%), II/b (3.4%) and IV (8%). These data indicated scores for approximately 20% of the obese patients. In another study the frequency of hyperlipoproteinaemia was 9% among patients with normal weight.

Finally, blood pressure of 32.4% of the patients was repeatedly higher than 140/90 mm Hg; 3% were smoking regularly and 85% did not participate in any kind of sport apart from school gymnastics. All the patients were obese and, thus, were automatically given scores.

Risk scores and increased risks have been calculated according to Nora [9] as follows.

| *Risk score* | *Increased risk* |
|---|---|
| 3 | 2× |
| 3.5 | 3× |
| 4 | 5× |
| 4.5 | 6× |
| 5 | 15× |
| 5.5 | not calculable by present methods |

TABLE II

Development of risk scores in obese children (n: 173)

| Score | No. of cases | Per cent |
|---|---|---|
| 1–2.5 without risk | 106 | 61 |
| 3 | 33 | 19 |
| 3.5 | 16 | 9 |
| 4 | 7 | 4 |
| 4.5 | 7 | 4 |
| 5 | 3 | 2 |
| 5.5 | 1 | 0.5 |
| Total endangered | 67 | 38 |

On the basis of their scores, the 173 obese patients could be divided into six groups (see Table II).

## DISCUSSION

Berwick et al. [3] mention among the possibilities of screening and prevention in childhood, the following procedures.

1. Universal screening examination in 10-year-old children by determination of serum cholesterol level twice in all children or twice only in those where the first value has been found elevated.

2. Target screening in all children on the basis of questionnaires. With a positive family history (coronary disease) the serum cholesterol level should be estimated.

3. Triggered screening: serum cholesterol estimation in children whose parents have recovered from cardiac infarction.

4. Population-wide campaign, in the first place through mass media, in order to give dietary and living habit instructions.

5. School education for children aged 10 through 15, to offer, in the first place, dietary regulations.

Universal screenning, though in this field experiences already exists, is expensive, especially if not only the serum cholesterol but the level of the important HDL-C is also planned [2, 3, 4].

Our questionnaire differs from that recommended by Nora [9] in the following. We have put the age of juve-

nile cardiac infarction to an earlier age, 45 years, in accordance with literary data [1]. The lowest limit of serum cholesterol has been set at 5.17 mmol/l, on the basis of some statistics for populations outside Hungary [5, 7]. Recent data have shown the protective role of HDL-C; it was, therefore, considered important to determine it among the lipoprotein parameters. Instead of body weight, it seemed more correct to determine body fat per cent by the skinfold method; the data for boys (25%) and girls (30%) are the conventional limits of "obesity" [11]. Typifying of behaviour seems to be difficult in practice and therefore it was left out from our questionnaire.

In the case of targeted screening, namely, if we would have examined the patients only on the basis of the positive family history, the lipoid metabolism would have been examined in not more than 31 cases. At the same time, among the 31 obese children we found a hyperlipoproteinaemia in 26 cases and these patients, of course, fall into high point and high risk groups.

Among the children, 32% had a blood pressure higher than 140/90 mm Hg, in 8 cases with changes in the ocular fundus. At the same time, in most children a loss of weight led to a normalization of blood pressure. Also, 85% of these children did not pursue any sport associated with serious physical exertion.

Screening of obese children belongs to the possibilities of targeted screening because it can be solved either by simple inspection by the school physician with weighing and height measuring, but also with anthropometrical methods (Kaup index, skinfold). According to our results, the questionnaire system, together with blood pressure, lipid and lipoprotein estimations was able to indicate a high proportion (39%) of endangered children with a high frequency of hyperlipoproteinaemia among them.

At the same time, in order to get correct results, some criteria in our questionnaire were stricter than those of Nora, as already mentioned.

It is obvious that screening is of importance only if we can do something in the interest of these children. Glueck [6] summarized the tasks to be done as follows. With the restriction of administering saturated fats and cholesterol, the total cholesterol level can be reduced. The diet, based on the reduction of all calories and carbohydrates generally normalizes the concentration of serum triglycerides. The reduction of body weight, according to the Muscatine study [8], where half of the children with hypertension were obese, is associated with a decrease of blood pressure.

We have to add that the effect of physical activity, increased in the interest of weight loss, improves the HDL-C level of these children [6]. Finally, the discontinuation of smoking assists profitably the above-mentioned tasks.

Screening and proper management of children is probably the only means to prevent vascular diseases which manifest themselves in adult age. We

have presented one variation of the many screening programmes, the screening of obese children. It was not our aim to develop a disease consciousness in either the children or their parents; we only wish to emphasize the possibilities of prevention of serious cardiovascular disease.

## References


1. Andersen GE, Heil M, Christensen NC, Bott H, Lous P, Hansen FB: Hyperlipemia among 1407 Danish children whose fathers have died from ischemic heart disease before age 45. Acta Paediatr Scand 70:843, 1981
2. Andersen GE, Lous P, Hansen BF: Hyperlipoproteinemia in newborn infants. Acta Paediatr Scand 68:683, 1979
3. Berwick DM, Cretin S, Keeler E: Cholesterol, children and heart disease: an analysis of alternatives. Pediatrics 68: 721, 1981
4. Christensen B, Glueck C, Kwiterovich P, Degroot I, Chase G, Heiss G, Mowery R, Tamir I, Rifkind B: Plasma cholesterol and triglyceride distributions in 13 665 children and adolescents. Pediatr Res 14:194, 1980
5. Czerny B, Plenert W, Petrich E, Spahn U: Hyperlipoproteinaemien im Kindesalter, eine Studie an 1004 Kindern. Kinderaerztl Prax 45:110, 1977
6. Glueck CJ: Detection of risk factors for coronary artery disease in children: Semmelweis revisited? Pediatrics 66: 834, 1980
7. Hartmann G: Prevalence and types of hyperlipaemia in Switzerland. In: Lipid Metabolism and Atherosclerosis, ed. DWK Cotton. Excerpta Medica, Amsterdam 1973, p. 86
8. Lee J, Lauer RM: Pediatric aspects of atherosclerosis and hypertension. Pediatr Clin North Am 25:909, 1978
9. Nora JJ: Identifying the child at risk for coronary disease as an adult: strategy for prevention. J Pediatr 97: 706, 1980
10. Parižková J, Roth Z: The assessment of depot fat in children from skinfold sickness measurements by Holtain caliper. Hum Biol 44:613, 1972
11. Peña M, Barta L, Regöly MA, Tichy M: Anthropometric considerations regarding obese children. Acta Paediatr Acad Sci Hung 20:333, 1979


*Received October 15, 1982*

A Czinner MD
Bókay J. u. 53
1083 Budapest, Hungary

# Book reviews

*Paediatric Pathology*. Edited by C L Berry. Springer Verlag, Berlin–Heidelberg–New York 1981. XI + 697 pages with 673 figures. Price DM 170.–

This book written by 12 authors embraces practically the whole of paediatric pathology but by far not in a uniform manner; some parts are treated in great detail and some quite briefly. This imbalance follows from the aim of the book: it was not written as a comprehensive text intended for use as a reference volume but with the purpose of informing the general pathologist without training in paediatric, especially infantile, pathology about the conditions specific to infants and children. This might explain the unusual distribution of the material.

The book consists of 16 chapters corresponding to the organ systems. Individual chapters are devoted to the fetus, the placenta, congenital malformations, embryonic tumours and to SIDS, the sudden infant death syndrome. Among the chapters, outstanding are the Nos 1, 2, 9 and 16. Chapter 1 discusses the fetal pathology giving a survey of the normal intrauterine conditions on the basis of many precise data and excellent figures demonstrating the normal course of organ development. Chapter 2 discusses the placenta and its pathology with special emphasis on its changes caused by intrauterine infections. Chapter 9 is devoted to the kidney and the urinary tract. Didactically and concerning its contents this seems to be the most successful and at the same time the most detailed part of the book. Among others it gives an excellent survey of glomerular disease and its types associated with the nephritis syndrome, of the cystic changes and developmental anomalies. The last chapter discusses the problematic SIDS, enumerating almost all the possible theories on its aetiology published in the literature. The importance of histological examination is stressed and the necropsy technique is described extensively, giving useful hints, e.g. sampling of vitreous humour for urea and electrolyte estimation. Chapter 12 deals with the pathology of the spleen, lymph nodes and the immunoreactive tissues. Some of its parts such as non-Hodgkin lymphoma are described in full detail but others such as the leukaemias are just touched upon. Chapter 3 which describes the different congenital malformations, appears to the reviewer to be the poorest of the book. The chromosomal abnormalities and malformations together with the four commonest pertaining conditions are discussed on not more than a single page and chromosomal pathology is not even mentioned nor are the techniques of chromosome investigation to be found.

A definite deficiency of the book is the absence of sonographic and even more the scarcity of electron microscopic pictures. This is the more regrettable as in many a condition, for instance in histiocytosis X, the diagnosis depends on the electronmicroscopical finding.

A copious list of references collected up to the late seventies is added to each chapter. Selection of the papers quoted must be praised as few of the really important ones are missing and few are obsolete. In this context may the reviewer mention that the designation Wilm's tumour used systematically in the book is incorrect, the tumour having been named after M. Wilms, the once highly esteemed German surgeon.

All in all, in spite of its deficiencies the book is a high-level manual which will be useful to both pathologists and paediatricians.

P Bucsky

*Developmental Toxicology*. Edited by Keith Snell. 350 pages, Croom Helm, London 1982. Price L 22.50

Reproduction toxicology including fertility teratology, behavioural teratology as well as peri- and postnatal studies is a comparatively new, rapidly developing part of toxicology. In view of its developing state, a survey and summing up of the applied new techniques is desirable. The editor of the book was able to ensure by a careful choice of the contributing authors that the reader should find information about the same compound from several different aspects e.g. in whole animal studies (F. Beck), in approaches in vitro using organ as well as cell cultures (N. B. Brown and S. E. Fabro; R. M. Clayton and A. Zehir), biochemical examinations (K. E. Williams; O. Pelkonen; K. Snell), autoradiographic distribution of compounds (Ullberg et al), role of placenta (M. R. Juchau), transplacental carcinogenicity (P. Keilhues), and problems of behavioural teratogenicity (C. V. Vorhees and R. E. Butcher).

Space does not permit to review all the chapters of the work, but to demonstrate its main characteristics one example might be sufficient. Vitamin A, both in excess and also its deficiency is a well-known experimental teratogen, but the same dose applied simultaneously to different strains of mice will result in various teratogenic actions due to the different genetic background of the animals (F. Beck). As Ullberg et al show, if an excess is applied during early, mid and late gestation, accumulation of the compound will vary in site: in the early embryo most of the radioactivity is detectable in the neuroepithelial tissues, while in mid and late gestation the usual localization is in the areas where cell proliferation is the highest (lung, liver, heart, large vessels). Clayton's chapter deals with the effects of hypervitaminosis A in organ (limb bud) and cell cultures (chondrogenic cells), showing the inhibited cartilage matrix synthesis, the abnormal type of cell-to-cell contacts, and the disturbed differentiation of the prechondrocyte mesenchyme. The youngest field of reproduction toxicology is behavioural teratology. Doses which do not induce CNS malformation produce behavioural defects after birth (C. V. Vorhees and R. E. Butcher).

Similar information is found for trypan blue, thalidomide, diphenylhydantoin, ethanol, etc. in the different chapters.

I warmly recommend the book for paediatricians, embryologists and teratologists interested in the mode of action of teratogens and in the methods of reproduction toxicology.

Alice Druga

B. Benjamin: *Atlas of Paediatric Endoscopy*. Oxford University Press, Oxford 1981. 133 pages with 135 figures. Price £ 30

One often reads that an author has filled a gap. This time the saying is perfectly true: to our best knowledge, Benjamin's atlas is the first of its kind and it really fills a much-felt gap in paediatric literature.

For bronchoscopy, the author used for many years the Negus instrument and is now working with the Storz–Hopkins

fibreoptic telescopes, taking pictures with Storz endocamera with flash generator. Microsurgery is done with carbon dioxide laser. After a very brief introductory part explaining the different techniques, the material is presented in nine chapters as follows. 1. Normal appearance; 2. nasal cavities and nasopharynx; 3. larynx and pharynx; 4. intubation, tracheotomy and trauma; 5. acute inflammatory airway obstruction; 6. foreign bodies; 7. tracheobronchial tree; 8. tracheo-oesophageal fistula and oesophageal atresia; and 9. the oesophagus.

The chapters do not contain any text except the legends to the pictures. Most of these are presented together with a lateral xeroradiogram and/or a CT picture of the region in question. The figures are excellent and didactic. No attempt is made at their clinical systematization but their study will mean a great help to paediatricians interested in diseases of the airways and their diagnostics. Some bronchograms are also presented but their quality is somewhat weaker than that of the other techniques.

The book will be a great gain to every paediatric pulmonologist and bronchologist and even to the practising paediatrician.

E Székely

F. Lampert: *Pädiatrie*. XII + 99 Seiten mit 10 Abbildungen. Springer Verlag, Berlin–Heidelberg–New York 1982. Preis DM 22.–

Das vorliegende Büchlein befaßt sich mit den Problemen der Ambulanzpädiatrie, und es erstreckt sich nicht auf die stationäre Versorgung. Aufgrund eigener Erfahrungen versucht der Autor, die häufig auftauchenden Symptome und Fragen zu beleuchten und mit entsprechenden Angaben einen nützlichen Leitfaden für die alltägliche Praxis zu geben.

Einleitend werden die Untersuchungsmethoden, sodann die Gesundheitsvorsorge von Neugeborenen, Säuglingen, Klein- und Schulkindern und Adoleszenten erörtert. In dem umfangreichen Kapitel „Krankheiten und Probleme" werden die Erkrankungen der einzelnen Organe, jeweils knapp doch klar, besprochen. Die Orientierung wird mit Hilfe von drucktechnischen Mitteln, Abbildungen und Tabellen erleichtert.

Das Taschenbuch bietet vor allem dem praktizierenden Nicht-Pädiater eine wertvolle Stütze für den Alltag und in der Sprechstunde.

K Schmidt

U. Kalbe: *Die Cerebral-Parese im Kindesalter*. 90 Seiten mit 66 Abbildungen. Georg Thieme Verlag Leipzig (Gustav Fischer Verlag Stuttgart–New York) 1981. Preis M 32.–

Das Krankheitsbild der kindlichen Cerebral-Parese dürfte so alt sein, wie die Menschheit selbst. Die Aufmerksamkeit der Kinderärzte richtete sich jedoch erst in letzter Zeit auf die vielfältigen, komplexen Probleme des hirngeschädigten Kindes und seiner Familie.

In dem vorliegenden Buch wird das Krankheitsbild, dessen Häufigkeit der Verfasser auf etwa 3–4 Promille schätzt, in allen Beziehungen eingehend behandelt. Die etwa 10 Milliarden Nervenzellen des menschlichen Gehirns sind äußerst sensibel, Schädigungen verursachen irreparable Defekte. Wie bei solchen Kindern dennoch günstige therapeutische Ergebnisse erreicht werden können, ist das Thema der Monographie. Nach einer kürzeren Besprechung der diagnostischen Untersuchungsverfahren, werden die verschiedenen Behandlungsmöglichkeiten ausführlich geschildert; außer den zu Hause vornehmbaren Übungen werden auch andersartige günstige sportliche Aktivitäten angeführt und auf die ergänzende medikamentöse Behandlung und die Chancen eines neurochirurgischen Eingriffes hingewiesen.

Das Buch ist in einem vorzüglichen Stil verfaßt, das reiche Abbildungsmaterial ist ausgezeichnet. Es stellt einen Leitfaden für Ärzte, Studenten, Therapeuten, Pädagogen und Pflegeberufe dar.

O Kohlhéb

*Aktuelle Therapie bösartiger Blutkrankheiten.* Herausgegeben von P G Scheurlen und H W Pees. XII + 298 Seiten mit 56 Abbildungen und 113 Tabellen. Springer Verlag, Berlin–Heidelberg–New York 1982. Preis: DM 88.–

Die Therapie der malignen Erkrankungen des hämopoetischen Systems hat sich in den vergangenen Jahren schnell und kontinuierlich verändert, wodurch die Prognose dieser Krankheitsbilder wesentlich besser wurde. Die Bedingung für die günstigeren Ergebnisse ist eine aggressive Polychemotherapie, die selbstverständlich mit entsprechenden supportiven Maßnahmen durchgeführt werden muß. Der Ausgangspunkt für Art und Grad der Therapie soll stets die genaue Klassifikation des Krankheitsbildes sein. Die Zielsetzung der Herausgeber des vorliegenden Bandes war, diese Fragen im Spiegel der neuen Erkenntnisse und Verfahren zu besprechen.

Der überwiegende Teil der Arbeit ist den verschiedenen Formen der Leukämien gewidmet: den akuten und chronischen myeloischen Leukämien und der akuten lymphatischen Leukämie. Einleitend wird der Wirkungsmechanismus der Antimetaboliten und des Anthrazyklin erörtert und die Fragen der Resistenzentwicklung behandelt. In den sich mit den akuten Leukämien befassenden Kapiteln wird in erster Linie die Chemotherapie bei Erwachsenen und Kindern bei nichtlymphatischen und akuten lymphatischen Leukämien geschildert und über die Immuntherapie berichtet. Ein Kapitel erläutert die Behandlung der atypischen Leukämien, ein anderes eine prognostisch verwertbare phänotypische Klassifikation akuter Leukosen durch funktionelle Parameter (in-vitro-Kulturwachstum, kolonienstimulierende Aktivität, TDT), und in einem weiteren Beitrag findet man eine gute Zusammenfassung der immunologischen Typisierung akuter lymphatischer Leukämien. Hinsichtlich der Therapie bieten die diesbezüglichen Kapitel nicht nur die Beschreibung der einzelnen Verfahren, sondern auch eine Klarlegung der Grundprinzipien der Behandlung.

Den supportiven therapeutischen Maßnahmen sind, ihrer Bedeutung gemäß, acht Beiträge gewidmet, wobei auch auf die Rolle der Knochenmarktransplantation eingegangen wird. Eine hiernach angeführte Podiumdiskussion über die einzelnen Methoden der akuten Leukämiebekämpfung soll besonders hervorgehoben werden.

Das letzte Drittel des Buches befaßt sich mit der Behandlung der Lymphogranulomatose, Non-Hodgkin-Lymphome, Plasmozytome und malignen Erkrankungen des Monozyten-Makrophagensystems.

Zusammenfassend kann festgestellt werden, daß die Beiträge des vorliegenden Werkes einen guten Überblick über die zeitgemäßen therapeutischen Möglichkeiten bei bösartigen Blutkrankheiten gewähren. Die thematische Auswahl ist günstig und aktuell und bietet Hämatologen und Nichtspezialisten entsprechende Information über den derzeitigen Stand unserer therapeutischen Möglichkeiten.

D Schuler

Somerville E W: *Displacement of the hip in childhood.* XIII + 200 pages with 262 figures. Springer Verlag, Berlin–Heidelberg–New York 1982. Price DM 112.–

The author of this book is a leading orthopaedic surgeon and an expert of international fame on displacement of the hip. This book is based on 82 000 neonatal examinations and 450 treated cases, some of them followed up since more than 30 years.

More than half of the book is devoted to congenital displacement of the hip. Chapter 1 discusses the pathology of the

condition as concluded from 25 years observation of 400 patients. Acetabular dysplasia, capsular laxity, intrauterine situation of the femur, the direction and the mechanism of displacement are discussed in detail. Chapter 2 reports on the possibilities of diagnostics and therapy from 0 to 9 months of age and Chapter 3 on the secondary changes. The two decisive factors in early diagnosis are said to be a sufficient experience and a due organization. X-rays are rarely necessary in the newborn, the condition must be diagnosed without X-rays and pictures should only be taken at 6 months and 1 year of age. For treatment in the first 9 months the Trejka pillow or the von Rosen splint are recommended. The complications are a tightness of the adductor, a failure of reduction, and redisplacement. The next chapter describes the changes secondary to the displacement, *viz.* the delay of ossification, the adaptive changes in the soft tissues, the deformity of the acetabulum and an increase even to 160° of the angle of anteversion. Chapter 4 illustrates the course of the displacement from 9 months to 3 1/2 years of age. This is the longest and most interesting part of the monograph; it gives detailed information on the possible treatments and their special techniques and the indications and techniques of arthrography. The data presented give means to evaluate the advantages of Somerville's operation.

In the next chapter we find a description of hip development after the treatment. It is said that development will be normal after early operation but later ossification disturbances and contractures may appear. Chapter 6 gives a review of the operations on the pelvis, the innominate osteotomy (Salter), the Pemberton osteotomy and the Chiari osteotomy.

In the remaining chapters are discussed the iatrogenic fractures of the femur and the extreme anteversion. Then a chapter reviews up-to-date knowledge on Perthes disease on the basis of 45 hips followed up for 4–20 years, and finally the development and disturbances of the proximal end of the femur.

The book with its interesting and excellent text illustrated with many pictures of high quality gives a very good and modern survey of congenital displacement of the hip and all the related problems.

T VIZKELETY

*Segmental idiopathic necrosis of the femoral head*. Edited by U H WEIL. Vol. 5 of the series Progress in Orthopaedic Surgery. VII + 121 pages with 68 figures and 30 tables. Springer Verlag, Berlin–Heidelberg–New York 1981. Price DM 66.–

This monograph, according to the preface, has the aim to discuss some methods of treatment of femoral head necrosis that are conspicuously lacking in American orthopaedic literature. The condition, called by some authors coronary disease of the hip, seems to have received attention only in recent times. While in 1962, Mankin and Brower could find not more than 22 cases in the English literature, by now there are a great number of papers and some of them report on more than 100 patients. The condition which is essentially a vascular disease due to a decreased blood supply or to an insufficiency of the circulation appears mostly after some injury, alcoholism, connective tissue disease like lupus erythematodes, gout, Gaucher disease, etc., but its real cause has not been clarified.

The volume contains 8 papers which have been published earlier in different periodicals. The first chapter by Wagenhäuser (Zurich) is an interesting and most entertaining essay on human posture, its development through millions of years and its up-to-date aspects. The next chapter has been written by Ficat (Toulouse) on early diagnosis and functional bone investigation. On the basis of experience with 132 cases he emphasizes the importance of intraosseous pressure recording together with transosseal venography (a very pain-

ful intervention to be carried out under anaesthesia) and the measurement of oxygen saturation. It is said that this haemodynamic examination ensures in 99% a correct diagnosis of osteonecrosis. The paper by Hungerford (Baltimore) discusses the same subject. Among his 130 patients there were only 9 whose disease was "idiopathic" i.e. not associated with some clinical condition.

The next four papers deal with the different methods of treatment, their techniques and results. Hori (Nara, Japan) performs revitalization by vascular bundle transplantation; the operation proved favourable in early stages but could not completely restore severe deformities of the femoral head. Kotz (Vienna) surveys the results attained by transtrochanteric ventral rotation osteotomy as recommended by Sugioka. In 24 treated patients the results gave a good : poor ratio of 21 : 3 while with earlier methods the ratio was 11 : 14. Willer et al (Göttingen, FRG) review their results achieved by flexion osteotomy. A total of 42 patients were operated upon; the pain was relieved in 84%, walking ability was improved in 76%, and 82% of the patients gave a positive evaluation. Gérard (Reims) applies on the femoral head a cylindrical cup of the kind described by Luck; of 68 hips in 63 the result ranged from good to excellent. Wagner and Zeiler (Schwarzenbruck, FRG) applied intratrochanteric flexion-valgus-rotational osteotomy on 108 hips and resurfacing by a cup on 13 hips; the outcome, especially in young patients, was mostly favourable.

The book offers a good survey of knowledge concerning the aetiology and pathogenesis of the disease, its early diagnosis and the possibilities of its treatment.

T Vizkelety

*Säuglingsernährung heute.* Herausgegeben von R Grüttner. Pädiatrie: Weiter- und Fortbildung. (Herausgegeben von H Ewerbeck) XIV + 195 Seiten mit 50 Abbildungen und 57 Tabellen. Springer Verlag, Berlin–Heidelber–New York 1982. Preis: DM 34.–

Dieses Büchlein ist ein Haupttreffer. Geschrieben von einem breiten Kreis von ausgezeichneten Autoren und Arbeitsgruppen überwiegend vom deutschen Sprachgebiet, befaßt es sich mit den neuesten Fragen der Säuglingsernährung, dieses zurecht wieder in Mode geratenen Faches der Kinderheilkunde.

Was sind die Neuigkeiten in diesem alten Gebiet? Bestrebungen, um zum Natürlichen und Einfachen zurückzukehren, Ernüchterung von unserem stolzen Allwissenheitsgefühl in Sache der genauen Bedürfnisse des menschlichen Säuglings auf verschiedenste Nahrungsbausteine, Angst vor zu hohem Einfuhr von Zucker, Salz und Eiweiß, Ahnung einer unüberschätzbaren Bedeutung der Ernährung im Säuglingsalter in Hinsicht auf das Schicksal des zukünftigen Erwachsenen. Alldies widerspiegelt sich in dieser Reihe kurzer Zusammenfassungen.

Besonders gut sind die Kapitel, die sich mit dem Eisenstoffwechsel, der sogenannten optimalen Säuglingsernährung, der Auswirkung der Ernährung auf die spätere Entwicklung, der Stilltätigkeit und ihrer Beeinflußbarkeit und mit der Beikost im ersten Lebensjahr beschäftigen. Die Bestrebung, die Muttermilch nachzuahmen, hat zu den verschiedensten Folgen geführt: sie hat einen unerhörten Vorsprung in der Ernährungsforschung und -technologie ausgelöst, sie hat zur gleichen Zeit viel zum Sinken der Stilltätigkeit beigetragen und schließlich hat sie uns gezwungen einzusehen, daß die menschliche Milch prinzipiell unnachahmbar ist.

Es wird mehrmals betont, daß die Muttermilch allein bis zum Ende des ersten Vierteljahres sicher den vollen Bedarf deckt, daß die Kuhmilchpräparate und die

Beikost noch stets zu früh eingeführt werden, daß Mehl während des ersten Halbjahres völlig überflüssig, ja schädlich ist, daß den Säuglingen zu viel Kohlenhydrat, besonders Saccharose angeboten wird. Sehr nützlich sind die kurzen Kapitel über Methoden der Ernährungsversuche und der Bilanzuntersuchungen.

Gerne hätten wir mehr über die Praxis und Auswirkung des frühen Brustkontaktes, der ad libitum Nahrung und überhaupt über die psychologische Seite der Ernährung gelesen. Es besteht auch eine gewisse Diskrepanz zwischen den Empfehlungen der meisten Autoren über die späte Einführung der Zerealien und dem Kapitel über prophylaktische Gesichtspunkte. Das Kapitel über Kuhmilchintoleranz ist an sich eine selbständige Studie über Pathologie. Dadurch ist das Fehlen der Erörterung der praktischen Schwierigkeiten in der Säuglingsernährung besonders auffällig.

Eine Fülle von neuesten Informationen ist in diesem Buch zugänglich. Jeder, der mit Säuglingen zu tun hat, sollte es lesen.

P Cholnoky

A L Scherzer and I Tscharnuter: *Early diagnosis and therapy in cerebral palsy*. 304 pages with illustrations. Marcel Dekker, Inc. New York 1982. Price SFr. 105.—

This book is dedicated to the important question of the methods suitable for the early discovery and rehabilitation of cerebral lesion in the young baby. Arguments for and against the possibility of early diagnosis and therapy are abundant and the need for more objective methods and more principled control of the results is often emphasised.

In the introductory chapter the authors define the nature of cerebral palsy. Up-to-date results of CT and ultrasound techniques in the follow-up of ante and perinatal brain damage reveal the development of brain defects in the first months of life. These data and new neurophysiological and psychophysiological information have remarkably changed our views on the delineation of cerebral palsy. Though the authors do not detail these important advances, they nevertheless cerefully describe the possibilities for early neurodevelopmental assessment of infants. Many useful methods are enumerated although some important and more or less objective methods such as polygraphy, pharyngeal and oesophageal electromanometry, impulse diagnosis of palatopharyngeal muscle function, electrotherapy of palatopharyngeal paresis, feedback training defective sucking and swallowing, to mention only a single field, are not mentioned. Evoked brain stem potentials, in differential polygraphy are essential in the investigation of auditive and visual behaviour with various stimulation programmes. A careful analysis of the elementary sensory and motor patterns is also indispensable. The importance of a thorough investigation of all infants suspected of having brain damage is underlined, because neither a due therapy nor rehabilitation can be recommended in the lack of a fully reliable diagnosis. Nor should any treatment or rehabilitation be initiated without a close longitudinal medical control.

The authors stress the importance of complex trainings because many patients develop complex (i.e. mental, sensory and motor) defects and need complicated rehabilitation programmes. There are, however, occasional difficulties due to other attached symptoms, for example epilepsy. The elimination of convulsions is imperative in order to attain any notable result in rehabilitation. On the other hand, a careful selection of anticonvulsive drugs is important to ensure maximum anticonvulsive effect with minimum inhibition of training capability, vigility, attention and sensory motor dynamics.

Important chapters of the book call

attention to various training methods and programmes. Thus paediatricians, physiotherapists and special pedagogues will much profit from the text which duly points to the great significance of early diagnosis and early neurohabilitation.

F. KATONA

*Advances in clinical nutrition.* Edited by I D A Johnston. 483 pages. MTP Press, Lancaster. Price £ 29.95

Nutrition science deals with the needs of the living organism for essential nutrients indispensable for growth, subsistence and renewal. It comprises research into the mechanisms of utilization as well. Dietetics is the practical application of these theoretical data. The book at issue, the proceedings of the 2nd international symposium held in Bermuda in May, 1982, is an ideal mixture of theory and practice. It shows that nutrient supply, a matter of existence or non-existence for the healthy and ill alike, is a decisive element of therapy, determining sometimes the patient's survival. The Editor is completely right in saying that during the five years having elapsed since the first such symposium, when enteral and parenteral feeding based on scientific facts could be performed only in a few leading centres possessing adequate equipment, nutrition science has become an important element of clinical routine.

In the eight chapters of the book, nearly all the aspects of theory, experimental research, practical therapy and future developments are discussed. Much attention is paid to the special role and importance of branched chain amino acids in the metabolism of the healthy human: they may serve as energy fuel stored in the peripheral muscles, they promote protein anabolism and may inhibit protein catabolism. Correction of their plasma level may be crucial in therapy e.g. in hepatogenic encephalopathy, a condition discussed in detail. A number of papers underlines the fact that in case of low protein intake and energy supply measurement, monitoring and influencing their plasma level is not satisfactory since there is not always a close correlation between the plasma levels and the intracellular amino acid and protein concentrations. This is quite obvious in conditions characterized by increased protein catabolism like injury, stress, etc. A special paper deals with experimental animal models of such catabolic conditions. In addition, a detailed description is offered of surgical stress, polytraumatization, burns, the postoperative period, chronic liver damage and hepatic regeneration, their experimental and clinical aspects and the role of branched chain amino acids. A separate chapter is devoted to the nutritional needs of patients affected by acute and chronic renal failure including those subjected to chronic haemodialysis. A most valuable aspect of the book is that it includes methods of enteral and parenteral, and also of local, feeding that promotes wound healing, describing the composition of solutions and all this on a wide theoretical and practical basis. Criticism is not lacking, either; there is a careful enumeration of the possible side-effects of the methods and materials.

New concepts of clinical nutrition are also offered. The problems of the promotion of carnitine transport by long-chain fatty acids to the site of beta-oxydation or of ketone bodies as alternative synthetic fuels are discussed in detail. Valuable chapters deal with parenteral nutrition in the patient's home and the problem of the so-called artificial gut. Prerequisites, complications, the devices necessary for home parenteral nutrition, expenses and social aspects are all cerefully examined in these chapters.

The book concludes with a short summary. Here the trends of the development to be expected are analysed. It is clear that the present facilities are more important for the patient who is ill now, but it is important to foresee what to expect in the future. Knowledge and facilities but also the hopes

of today's practitioners may decide the patient's fate. The book at issue will add much to this and also to the hopes. Not only the expert in nutrition but also the practitioner will profit of what he reads in the papers that were given at the Symposium.

V VARRÓ

M SUGAR: *The premature in context*. MTP Press, Lancaster 1983. 141 pages. Price £ 15.50

The author, who is a Louisiana psychiatrist, presents a review of the psychological and neurological aspects of premature and ex-premature babies in the light of the explosion-like progress of neonatological diagnosis and therapy experienced during the last decade. An outstanding feature of the book is that in addition to neuropsychiatry a large spectrum of other fields such as obstetrics, neonatology, physiology, electrophysiology, psychology etc., are dealt with. The backbone of the book is the healthy doubt in the principle that a premature remains life-long a premature. The most important statements are summarized in several well-constructed tables. The five main chapters are preceded by a short historical introduction and followed by lists of references.

Chapter 1 describes the stages of the development of premature babies. The milestones of psychomotor development in infancy and early childhood up to the appearance of speech development are reviewed on the basis of seventeen criteria. The findings are summarized and analysed in a number of tables. No marked differences were found by the author in the development of prematures and babies born at term and this has prompted him to doubt the validity of statements on the retardation of prematures. In his view new standards and reference data have to be elaborated.

The following chapter deals with three primitive reflexes, the Moro, sucking and grip reflexes in the premature body. As in normal ones, these primitive reflexes disappear by the fourteenth week of extrauterine life also in prematures and this speaks for the idea that these reflexes and myelinization are independent of gestational age and perinatal events.

Premature care is presented in a separate chapter. The need of the preterm baby, problems arising when dealing with his parents and mother-child interactions, are here the main topics. An impressive description of gradual changes of the parents' presence in premature wards since the basic observations made by Hess in the USA in 1922 is offered. In the author's mind, optimal parent-child links are as important as progress in knowledge and equipment. Relationships between physical and emotional development and the links between pleasant and unpleasant events are also discussed.

The last chapter is a review of prematurity. It deals with the possible causes, morbidity and mortality data, expectancies for intellectual development and with the possibilities of preventing preterm birth.

Max Sugar's book comprises much knowledge on several various aspects of prematurity; it will facilitate the work of practising paediatricians and investigators alike.

V FARKAS

PRINTED IN HUNGARY
Akadémiai Nyomda, Budapest

# INSTRUCTIONS TO AUTHORS

*Form of manuscript*

Two complete copies of the manuscript including all tables and illustrations should be submitted. Manuscripts should be typed double-spaced with margins at least 4 cm wide. Pages should be numbered consecutively.

Manuscripts should include the title, authors' names and address of the institution where the work was done.

An abstract of not more than 200 words should be supplied typed before the text of the paper.

*Abbreviations* should be spelled out when first used in the text. *Drugs* should be referred to by their WHO code designation (Recommended International Nonproprietary Name); the use of proprietary names is unacceptable.

The *International System of Units* (SI) should be used for all measurements.

*References*

References should be numbered in alphabetical order and only the numbers should appear in the text (in parentheses). The list of references should contain the name and initials of all authors (the use of et al. instead of authors' name in the reference list is not accepted); for journal articles the title of the paper, title of the journal abbreviated according to the style used in Index Medicus, volume number, first page number and year of publication; for books the title followed by the publisher and place of publication.

Examples:

Kerpel-Fronius E, Gács GK: Serum insulin values in infants. Acta Paediatr Acad Sci Hung 16:197, 1975

Crosse VM: The Preterm Baby. Churchill Livingstone, Edinburgh and London 1971

Detter JC: Biochemical variation. In: Textbook of Human Genetics, ed. Fraser O, Mayo O, Blackwell Scientific Publications, Oxford 1975, p. 115

*Tables and illustrations*

*Tables* should be comprehensible to the reader without reference to the text. The headings should be typed above the table.

*Figures* should be identified by number and authors' name. The top should be indicated on the back. Their approximate place should be indicated in the text. Captions should be provided on a separate page.

*Proofs and reprints*

Reprints and proofs will be sent to the first author unless otherwise indicated.

A hundred reprints of each paper will be supplied free of charge.

The name and address of the first author should be given after the list of references.

CONTENTS

Thyrotropin and prolactin response to thyrotropin-releasing hormone in healthy and asphyxiated full-term neonates. *F Ruppert, M Adonyi, T Ertl, E Sulyok, K Zámbó, IF Csaba, F Varga* ..... 111

Accidents in schoolchildren: epidemiologic, aetiologic and prognostic considerations. *M Sillanpää, P Terho, Helena Westerén, Harriet Pisirici* ..... 119

Disaccharidases in coeliac disease. *K Horváth, Gabriella Horn, Hedvig Bodánszky, Katalin Tóth, S. Váradi* ..... 131

Effect of lithium carbonate on the peripheral leukocyte count in children suffering from haematological malignancies. *S Molnár, P Kajtár* ..... 137

Fetal alcohol syndrome: amino acid pattern. *R Tichá, J Santavy, Z Matlocha* ..... 143

Isolation and physicochemical properties of an adenosine-rich gluten fraction. *M Szabolcs, S Csorba, M Hauck* ..... 149

Primary aortitis in childhood. *G Jójárt, B Záborszky, E Szondy, M Horváth, I Hegedüs* ..... 159

The importance of cow's milk protein intolerance in chronic diarrhoea of children. *Ágnes Várkonyi, Márta Boda, Ida Szabó* ..... 169

Six years mortality statistics in a Libyan paediatric hospital. *R Singh, A Abudejaja* 175

Positive skin prick tests of immediate type in non-allergic children. *E Cserháti, Annemarie Gegesi Kiss, Györgyi Mezei, J Kelemen, Julianna Puskás* ..... 189

Prevention of adult cardiovascular disease in obese children. *A Czinner, Mária Tichy, L Barta* ..... 195

Book reviews ..... 201

**Index: 26.021**

FORMERLY ACTA PAEDIATRICA ACADEMIAE SCIENTIARUM HUNGARICAE

# Acta Paediatrica Hungarica

VOLUME 24, NUMBER 3, 1983



**Akadémiai Kiadó, Budapest**
ACTA PAEDIATR HUNG HU ISSN 0001-6527

# ACTA PAEDIATRICA

## HUNGARICA

A Quarterly of the Hungarian Academy of Sciences



---

*Acta Paediatrica* publishes original reports of studies in paediatrics and borderline fields.

Manuscripts and editorial correspondence should be addressed to

*ACTA PAEDIATRICA*
Bókay J. u. 53.
H-1083 Budapest
Hungary

*Subscription information*

Orders should be addressed to

KULTURA Foreign Trading Company
P. O. Box 149, Budapest
H-1389

or its representatives

*Acta Paediatrica* is published in yearly volumes of four issues by

AKADÉMIAI KIADÓ

Publishing House of the Hungarian Academy of Sciences
Alkotmány u. 21.
H-1054 Budapest

*Acta Paediatrica Hungarica, 24 (3), pp 211–216 (1983)*

# Effect of lithium carbonate on the bone marrow of patients treated for haematological malignancies

S Molnár, P Kajtár

Department of Paediatrics, University Medical School, Pécs, Hungary

Patients suffering from haematological malignancies were treated with $Li_2CO_3$ in order to investigate its effect on the bone marrow depleted by cytotoxic therapy. The results revealed that lithium induced a great number of cells, especially myeloids, in the previously hypoplastic bone marrow. There was a close relationship between the cellularity of the bone marrow and the changes in peripheral WBC and granulocyte counts during lithium carbonate treatment.

Leukocytosis and neutrophile granulocytosis are well known side effects of lithium carbonate which is used in the treatment of various psychiatric disorders [14, 20]. Several authors have tried to make use of these effects of lithium in adults suffering from solid tumours, in order to reduce the duration and mitigate the degree of leukopenia and granulocytopenia caused by cytotoxic agents, and thus to reduce the severity and the rate of occurrence of infections [4, 5, 12]. Similar attempts have been made in children treated for solid tumours [19]. In these instances, however, the bone marrow is rarely involved in contrast to haematological malignancies, in which it appears more reasonable to administer lithium for alleviation of the severity and duration of granulocytopenia either during induction of remission as Stein et al. [18] reported in adults treated for acute myelogenous leukaemia, or in any other phase of treatment.

In view of the regenerative capacity of the bone marrow culture under normal conditions [10, 17, 21], and after incubation with cytotoxic drugs [3] in response to lithium, it appeared interesting to explore its usefulness in clinical study. So far no studies performed in children have been reported.

## Materials and Methods

Thirteen patients, ten boys and three girls, with acute lymphoblastic leukaemia had been treated with lithium carbonate [13], then bone marrow biopsy was performed as part of the regular half-yearly control. All the patients were in remission and treated according to the protocol of the Hungarian Leukaemia Study Group for Children [15], which is similar to the BFM protocol developed by Riehm et al [16].

Further four patients with ALL had been treated with $Li_2CO_3$ during the last two weeks of their therapy for induction of remission, and then bone marrow biopsy was done. Bone marrow reserves of two patients with highly malignant non-Hodgkin lymphoma were also investigated. They were treated according to the maintenance part of the therapeutic protocol of Wollner et al [22]. Both these patients were in remission but bone marrow suppression developed under the effect of the vigorous cytotoxic treatment. The biopsy was done immediately before and after lithium carbonate treatment.

Lithium carbonate was administered orally in a single dose of 700 mg/m² daily for two weeks while cytotoxic therapy was left unchanged. Quantitative and qualitative changes of peripheral white blood cells were recorded, and the serum lithium levels were also determined. 500 leukocytes were counted for differentials. The cellularity of the bone marrow, the ratio of erythroids and myeloids, and the maturation of different cell lines were examined in bone marrow specimens taken by Yamshidi needle.

For statistical analysis Student's *t*-test was used. The results were compared to baseline data measured at the beginning of lithium treatment, or with controls. Control cases receiving the same cytotoxic therapy were chosen by randomization.

## Results

Two groups could be distinguished on the basis of bone marrow cellularity (Fig. 1). The first group was characterised by a normal myeloid-erythroid ratio in the bone marrow ($M/E > 2.5$), and the second one showed erythroid hyperplasia ($M/E < 0.5$). Hypercellularity and a distinct myeloid predominance developed in the bone marrow only in patients treated with lithium. The cellularity of the bone marrow of controls of the first group was normal with a slight myloid predominance. In the 2nd and 4th weeks there was a significant difference in peripheral WBC count between patients treated with $Li_2CO_3$

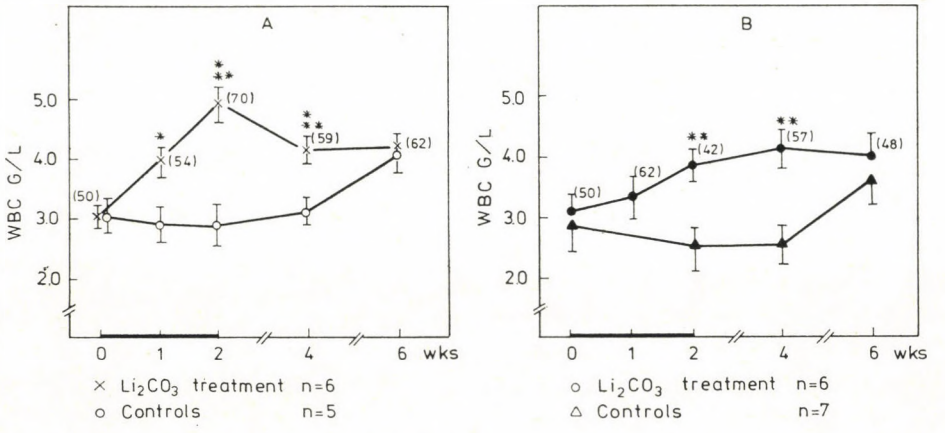



Fig. 1. Effect of $Li_2CO_3$ treatment (heavy line) on WBC count in patients with normal myeloid-erythroid ratio (A) or with erythroid hyperplasia (B) in the bone marrow ($\bar{x} \pm SE$). Number in brackets, granulocyte ratio in blood. * $p < 0.05$ in comparison to baseline data, ** $p < 0.05$ in comparison to controls

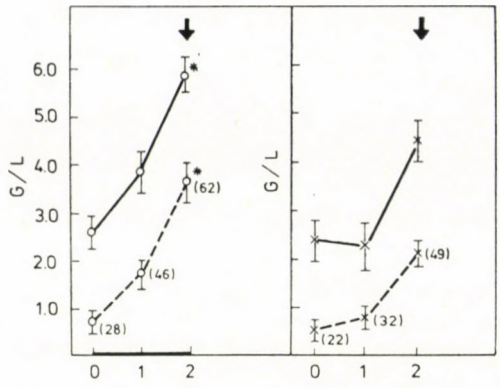



FIG. 2. Effect of $Li_2CO_3$ treatment (heavy line) on WBC (thin line) and granulocyte (broken line) count in the last two weeks of remission induction of ALL ($\bar{x} \pm SE$). Dots, patients treated with $Li_2CO_3$; crosses, controls. Number in brackets, granulocyte ratio in blood. Arrow, bone marrow biopsy. * $p < 0.05$ in comparison to controls

and controls. Significant differences from baseline data were observed not only in the peripheral WBC counts but in the absolute granulocyte counts as well.

Lithium was effective but to a much less extent when bone marrow was normocellular with erythroid predominance. In these cases differences were significant in the 2nd and 4th week in respect of leukocyte and absolute granulocyte counts in comparison with controls whose bone marrow was dominated by erythroid hyperplasia ($M/E < 0.5$), but not in comparison with baseline data.

Lithium carbonate administered during induction of remission (Fig. 2) significantly increased the number of WBC and absolute granulocytes by the end of the treatment. An increase in the granulocyte ratio was also seen.

Cytomorphologic analysis of the bone marrow specimen taken at the end of induction of remission showed that the cellularity of the bone marrow and the predominance of myeloid cells in the patients treated with lithium carbonate significantly exceeded that of controls (Figs 3 and 4). Histological analysis of the bone marrow depleted by cytotoxic drugs revealed that $Li_2CO_3$ induced a great number of cells in the previously hypoplastic tissue (Figs 5 and 6). Especially the production of myeloids had been stimulated restoring the normal myeloid-erythroid ratio. This striking effect of lithium carbonate was reflected by a distinct leukocytosis in peripheral blood.

## DISCUSSION

Examination of bone marrow is a more reliable index of the effect of lithium than are the quantitative and qualitative changes of white blood cells in peripheral blood. There are strict indications for bone marrow examination, and we used this oppor-

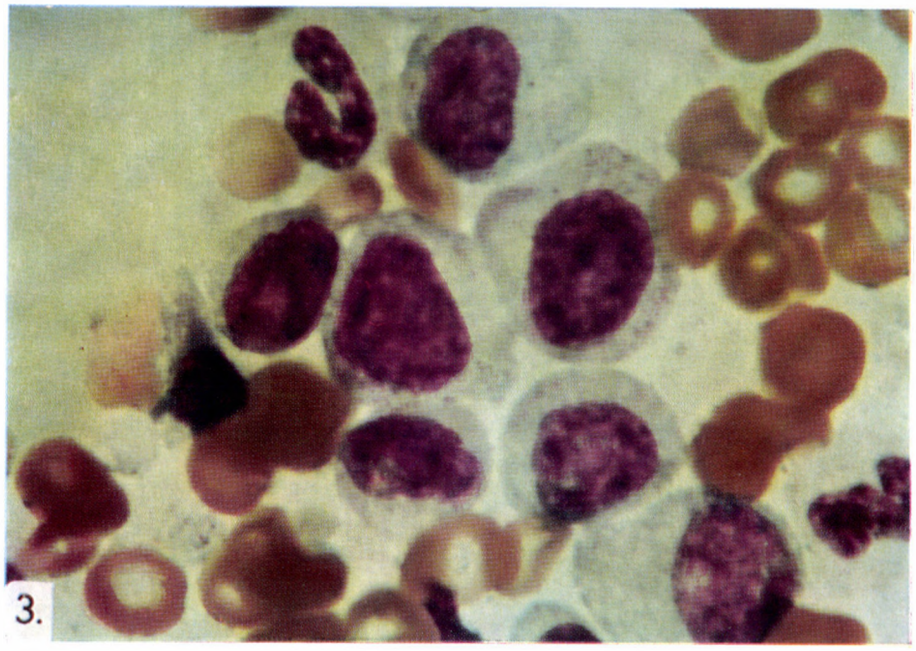
tunity to compare the effect of the drug on bone marrow and peripheral blood.

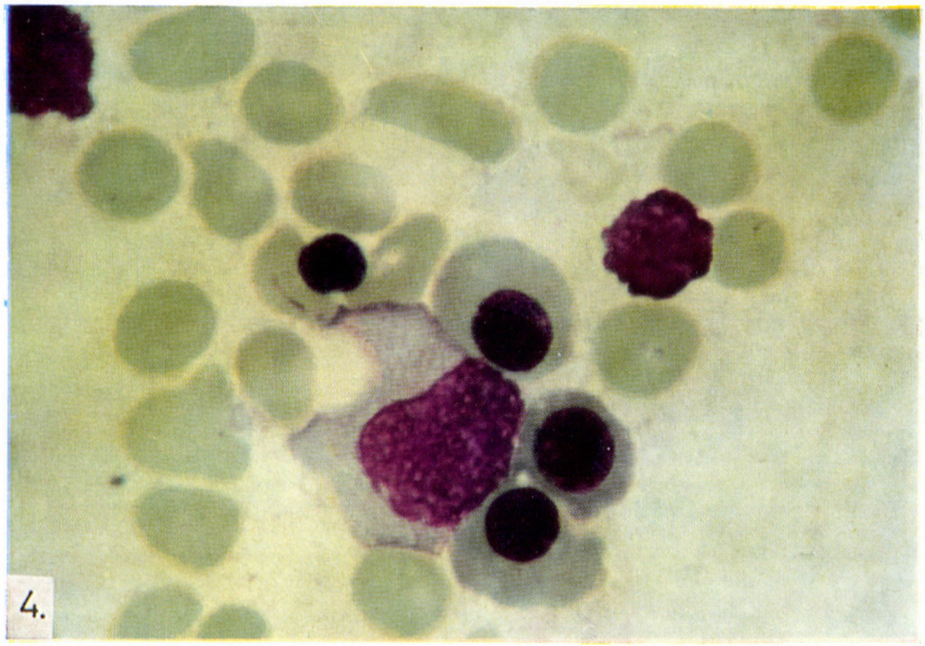
Our observations suggest that lithium carbonate administered during induction of remission enhances the cellularity of the bone marrow and increases the peripheral leukocyte and granulocyte count. Gallicchio et al. [7] observed the same increase in bone marrow in lithium treated mice. The myeloid predominance in the bone marrow and the granulocyte ratio in peripheral blood seem to have increased simultaneously, thus there is a close relationship between the bone marrow cellularity and the changes in peripheral WBC and granulocyte counts during lithium treatment. In the case of a normal bone marrow cellularity, a sudden increase in WBC and a sharp and lasting increase in the peripheral granulocyte count could be observed (early reaction). A less marked and delayed leukocytosis and granulocytosis developed when the bone marrow was hypocellular and contained only few myeloids (delayed reaction). The bone marrow reserve capacity and its mobilization were normal in patients with clinical expression of bone marrow depression.

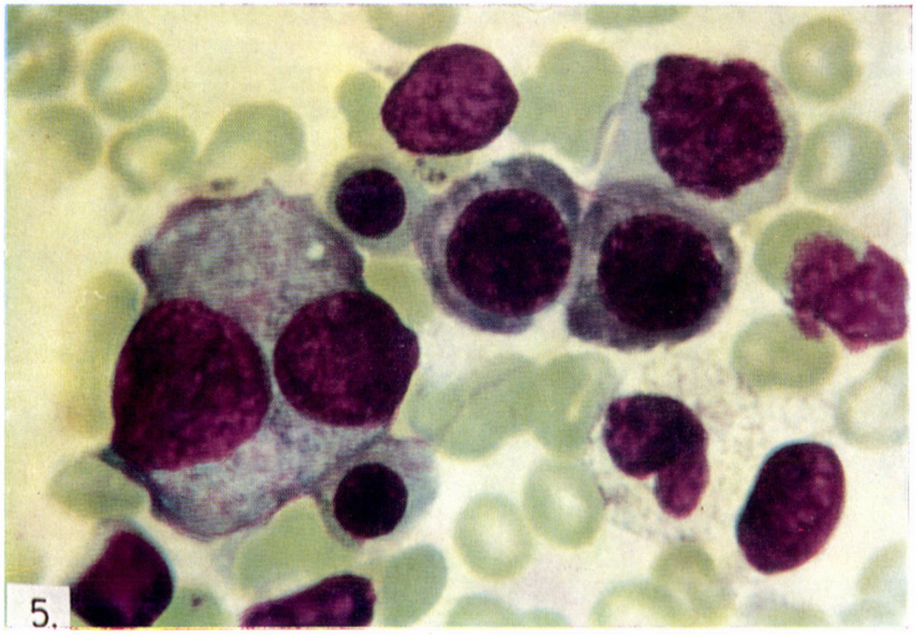
There are several possibilities to explain the present results. Lithium seems to have different effects on haematopoiesis, thus on the increase in the number of cells in the bone marrow and in peripheral blood. Lithium, added to normal bone marrow cells cultured in vitro, stimulated the growth of granulocytic colonies [17], increased the number of granulocyte progenitor cells [11], and the number of granulocyte/macrophage colony forming units (CFU-GM) [20], but only in the presence of colony stimulating activity (CSA) [8, 10, 11]. Lithium enhances the production of CSA [10] especially by peripheral mononuclear cells [21]. Lithium is able to induce cells that are normally quiescent and non-cycling [8].

The site of action of lithium on the bone marrow is not clear. Lithium may act at the level of granulocyte progenitor cells and directly stimulate the proliferation of pluripotential stem cells, as has been shown in cell cultures [11] and in mice [7]. Lithium stimulates the mononuclears to produce a humoural pluripoietin-analogous substance, and thus it may induce pluripotent stem cells to differentiate into various cell lines [11]. Fernandez and MacSween [6] found that lithium decreased the number of T-cell colonies, so they assumed that it would affect the even more immature totipotent stem cells as well. This suggests that lithium may be useful in the treatment of different disorders supposed to be due to a deficiency of pluripotent stem cells [1, 2, 9].

Since in studies in vitro no close correlation could be found between the lithium concentration in the medium and the stimulatory effect, some indirect mechanism appears to be more likely than a direct one. There are several factors influencing the actual condition and the reaction of the bone marrow to lithium, especially under circumstances in vivo.



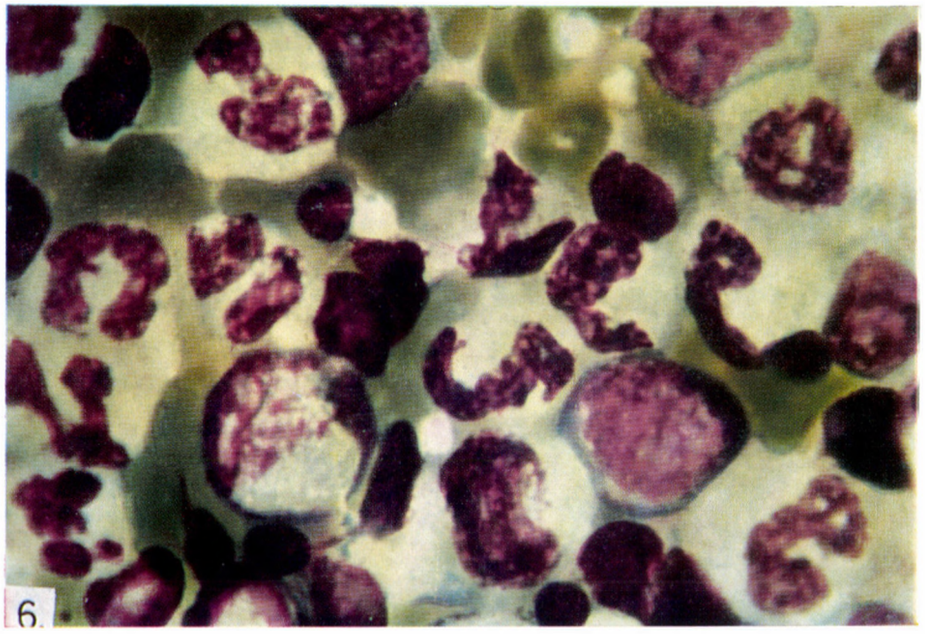




FIG. 3. Bone marrow at the end of induction of remission after lithium treatment. Bone marrow biopsy, imprint preparation, May–Grünwald–Giemsa staining, ×1000

FIG. 4. Bone marrow at the end of induction of remission, control. Bone marrow biopsy, imprint preparation, May–Grünwald-Giemsa staining, ×1000

FIGS 5–6. Effect of $Li_2CO_3$ on bone marrow depleted by cytotoxic drugs. Before treatment hypocellularity and erythroid hyperplasia (Fig. 5), after treatment hypercellularity and myeloid predominance (Fig. 6). Bone marrow biopsy, imprint preparation, May–Grünwald–Giemsa staining, ×1000

Thus, nutritional status, hepatic and renal function, the presence or absence of infection and especially the reserve capacity of the bone marrow and a cytotoxic therapy may modify the reaction [19]. It has to be emphasized that if there is a reasonable reserve of marrow stem cells, lithium may induce a transient or sustained increase in their production [11]. The same has been shown by Casirola et al [4] in that if there was only a little stem cell pool in the marrow the granulopoiesis induced by lithium was poor.

Bone marrow can be sampled only under strict indications, and so the reserve capacity cannot be examined often. For this reason, every observation referring to the actual condition of the bone marrow may be important. Our observations were made in a small number of patients, but the results indicate that a short term lithium treatment may be useful for estimation of the actual condition and of the reserve capacity of the bone marrow. As the clinical signs of its exhaustion and inhibition are the same, a lithium-test may help to differentiate and to decide upon adequate therapy.

## References


1. Barrett AJ, Griscelli C, Buriot D, Faille A: Lithium therapy in congenital neutropenia. Lancet 2:1357, 1977
2. Blum SP: Lithium therapy of aplastic anemia. N Engl J Med 300:677, 1979
3. Botnick LE, Hannon EC, Hellman S: Limited proliferation of stem cells surviving alkylating agents. Nature 262:68, 1976
4. Casirola G, Invernizzi R, Ippoliti G, Pavia G, Bottoni A: Effetti del litio carbonico sulle neutropenie primitive e secondarie. Haematologica 65:746, 1980
5. Catane R, Kaufman J, Mittelman A, Murphy GP: Attenuation of myelosuppression with lithium. N Engl J Med 197:452, 1977
6. Fernandez LA, MacSween JM: Lithium and T cell colonies. Scand J Haematol 25:382, 1980
7. Gallicchio VS, Chen MG: Modulation of murine pluripotential stem cell proliferation in vivo by lithium carbonate. Blood 56:1150, 1980
8. Gallicchio VS, Chen MG: Cell kinetics of lithium-induced granulopoiesis. Cell Tissue Kinet 15:179, 1982
9. Hammond WP, Dale DC: Cyclic hematopoiesis: effects of lithium on colony-forming cells and colony-stimulating activity in grey Collie dogs. Blood 59:179, 1982
10. Harker WG, Rothstein G, Clarkson DR, Athens JW, Macfarlane JL: Enhancement of colony stimulating activity production by lithium. Blood 49:263, 1977
11. Lewitt LJ, Quesenberry PJ: The effect of lithium on murine haematopoiesis in a liquid culture system. N Engl J Med 302:713, 1980
12. Lyman GH, Williams CC, Preston D: The use of lithium carbonate to reduce infection and leukopenia during systemic chemotherapy. N Engl J Med 302:257, 1980
13. Molnár S, Kajtár P: Effect of lithium carbonate on peripheral leukocyte counts in children suffering from haematological malignancies. Acta Paediatr. Acad Sci Hung (in press)
14. Radomski JL, Fuyat HN, Nelson AA, Smith PK: The toxic effects, excretion and distribution of lithium chloride. J Pharmacol Exp Ther 100:429, 1950
15. Révész T, Kardos G, Vargha M, Schuler D: The treatment of childhood leukaemia in Hungary. Haematologia 15:103, 1982
16. Riehm H, Gadner RH, Welte K: Die West-Berliner Studie zur Behandlung der akuten lymphoblastischen Leukämie des Kindes. Erfahrungsbericht nach 6 Jahren. Klin. Padiatr. 189:89 1977
17. Rothstein G, Clarkson DR, Larsen W, Grosser BI, Athens JW: Effect of lithium on neutrophil mass and production. N Engl J Med 298:178, 1978
18. Stein RS, Flexner JM, Graber SE: Lithium and granulocytopenia during

induction therapy of acute myelogenous leukaemia. Blood 54:636, 1979
19. Steinherz PG, Rosen G, Ghavini F, Wang Y, Miller DR: The effect of lithium carbonate on leukopenia after chemotherapy. J Pediatr 96:923, 1980
20. Tisman G, Herbert V, Rosenblatt S: Evidence that lithium induces human granulocyte proliferation, elevated serum vitamin $B_{12}$ binding capacity in vivo and granulocyte colony proliferation in vitro. Brit J Haematol 24:767, 1973
21. Turner AR, Allalunis MJ: Mononuclear cell production of colony stimulating activity in humans taking oral lithium carbonate. Blood 52: Suppl 1 234, 1978 (abstract)
22. Wollner NP, Burchenal JH, Lieberman PH, Exelby PR, D'Angio GJ, Murphy ML: Non-Hodgkin's lymphoma in children. Cancer 37:123, 1976

*Received 20 November 1982*

S Molnár MD
József A. u. 7
H-7623 Pécs, Hungary

*Acta Paediatrica Hungarica, 24 (3), pp 217–220 (1983)*

# Metabolic relations of serum lipids and lipoproteins in diabetic children

Márta Peja, L Madácsy, L Kassay, Mária Bognár

County Children's Centre, Miskolc, Hungary

Serum lipids and lipoproteins of 29 insulin dependent diabetic children have been determined and related to the metabolic status of the patients. The findings were compared to results obtained in 30 healthy children. The diabetic children showing unsatisfactory metabolic parameters had significantly higher total lipid and total triglyceride levels than did the healthy children ($p < 0.01$). All diabetic children, independently of their metabolic status, exhibited an increased low density lipoprotein cholesterol level ($p < 0.01$). On the other hand, high density lipoprotein cholesterol levels found in diabetics did not differ from normal values and showed no relationship with their metabolic status.

Prevention of vascular complications of diabetes must be started in childhood by attentive care directed to all details of the pathomechanism.

Atherosclerosis is one of the early complications of insulin dependent diabetes in childhood. The early onset may be related to the quality of metabolic control and to changes in plasma lipid and lipoprotein composition. It is obvious that the long-term prognosis of juvenile diabetes is determined by the degree of derangements in lipid metabolism; for this reason, investigation of plasma lipids and lipoproteins of diabetic children is of utmost importance [4].

Chase and Allen [2] observed increased serum total cholesterol, triglyceride and low-density lipoprotein (LDL) and decreased high density lipoprotein (HDL) levels even in well-controlled diabetics. Lopes-Virella et al. [6] found a significant positive correlation between haemoglobin $A_{1c}$ and low density lipoprotein cholesterol (LDL-C) and an inverse relationship between haemoglobin $A_{1c}$ and high density lipoprotein cholesterol (HDL-C) levels in diabetic children. No relationship between metabolic control and HDL-C levels were found by Sosenko et al [12], Madácsy et al [7] and Ratzmann et al [9] in juvenile diabetes. Eckel et al [3] described increased HDL-C levels in juvenile insulin dependent diabetes. More recently, Regöly-Mérei et al [10] investigated changes in lipoprotein fractions of diabetic children under organised camping conditions: they observed an increase of the HDL-C level as a result of more physical activity.

A positive correlation between haemoglobin $A_{1c}$ and HDL-C levels was demonstrated by Klujber et al [5]. Soltész et al [11] found a relationship between HDL-C levels and

insulin doses but did not observe significant differences in other lipoprotein fractions between well- and poorly controlled diabetic children.

All this has prompted us to study the lipid and lipoprotein levels of diabetic patients in order to find eventual relationships between metabolic control and lipid metabolism.

## Materials and Methods

Twenty-nine diabetic children, fourteen girls and fifteen boys, participated in the study. Their mean age was 10.6 $\pm$ 3.8 years, the range was 4 to 18 years. Mean duration of diabetes was 2.8 $\pm$ 2.7 years. The control group consisted of thirty children admitted for minor airway complaints. They were healthy at the time of the study; their mean age was 8.2 $\pm$ 3.9 years with a range of 8–14 years.

The diabetic children were divided into two groups. Group 1 comprised children with well- controlled diabetes: these patients had a haemoglobin $A_{1c}$ level below 8% and during three months preceding the study they did not have a urinary glucose concentration exceeding 3% at any occasion of outpatient control.

Group 2 consisted of children with poorly controlled diabetes. They had a haemoglobin $A_{1c}$ level higher than 8% and during the preceding three months period they repeatedly exhibited glucosuria exceeding 3%.

The blood samples were taken from fasting outpatients before injection of the morning dose of insulin. The samples were analysed for serum total lipid, total cholesterol, triglyceride, HDL-C, LDL-C and very low density lipoprotein cholesterol (VLDL-C), and haemoglobin $A_{1c}$.

Total lipid was determined by the phosphovanyllic acid method, all other lipids and lipoproteins and urinary glucose by Boehringer's enzyme test, and haemoglobin $A_{1c}$ by a colour glycohaemoglobin test.

## Results

Results are shown in Table I.

Serum total lipid and total triglyceride were elevated in both diabetic groups compared with the control group. Total cholesterol and VLDL-C were normal in both groups of diabetic children. The HDL-C value did not show any correlation with the quality of control of diabetes and it fell within the normal limits.

The LDL-C level was significantly higher in both diabetic groups than in the healthy controls.

## Discussion

Nowadays the outlook of diabetic children is determined by the time of onset and the severity of vascular complications. Various forms of hyperlipoproteinaemia are risk factors in the development of atherosclerosis.

Hyperlipoproteinaemia developing in diabetes is caused by insulin deficiency since this hormone plays a key role in lipid balance. It enhances the conversion of glucose to fatty acids and stimulates lipoprotein lipase activity in the adipose tissue [13]. The latter enzyme facilitates lipoprotein catabolism, and this in turn leads to increased HDL-C levels [2].

Our findings showed that the HDL-C levels are not higher in diabetic children than in healthy controls nor are they dependent of the quality of control of diabetes. On the other hand, serum total lipid and total triglycerides were higher in children

TABLE I

Serum lipid and lipoprotein values (mean + S.D.) of diabetic children and healthy controls

| | Healthy controls (30) | Diabetic children | |
|---|---|---|---|
| | | Group 1 (16) | Group 2 (13) |
| Haemoglobin $A_{1c}$, per cent | 0.83 ± 0.73 | 7.66 ± 0.55 | 11.3 ± 0.73 |
| Total lipid, g/l | 6.12 ± 1.54 | 6.53 ± 1.82 N.S. | 6.63 ± 1.47 $P < 0.01$ |
| Total cholesterol, mmol/l | 4.34 ± 0.66 | 4.52 ± 0.75 N.S. | 4.59 ± 0.74 N.S. |
| Total glyceride, mmol/l | 1.35 ± 0.15 | 1.40 ± 0.31 N.S. | 2.15 ± 0.55 $P < 0.01$ |
| VLDL-C, mmol/l | 3.25 ± 0.45 | 3.33 ± 0.75 N.S. | 3.46 ± 1.02 N.S. |
| LDL-C, mmol/l | 2.04 ± 0.68 | 2.98 ± 0.35 $P < 0.01$ | 3.13 ± 1.00 $P < 0.01$ |
| HDL-C, mmol/l | 1.09 ± 0.50 | 1.07 ± 0.41 N.S. | 1.11 ± 0.40 N.S. |

No. of cases in parentheses

with poor metabolic control than in diabetic children under good control.

Our observation concerning increased LDL-C levels in both diabetic groups is in accordance with the findings of other authors [2].

Our finding of normal HDL-C levels in diabetics may be attributed to the fact that the study was performed in outpatients who had possibilities for physical activity. Physical exercise is known to increase HDL-C levels. In addition, our patients had been treated with insulin for years. Insulin itself stimulates lipoprotein lipase activity and, by that, also leads to an increase of the HDL-C level [8, 13].

The present findings corroborate the necessity of a complex care of diabetes, comprising the control of glucose and fat metabolism and organising home facilities for regular physical exercise. None of our diabetic patients are exempted from school gymnastics and many of them regularly play some ball-games.

Prevention of diabetic angiopathy has to be started in childhood by complex care directed at all factors of diabetic complications.

## REFERENCES

1. Barta L: Über die Bedeutung der Blutlipide beim Diabetes mellitus im Kindesalter. Endokrinologie 53:261, 1968
2. Chase HP, Allen MV: Juvenile diabetic plasma lipids and lipoprotein levels. Am J Dis Child 130:1112, 1976
3. Eckel H, Albers JJ, Chenung MC, Wahl PW, Lindgren FT, Bierman EL: High density lipoprotein composition in insulin-dependent diabetes mellitus. Diabetes 30:132, 1981
4. Erxleben B, Spahn U, Kauf E, Petrich E, Knaut C, Winter K: Zur Hyper-

lipidaemie bei juvenilem Diabetes mellitus. Kinderarztl Prax 8:407, 1980
5. Klujber L, Molnár D, Kardos M, János V, Soltész Gy, Mestyán J: Metabolic control, glycosylated haemoglobin and high density lipoprotein cholesterol in diabetic children. Eur J Pediatr 132:289, 1979
6. Lopes-Virella MF, Wohltman HJ, Loadholt CB, Buse MG: Plasma lipids and lipoproteins in young insulin-dependent patients. Relationship with control. Diabetologia 21:216, 1981
7. Madácsy L, Peja M, Bognár M, Kassay L: Metabolic control and lipoprotein metabolism in diabetic children. Pediatr Res 15:1198, 1981
8. Ratkis T, Boyden TW, Pamenter RW, Stanforth P, Wilmore J: High density lipoprotein cholesterol and body composition of female runners. Metabolism 10:994, 1981
9. Ratzmann KP, Witt S, Hidmann W, Schutz V: Zur klinischen Bedeutung des HDL-Cholesterols bei Patienten mit gestörter Glykosetoleranz und Typ I Diabetes mellitus. Dtsch Gesundh-Wes 36:1682, 1981
10. Mérei-Regöly A, Barta L, Molnár M, Tichy M, Pena M: Besserung des Zustandes der diabetischen Kinder unter der Wirkung des Sommercampings. Wien Med Wochenschr 131 Suppl 67:21, 1981
11. Soltész Gy, Molnár D, Kardos K, Klujber L: Insulin therapy, metabolic control and plasma lipoprotein levels in diabetic children. Pediatr Res 15:1192, 1981
12. Sosenko JM, Breslow JL, Mietinen OS, Gabbay KH: Hyperglycemia and plasma lipid levels. N Engl J Med 302:650, 1980
13. Taskinen MR, Nikkila EA, Gordin RNA: Lipoprotein lipase activity in adipose tissue in skeletal muscle of human diabetics during insulin deprivation and restoration. Scand J Clin Lab Invest 41:263, 1981

*Received 23 November 1982*

M Peja MD
Szentpéteri k. 76
H-3501 Miskolc, Hungary

*Acta Paediatrica Hungarica, 24 (3), pp 221—229 (1983)*

# Assessment of skeletal age in the first year of life on basis of the caput humeri ossification centres

B LOMBAY

Section of Radiology, County Children's Hospital, Miskolc, Hungary

A new procedure has been worked out to estimate skeletal maturity in infancy. The size of the caput humeri ossification centres was determined with the help of a pattern set from the antero-posterior chest roentgenogram. In each month of the first year of life 100 examinations were carried out and from their data percentile lines were constructed for every month of life.

Determination of skeletal age by means of X-rays is a generally accepted method to evaluate biological maturity. Examination of the appearance, shape and number of ossification centres (OC) may reveal deviations from normal characteristic of certain diseases and sometimes has a role in the evaluation of therapy, for instance in hypothyroidism, adrenogenital syndrome, growth hormone deficiency, etc. Tables for estimation of skeletal age have been compiled by many authors. Most of them dealt with the ossification of the hand and wrist as well as the leg, knee and elbow. These methods are useful for older children, but an accurate evaluation in infancy is hindered by the late appearance of the OC [4]. Elgenmark [2] determined skeletal age from X-rays of the left side of the body with special regard to OC of the foot, leg, femur, hand, forearm and upper arm. Caution is however recommended, especially in the case of control examinations, in view of the radiation exposure. Recently Senecal et al [11] and Erasmie and Ringertz [3] have developed a new method by measuring the OC of the lower limb of newborn babies.

We have attempted to study the OC of the proximal epiphysis of the humerus as it appears on chest X-rays. This OC is mostly present at birth and its development can be easily observed and might be convenient for the determination of skeletal age in infancy. We have therefore elaborated a uniform method for measuring the proximal OC of the humerus and studied its relation to skeletal age.

In the first year of life purely enchondral ossification prevails in the epiphysis of the humerus [7] and two of the three proximal OC appear, the medial and the lateral one. Their radiomorphology has been described by Marique [8]. Depending on birth weight and racial characteristics the

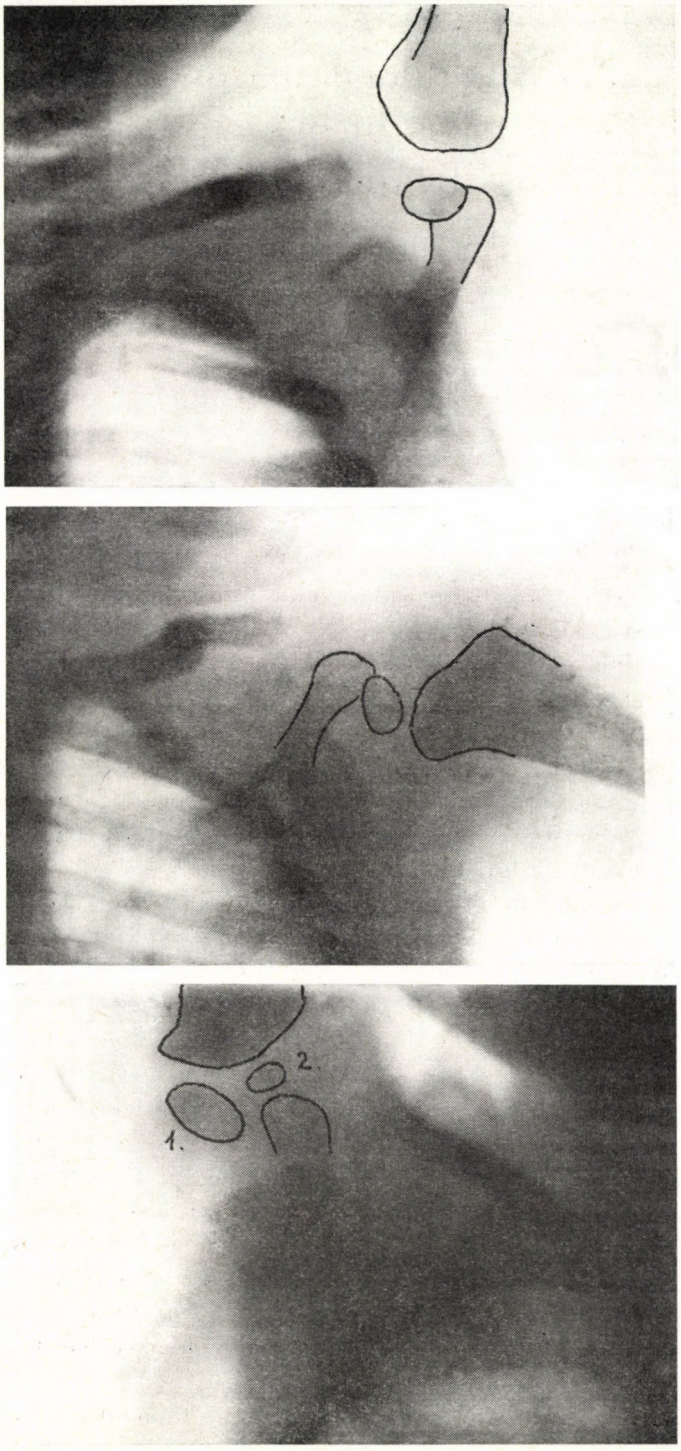



FIG. 1. A — p chest roentgenogram of a 7 months *(a–b)* and a 11 months old *(c)* infant *a* upright, *b* recumbent position. The projections of the medial OC of the same infant are similar. *c* Both the medial (1) and the lateral (2) OC have appeared (upright position).

medial OC is usually present at birth. It is certain to appear during the first three months while the lateral OC becomes visible after the sixth month [1, 5]. Both are easily detected on a–p chest films near the proximal metaphysis of the humerus (Fig. 1).

## Materials and Methods

The routine X-ray pictures of the chest have been studied in patients admitted because of some acute disease such as bronchitis, gastroenteritis, hernia, injury, burns, etc. Patients displaying somatic retardation owing to chronic disease, enzymopathy, metabolic disease, etc., were not included. From the age of 1 to 12 months, 100 children were studied for each month of age. Pertinence to an age group was reckoned from the time of birth and that of radiography by adding two weeks to the difference; e.g. infants between two weeks and six weeks were classified into the one month age group.

*Measuring technigue.* A — p chest roentgenograms at 150 cm focus-film distance were made of infants suspended in upright position. The method can be used in recumbent position too, but the focus-film distance must be longer than 100 cm; in this

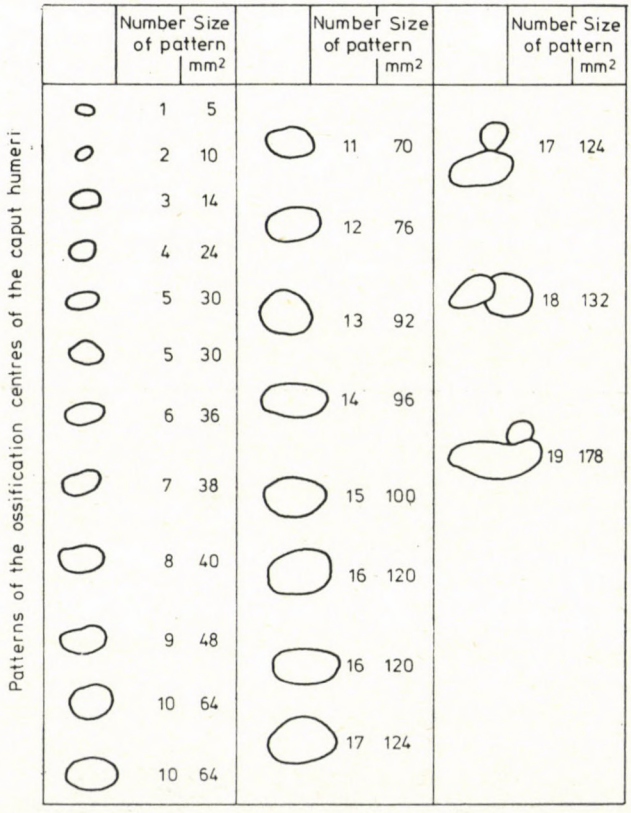



Fig. 2. Pattern set for measurement of the proximal OC of the humerus, and the size of patterns in mm². The set comprises 19 patterns. Nos 5, 10 and 16 are different in shape but identical in size. Size of the irregularly shaped figures is approximate. The size and shape of the centres can be copied on transparent paper or film. Nos 17, 18 and 19 show both the medial and lateral centres

case, projection of the OC is nearly similar (Fig. 1*a–b*).

The roentgenogram is examined on a projector screen and the OC is copied on transparent film. We have done this until we have obtained a pattern for each size, then we prepared sets accordingly and measured the size of each pattern on squared plotting paper (Fig. 2). The pattern proved suitable to measure both the medial and the lateral OC since their shape and development are identical (Fig. 1*c*). In older infants in whom the lateral OC has already appeared, the latter area was added to the medial OC. Thereafter calculations were based on the sum of the area of the two centres. It is not justified to study the two OCs separately, as the head of the humerus ossifies from the two centres. Measurement of OC on both sides gave practically no difference between the two sides in most of the patients. In the case of a minor difference the higher value was used.

Evaluation may be difficult or sometimes impossible when the shadow of the OC projects into the humerus or the scapula, or the X-ray picture is of poor quality. In the latter case a careful study may still allow for differentiation.

Mean and percentile values were calculated.

## Results

From 1 month to 12 months the monthly rate of the OC was calculated in both sexes on the basis of the mean values (Table I). The 10th, 25th, 50th, 75th and 90th percentile values were calculated in each age group; they are seen in Fig. 3.

*Estimation of bone age on the basis of the pattern set and the percentile table.* On the basis of a large number of measurements, the method was found suitable for clinical use. Details of the measurements were as follows:

*Measurement of one OC (medial).* Using the pattern set, the OC was

Table I

Mean size and monthly growth of ossification centres

| Age month | Girls | | | Boys | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | Mean mm² | Growth mm² | No. of cases | Mean mm² | Growth mm² | No. of cases | Mean mm² | Growth mm² |
| 1 | 43 | 6 | | 57 | 6 | | 100 | 6.0 | |
| 2 | 44 | 9 | 3 | 56 | 11 | 5 | 100 | 10.0 | 4.0 |
| 3 | 49 | 16 | 7 | 51 | 18 | 7 | 100 | 17.0 | 7.0 |
| 4 | 45 | 24 | 8 | 55 | 28 | 10 | 100 | 26.0 | 9.0 |
| 5 | 51 | 32 | 8 | 49 | 36 | 8 | 100 | 34.0 | 8.0 |
| 6 | 44 | 42 | 10 | 56 | 44 | 8 | 100 | 43.0 | 9.0 |
| 7 | 43 | 52 | 10 | 57 | 52 | 8 | 100 | 52.0 | 9.0 |
| 8 | 47 | 61 | 9 | 53 | 58 | 6 | 100 | 59.5 | 7.5 |
| 9 | 39 | 68 | 7 | 61 | 65 | 7 | 100 | 66.5 | 7.0 |
| 10 | 51 | 74 | 6 | 49 | 74 | 9 | 100 | 74.0 | 7.5 |
| 11 | 49 | 81 | 7 | 51 | 84 | 10 | 10 | 82.5 | 8.5 |
| 12 | 37 | 93 | 12 | 63 | 91 | 7 | 100 | 92.0 | 9.5 |

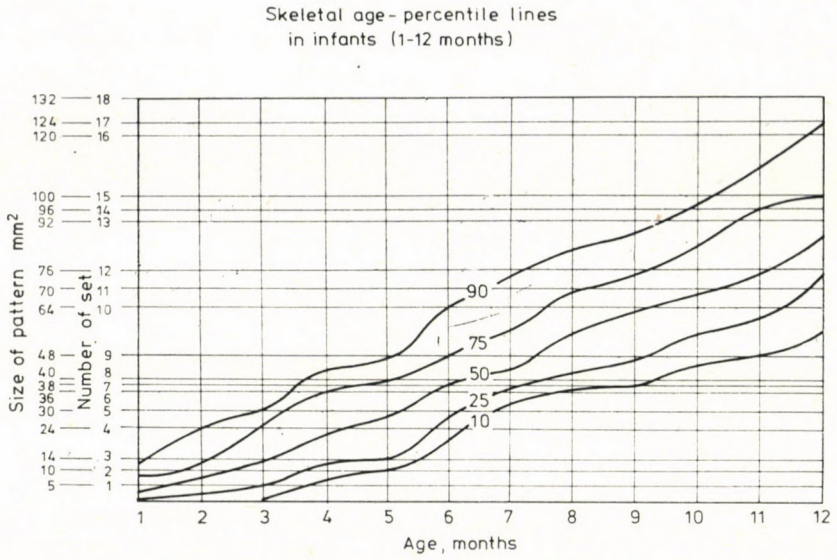



FIG. 3. Percentile graphs of OC development. Abscissa: age in months; ordinate: size of pattern in mm², and number of pattern. For further details, see text

measured and the value looked up on the ordinate of the percentile curve. The intersection of the horizontal line drawn from the ordinate and the vertical line drawn from the age on the abscissa yielded the bone age in percentiles.

*Measurement of two OC (medial and lateral).* Each of the two OC were measured separately, their area was added and the value determined as mentioned above. Having reached a certain size the two centres ossify together; in such cases the two centres were measured with the last three patterns.

The method was simplified by tabulating the numbers of the patterns corresponding to those sizes of the OC which after minimal correction denote the percentile curve data (Table II).

Bone age is easily determined from Table II in percentiles if one OC is present. If both centres are present the number of the pattern corresponding to the added amount of the two areas is looked up and used for the determination of bone age. The following cases will demonstrate the procedure.

*Case 1.* For a certain 7 months old infant the number of the pattern was 7. No 7 in Table II corresponds to 25 percentile of actual age, accordingly the baby's bone age is 25 percentile (Fig. 1*a*).

*Case 2.* If we suppose that the previous infant was 10 months of age, the number of patterns 7 does not figure at 10 months. The nearest number is found at the 10th percentile of 9 months and at 50th percentile at 6 months. Thus, bone age

TABLE II

Estimation of skeletal age on the basis of pattern set in percentiles

| Percentiles | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <10 | | | | 0 | 1 | 3 | 4 | 5 | 6 | 8 | 8 | 9 |
| 10 | | | 0 | 1 | 2 | 4 | 5 | 6 | 7 | 9 | 9 | 10 |
| | | | | 2 | | | 6 | 7 | 8 | | | |
| 25 | 0 | 0 | 1 | 3 | 3 | 5 | 7 | 8 | 9 | 10 | 10 | 11 |
| | | | 2 | | 4 | 6 | | | | | 11 | 12 |
| 50 | 1 | 1 | 3 | 4 | 5 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| | | | | 5 | 6–7 | 8 | 9 | 10 | 11 | | 13 | 14 |
| 75 | 2 | 2 | 4 | 6 | 8 | 9 | 10 | 11 | 12 | 12 | 14 | 15 |
| | | 3 | | 7 | | | | | | 13 | | |
| 90 | 3 | 4 | 5 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| 90< | | 5 | 6 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
| Age, months | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |

TABLE III

Appearance of the medial ossification centre of the head of the humerus between 1 and 5 months of age

| Age, month | Girls | | | Boys | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | No. of cases | No. of OC | per cent | No. of cases | No. of OC | per cent | No. of cases | No. of OC-per cent |
| 1 | 43 | 29 | 67 | 57 | 33 | 57 | 100 | 62 |
| 2 | 44 | 33 | 75 | 56 | 43 | 77 | 100 | 76 |
| 3 | 49 | 38 | 78 | 51 | 44 | 86 | 100 | 82 |
| 4 | 45 | 43 | 96 | 55 | 54 | 98 | 100 | 97 |
| 5 | 51 | 51 | 100 | 49 | 49 | 100 | 100 | 100 |

could be 9 months at 10 percentile, or alternatively, 6 months at 50 percentile. These forms allow to establish whether the value is within the variations of a certain age group. Moreover, they show that the value corresponds to the 50th percentile.

*Case 3.* In this 11 months old infant (Fig. 1*c*) two centres (Nos 10 and 3) were present; the added size of the medial (64 mm$^2$) and the lateral one (14 mm$^2$) was 78 mm$^2$. This is nearest to the pattern No 12 (76 mm$^2$). According to Table II, the value corresponds to 50th percentile of 11 months.

## DISCUSSION

In agreement with data in the literature, the medial OC of the humerus usually appears earlier in girls than

boys during the first month of life [1, 4, 6]. After the second month there is no difference between the sexes (Table III). The monthly growth rate of OC amounts to 7–9.5 $mm^2$ after the second month (Table I).

As data on the width and height of the OC of the head of the humerus during the first year of life were given only by Schmid [10], we took the same measures; our findings proved to be nearly identical. The monthly size of the OC displayed a considerable scatter. The percentile curves showed, except for the first month, 7–8 size variations in each age group, thus the 10th and 90th percentile curves were rather far from each other. The 50th percentile curve lies slightly below the curve for the mean value in each group. The above mentioned size differences might have been due partly to the fact that the patients studied were not healthy, and partly indicate a wide variability of the size of the OC [4].

Considerable acceleration of the growth of the OC was seen in 3 cases. Aortic stenosis had been diagnosed in 2 of these patients and haemodynamic changes may have been responsible for the increased calcification. In the third patient the clinical symptoms suggested Marshall syndrome [9]. These cases have not been omitted from statistical analysis.

Osseous age determined by the OC of the hands and humerus was compared in some cases (Table IV). Apparently, the method described in the present paper seemed to offer more reliable results than the OC of the hands, especially when the carpal bones appear in an irregular fashion (Case 2) (Table IV, Fig. 4).

The method has the following advantages:

1. The size of the OC can be deter-

TABLE IV

Application of the method

| No. | Age months | Sex | Clinical diagnosis | No. of pattern | Skeletal age | |
|---|---|---|---|---|---|---|
| | | | | | Humerus month percentile | OC of hand |
| 1 | 3 | m | Adrenogenital | 1 | 3/25 | no |
| | 6 | | syndrome | 6 | 6/25–50 | no |
| | 8 | | | 10 | 10/50–75 | ab 4 months |
| 2 | 11 | f | Hypothyroidism | 9 | 11/10* | ? (Oc of radius) |
| | | | | | 8/50** | |
| 3 | 12 | m | VSD | 5 | 7/10* | ab |
| | | | | | 5/50** | 4–8 months |
| 4 | 12 | m | MPS | 5 | 7/10* | ab |
| | | | | | 5/50** | 4–8 months |

* nearest percentile value,
** 50th percentile value

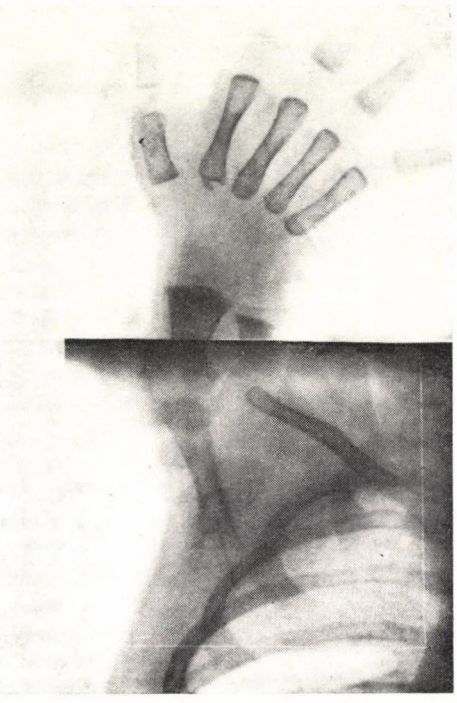


FIG. 4. A — p roentgenogram of the chest and of the hand of an 11 months old hypothyroid infant. For further details, see text

mined from the routine a—p chest roentgenogram. This is still taken of practically every patient admitted to hospital. Additional X-rays are not needed for the determination of skeletal age.

2. The method requires no technical staff in contrast to hand roentgenograms.

3. Bone age can be determined independently from the examiner's impression.

4. The value given in percentiles may complete the similarly expressed values of length, weight, etc.

The method is based on the observation of a single OC although some examiners prefer to determine more centres; in this case, additional X-rays can always be done although in our experience they add little to the information yielded by the head of the humerus. Its late appearance means the only drawback we know in this case some other method should be applied.

ACKNOWLEDGEMENT

I am greatly indebted to Prof. Ch. M. Gefferth for valuable advices.

REFERENCES

1. Caffey J: Paediatric X-ray Diagnosis. Vol 2, Lloyd-Luke, London 1973
2. Elgenmark O: Normal development of the ossification centres during infancy

and childhood. Clinical roentgenologic and statistical study. Acta Paediatr Scand 33 Suppl 1, 1946
3. Erasmie U, Ringeritz H: A method for assessment of skeletal maturity in children below one year of age. Pediatr Radiol 9:225, 1980
4. Gefferth K: Critical evaluation of a method of skeletal age estimation. Magy Radiol 22:300, 1970
5. Groskopff K, Tischendorf R: Das normale menschliche Skelett in Röntgenskizzen. G Thieme, Leipzig 1962
6. Lassrich M, Prévot R, Schäfer, KH: Pädiatrischer Röntgenatlas. G Thieme, Stuttgart 1955
7. Kiss F, Szentágothai J: Atlas of Human Anatomy. 17th ed, Pergamon Press, Oxford 1976
8. Marique P: Aspect radiographique anormale de la tête humérale. Arch Franco-belges Chir 31:236, 1928
9. Marshall R: Syndrome of accelerated maturation and relative failure to thrive: a newly recognized growth disorder. J Pediatr 78:95, 1971
10. Schmid F: Pädiatrische Radiologie. Vol 2, Springer Verlag, Berlin–Heidelberg–New York 1973
11. Senecal M, Grosse A, Vincent J, Simon J, Lefrèche N: Maturation osseuse du foetus et du nouveau-né. Arch Fr Pediatr 34:424, 1977

*Received 23 November 1982*

B Lombay MD
Szentpéteri k. 72
3501 Miskolc, Hungary

*Acta Paediatrica Hungarica, 24 (3), pp 231—245 (1983)*

# Testing of two score systems for the diagnosis of malnutrition

M Amador, C Rodriguez

Department of Paediatrics, Higher Institute of Medical Sciences and Department of Physical Development, Institute of Sports Medicine, INDER, Havana, Cuba

Two score systems, one for the diagnosis of obesity and another for diagnosing undernutrition were tested in thirteen overweight and seven underweight children aged five years and preliminarily classified as malnourished. These score-systems included indicators grouped into three categories, those which evaluate total body mass changes (one-point group); those which assess fatness (two-point group); and those which assess fatness and/or body composition through complex indices (three-point group). Indicators such as Energy/Protein Index, AKS Index, Somatotype ratings, and Somatotype Dispersion Distances were included in the third group and played an important role in the final score.

A subject was classified as malnourished if he reached 80% of the maximum possible score. According to these criteria, only six among the thirteen overweight children could be considered obese and none of the seven underweight ones could be classified as undernourished.

Mild or moderate overweight or underweight may be misleading and an incorrect diagnosis of either obesity or undernutrition can be made if the possibility of constitutional corpulence or thinness is not taken into account.

When clinical and anthropometric features of malnutrition are evident, the diagnosis of either obesity or undernutrition can be made easily, but the problem of identifying nutritional imbalance arises when the commonly used methods of assessment fail to establish whether changes beyond the typical ranges are due to malnutrition or correspond to constitutional peculiarities of a given individual [5] due mainly to the influence of genetic factors than to nutritional ones [16, 17].

It is well known that there is no unique criterion capable to discriminate among typical subjects those who are malnourished [5]; moreover, the estimates of obesity and leanness in a population vary with the criteria used [9, 24, 43]; and a given criterion differs in its diagnostic value according to the purpose we use it: for screening, for ascertaining the true prevalence of disease, or for use in surveillance [22]; or according to the type [39] or degree [22] of malnutrition we are assessing. Anyhow, a simple division of children into well-nourished and malnourished on the basis of a single parameter can be misleading [39]; therefore in order to achieve better results and obtain a precise diagnosis, it is necessary to combine several criteria [39].

The selection of these criteria has

to be made on the basis of several premises, considering the changes in body mass and body composition which occur as consequences of nutritional disturbances. The premises should be

1. Total body mass is increased in obesity and decreased in undernutrition.

2. Obesity is characterized by an increase in Fat Body Weight (FW).

3. Mean feature in undernutrition is the decrease of Lean Body Weight (LBW), with a more or less marked decrease of FW.

Considering these three premises, we have made an attempt to establish a score system based upon several criteria, some of them classic and others not commonly used in nutritional assessment, testing this system in two small samples of selected supposedly malnourished children.

## Materials and Methods

A group of twenty supposedly malnourished children admitted with the preliminary diagnosis of obesity or undernutrition was studied. Thirteen of these children, 8 girls and 5 boys, showed mild or moderate overweight (weight for stature up to 160%); and the other seven, 4 girls and 3 boys, were slightly or moderately underweight (weight for stature not less than 75%). The children were otherwise healthy. Their age ranged from 4.2 to 5.3 years of decimal age.

Anthropometric assessment consisted in the following measurements:

1. Body Weight (BW)
2. Stature (HT)
3. Humerus Width (biepicondylar diameter)
4. Femoral Width (bicondylar diameter)
5. Upper Arm Circumference (UAC)
6. Flexed Biceps Girth (FUAC)
7. Calf Girth (CC)
8. Triceps Fatfold (T)
9. Subscapular Fatfold (SS)
10. Suprailiac Fatfold (SI)
11. Calf Fatfold (C)

Date of birth and date of recording were registered for obtaining the decimal age as described by Tanner et al [41].

All measurements were done on the right side of the body as required for somatotyping. The general aspects of the methodology employed including general recommendations, subject position, instruments and apparatus, were those recommended by the International Biologic Programme [41], and have been described elsewhere [2, 3].

Expected BW for HT (BW/HT), was obtained according to Ounsted and Simmons [31] as follows.

$$\mathrm{BW/HT} = \frac{\mathrm{A}}{\mathrm{B}}\,100$$

where $\mathrm{A} = \dfrac{\text{Actual BW of the subject}}{\text{Actual HT of the subject}}$

and $\mathrm{B} = \dfrac{\text{50th percentile BW for age}}{\text{50th percentile HT for age}}$

Expected values for BW, HT, UAC, CC and fatfolds were referred to the 50th percentile of Cuban standards [26].

Energy/Protein Index (E/P) was calculated in each child by the expression [2]:

$$\mathrm{E/P} = \frac{\mathrm{TT}}{\mathrm{TUAMC}}$$

where TT is transformed T [13], TUAMC is $\log_{10}$ of upper arm muscle circumference [25].

The somatotype components were obtained according to Heath and Carter [23], and Ross et al [34]. Using the somatotype plotting grid [34], the somatotype of each subject was plotted by the formulae

$$\mathrm{X} = \mathrm{III} - \mathrm{I} \text{ and } \mathrm{Y} = 2\mathrm{II} - (1+\mathrm{III})$$

where I is the first component of endomorphy, II is the second component of

mesomorphy, III is the third component of ectomorphy.

Somatotype Dispersion Distances were calculated in each subject according to the expression [34]:

$$SDD = \sqrt{3(X_1 - X_2)^2 + (Y_1 - Y_2)^2}$$

where $X_1$ and $Y_1$ represent the coordinates of a given subject, and $X_2$ and $Y_2$ are the previously reported mean reference values for age and sex [7].

Fat Body Weight (FW) was calculated by means of Dugdale and Griffiths' regression equations [12], starting from BW, HT, T and SS. Lean Body Weight (LBW) was obtained by substracting FW from BW. Body Fat percent (%BF) was obtained by the expression

$$\%BF = \frac{FW \times 100}{BW}$$

Aktiver Körpersubstanz Index (AKS) was obtained according to Wutscherk [42] as follows

$$AKS = \frac{LBW}{HT^3}\ 100$$

Previous reports regarding percentile distribution for E/P [3] and for FW, %BF, LBW, and AKS [8] were taken as reference.

Twelve different criteria which could be considered indicators of obesity were tested in each of the 13 overweight subjects. In order to quantify the results, we established a score system in which each criterion present in the subject received a number of points according to its quality as indicator of the nutritional status as follows.

*(a)* Criteria which evaluate total body mass changes obtained one point; these were

1. BW for age above 90th percentile
2. BW for HT (BW/HT) above 120%
3. UAC above 90th percentile
4. CC above 90th percentile

*(b)* Criteria which assess fatness from single measurements obtained two points; these were

5. Triceps fatfold above 90th percentile
6. Subscapular fatfold above 90th percentile
7. Suprailiac fatfold above 90th percentile

*(c)* Criteria which assess fatness and/or body composition through more complex indices obtained three points; they were

8. FW above 90th percentile
9. %BF above 90th percentile
10. E/P above 90th percentile
11. Endomorphy (1st component) $\geq$3.5 in girls and $\geq$3.0 in boys
12. SDD $\geq$6.00

According to this score, the maximum for an individual is 25 points and we established an arbitrary cut-off cumulative value of 20 (80% of the total possible) above which a subject could be classified as obese.

Fifteen different criteria which could be considered indicators of undernutrition were tested in each one of the seven underweight subjects comprising the sample. Like in overweight subjects, a similar score system was established as follows.

*(a)* One-point group

1. BW for age under 10th percentile
2. BW/HT under 90%
3. BW/HT under 80%
4. UAC under 10th percentile
5. CC under 10th percentile

*(b)* Two-point group

6. T under 10th percentile
7. SS under 10th percentile
8. SI under 10th percentile
9. FW under 10th percentile
10. %BF under 10th percentile

*(c)* Three-point group

11. LBW under 10th percentile
12. AKS Index under 10th percentile
13. E/P Index under 10th percentile
14. Mesomorphy (2nd component) $<$4.0 (in both sexes)
15. SDD $\geq$7.00

The maximum cumulative score in this case was 30, and the 80% regarded as cut-off point was 24.

All statistical and computational work was carried out at the Centre of Cybernetics Applied to Medicine of the Higher Institute of Medical Sciences of Havana.

Table Ia

Anthropometric measurements in 13 overweight (supposedly obese) children

| Subject No. | Age Sex | BW kg | HT cm | Girths, cm | | Circumferences, cm | | | Fatfolds, mm | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Humer | Femor | UAC | FUAC | CC | T | SS | SI | C |
| 1 | 4.6 | 26.2 | 109.3 | 4.5 | 7.0 | 20.0 | 21.0 | 24.0 | 13.0 | 9.6 | 8.2 | 8.6 |
| | F | (8) | (6) | (a) | (a) | (8) | (a) | (7) | (7) | (7) | (7) | (a) |
| 2 | 4.8 | 21.0 | 104.2 | 4.3 | 7.0 | 20.6 | 21.3 | 25.1 | 11.6 | 6.1 | 6.2 | 6.9 |
| | F | (7) | (5) | (a) | (a) | (8) | (a) | (7) | (7) | (5) | (6) | (a) |
| 3 | 4.9 | 20.8 | 109.1 | 4.7 | 7.0 | 19.8 | 20.9 | 23.2 | 11.4 | 8.6 | 7.5 | 9.3 |
| | F | (8) | (6) | (1) | (a) | (8) | (a) | (6) | (7) | (6) | (6) | (a) |
| 4 | 4.3 | 20.4 | 107.3 | 4.9 | 7.0 | 19.1 | 20.8 | 24.1 | 11.2 | 7.3 | 8.2 | 8.1 |
| | F | (7) | (6) | (a) | (a) | (7) | (a) | (7) | (7) | (5) | (7) | (a) |
| 5 | 4.4 | 21.5 | 110.9 | 4.5 | 6.5 | 19.2 | 20.7 | 24.4 | 13.1 | 9.6 | 9.7 | 9.2 |
| | F | (8) | (6) | (a) | (a) | (7) | (a) | (7) | (7) | (7) | (7) | (a) |
| 6 | 4.2 | 22.2 | 109.6 | 4.5 | 6.8 | 18.6 | 19.6 | 23.7 | 12.6 | 9.8 | 9.6 | 6.2 |
| | F | (8) | (6) | (a) | (a) | (7) | (a) | (7) | (7) | (7) | (7) | (a) |
| 7 | 5.0 | 25.9 | 110.0 | 4.6 | 7.1 | 21.2 | 22.3 | 24.2 | 13.2 | 9.0 | 8.1 | 8.2 |
| | F | (8) | (6) | (a) | (a) | (8) | (a) | (7) | (7) | (7) | (7) | (a) |
| 8 | 5.2 | 23.8 | 110.6 | 4.8 | 7.2 | 21.9 | 22.8 | 24.3 | 12.9 | 9.6 | 7.8 | 7.7 |
| | F | (8) | (6) | (a) | (a) | (8) | (a) | (7) | (7) | (7) | (6) | (a) |
| 9 | 4.3 | 19.6 | 103.2 | 4.5 | 7.0 | 19.8 | 20.6 | 22.9 | 13.2 | 9.6 | 8.4 | 9.6 |
| | M | (7) | (5) | (a) | (a) | (8) | (a) | (7) | (8) | (8) | (7) | (a) |
| 10 | 4.4 | 19.1 | 104.2 | 4.6 | 7.2 | 18.6 | 19.2 | 23.1 | 12.1 | 6.2 | 7.1 | 8.4 |
| | M | (7) | (5) | (a) | (a) | (7) | (a) | (7) | (8) | (5) | (7) | (a) |
| 11 | 4.2 | 19.6 | 108.0 | 4.4 | 6.8 | 18.8 | 19.4 | 23.6 | 11.1 | 8.8 | 7.8 | 8.5 |
| | M | (7) | (7) | (a) | (a) | (8) | (6) | (7) | (7) | (7) | (7) | (a) |
| 12 | 5.2 | 21.5 | 108.8 | 4.5 | 6.7 | 18.1 | 18.6 | 22.4 | 11.9 | 7.9 | 7.6 | 7.1 |
| | M | (7) | (5) | (a) | (a) | (7) | (a) | (5) | (7) | (7) | (7) | (a) |
| 13 | 5.3 | 21.9 | 111.0 | 4.6 | 6.8 | 19.3 | 20.1 | 23.7 | 11.5 | 8.8 | 8.4 | 7.7 |
| | M | (7) | (5) | (a) | (a) | (8) | (a) | (7) | (8) | (7) | (7) | (a) |

BW: Body weight
HT: Stature
UAC: Upper arm circumference
FUAC: Flexed UAC
T: Triceps fatfold
SS: Subscapular fatfold
SI: Suprailiac fatfold
C: Calf fatfold

in parentheses:
percentile channels
8: >97th
7: >90th ≤97th
6: >75th ≤90th
5: >50th ≤75th
(a), Cuban standards not available.

## Results

The recorded data of anthropometric measurements and calculated indices in the 13 overweight children are shown in Tables Ia and Ib. Table Ic includes an analysis of the twelve different indicators expressed above which could be regarded as criteria of obesity. According to the score-system established, only six out of the thirteen subjects accumulated twenty points or more. Subjects 1, 7 and 13 showed a score of 25, and subjects

TABLE Ib

Anthropometric indices in 13 overweight (supposedly obese) children

| Subject No. | BW/HT % | FW kg | %BF | LBW kg | AKS | E/P | Somatotype components | | | SDD |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1st | 2nd | 3rd | |
| 1 | 155.8 | 9.01 (8) | 34.38 (8) | 17.19 (8) | 1.32 (7) | 1.896 (7) | 3.5 | 5.5 | 0.5 | 6.43 |
| 2 | 126.6 | 5.88 (6) | 28.02 (6) | 15.12 (6) | 1.34 (7) | 1.804 (6) | 2.5 | 6.0 | 0.5 | 5.84 |
| 3 | 122.5 | 5.43 (6) | 26.09 (6) | 15.37 (7) | 1.22 (5) | 1.796 (6) | 3.0 | 5.5 | 1.0 | 5.56 |
| 4 | 125.1 | 5.24 (6) | 25.66 (5) | 15.16 (6) | 1.23 (5) | 1.785 (6) | 2.5 | 5.5 | 0.5 | 5.62 |
| 5 | 128.4 | 5.73 (6) | 26.63 (6) | 15.77 (7) | 1.16 (4) | 1.798 (6) | 3.5 | 5.5 | 1.0 | 5.96 |
| 6 | 132.9 | 6.42 (7) | 28.92 (6) | 15.78 (7) | 1.20 (5) | 1.815 (6) | 3.0 | 5.0 | 0.5 | 5.96 |
| 7 | 150.4 | 8.58 (8) | 33.11 (7) | 16.32 (8) | 1.23 (5) | 1.877 (7) | 3.5 | 5.5 | 0.5 | 7.29 |
| 8 | 135.1 | 7.97 (8) | 31.72 (7) | 16.53 (8) | 1.22 (5) | 1.861 (7) | 3.0 | 6.0 | 0.5 | 6.48 |
| 9 | 123.6 | 5.55 (8) | 28.06 (8) | 14.06 (5) | 1.28 (6) | 1.789 (7) | 3.5 | 6.0 | 0.5 | 5.75 |
| 10 | 118.0 | 4.02 (7) | 21.05 (7) | 15.08 (5) | 1.33 (7) | 1.762 (6) | 2.5 | 6.0 | 0.5 | 3.99 |
| 11 | 123.0 | 4.11 (7) | 20.95 (7) | 15.50 (5) | 1.23 (5)) | 1.758 (6) | 3.0 | 5.5 | 1.0 | 4.31 |
| 12 | 122,1 | 5.04 (8) | 25.07 (8) | 15.06 (5) | 1.17 (4) | 1.795 (7) | 3.0 | 4.5 | 1.0 | 5.39 |
| 13 | 122.9 | 6.06 (8) | 27.66 (8) | 15.84 (5) | 1.17 (4) | 1.802 (7) | 4.0 | 5.0 | 1.0 | 6.78 |

BW/HT: Body weight for stature
FW: Body weight in fat
%BF: Body fat percent
LBW: Lean body weight
AKS: AKS Index
E/P: Energy/Protein Index
SDD: Somatotype dispersion distance

in parentheses:
percentile channels
8: >97th
7: >90th ≤97th
6: >75th ≤90th
5: >50th ≤75th
4: >25th ≤50th

8, 9 and 12 exhibited scores of 20, 22 and 21 respectively.

The anthropometric measurements and indices in seven underweight children appear in Tables IIa and IIb. Table IIc includes the cumulative score of the fifteen criteria of undernutrition. None of the seven subjects studied reached a score of 24.

Figures 1 and 2 show the individual cases (boys and girls respectively) plotted in somatocharts. Each somatochart includes the mean value for age and sex as reported previously

TABLE Ic

Selected criteria for classification as obese of 13 overweight children

| Criteria considered positive of obesity | | Subject No. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Body Weight above 90th percentile | (1) | × | × | × | × | × | × | × | × | × | × | × | × | × |
| Upper Arm Circumference above 90th percentile | (1) | × | × | × | × | × | × | × | × | × | × | × | × | × |
| Calf Circumference above 90th percentile | (1) | × | × | — | × | × | × | × | × | × | × | × | — | × |
| Body Weight for Stature above 120% | (1) | × | × | × | × | × | × | × | × | × | — | × | × | × |
| Triceps Fatfold above 90th percentile | (2) | × | × | × | × | × | × | × | × | × | × | × | × | × |
| Subscapular Fatfold above 90th percentile | (2) | × | — | — | — | × | × | × | × | × | — | × | × | × |
| Suprailiac Fatfold above 90th percentile | (2) | × | — | — | × | × | × | × | — | × | × | × | × | × |
| Body Weight in Fat above 90th percentile | (3) | × | — | — | — | — | × | × | × | × | × | × | × | × |
| Body Fat percent above 90th percentile | (3) | × | — | — | — | — | — | × | × | × | × | × | × | × |
| E/P Index above 90th percentile | (3) | × | — | — | — | — | — | × | × | × | — | — | × | × |
| Endomorphy (1st component) ≥3.5-girls-≥3.0-boys | (3) | × | — | — | — | × | — | × | — | × | — | × | × | × |
| Somatotype Dispersion Distance (SDD) ≥6.00 | (3) | × | — | — | — | — | — | × | × | — | — | — | — | × |
| Total score | | 25 | 6 | 5 | 8 | 13 | 13 | 25 | 20 | 22 | 13 | 19 | 21 | 25 |
| Classified as obese | | × | — | — | — | — | — | × | × | × | — | — | × | × |

Number of points given to each criterion appears in parentheses

[7], and the distribution of overweight as well as underweight subjects.

## DISCUSSION

In this paper we have attempted to give answers to the practical questions what to do with those children whose parents are worried about their nutritional status, a preoccupation usually reinforced by hasty medical diagnosis of malnutrition based upon weight for age, weight for stature or similar criteria, when the children show no apparent cause of malnutrition either organic or socioeconomic; and are such children actually mal-

TABLE IIa

Anthropometric measurements in 7 underweight (supposedly undernourished) children

| Subject No. | Age Sex | BW kg | HT cm | Girths, cm | | Circumferences, cm | | | Fatfolds, mm | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Humer. | Femor. | UAC | FUAC | CC | T | SS | SI | C |
| 1 | 4.6 F | 12.7 (2) | 103.9 (5) | 4.2 (a) | 6.1 (a) | 14.1 (2) | 14.5 (a) | 19.7 (3) | 6.0 (2) | 4.6 (2) | 3.4 (2) | 4.8 (a) |
| 2 | 4.3 F | 12.2 (2) | 98.6 (3) | 4.1 (a) | 6.0 (a) | 14.5 (2) | 14.8 (a) | 19.2 (2) | 5.8 (2) | 4.2 (1) | 2.8 (1) | 4.1 (a) |
| 3 | 4.5 F | 11.9 (a) | 100.1 (4) | 4.0 (a) | 5.9 (a) | 13.9 (1) | 14.1 (a) | 19.6 (3) | 4.6 (1) | 4.4 (2) | 3.4 (2) | 3.7 (a) |
| 4 | 4.2 F | 12.2 (2) | 102.0 (5) | 4.2 (a) | 6.2 (a) | 14.4 (2) | 14.9 (a) | 19.0 (2) | 5.8 (2) | 4.6 (2) | 3.7 (3) | 4.6 (a) |
| 5 | 4.3 M | 12.7 (2) | 102.2 (5) | 4.1 (a) | 6.0 (a) | 14.5 (2) | 15.0 (a) | 1.94 (2) | 5.5 (2) | 3.9 (2) | 2.9 (1) | 4.0 (a) |
| 6 | 4.4 M | 13.3 (2) | 104.8 (5) | 4.3 (a) | 6.4 (a) | 14.6 (2) | 15.0 (a) | 19.2 (2) | 4.5 (1) | 3.9 (2) | 3.2 (2) | 4.3 (a) |
| 7 | 4.3 M | 12.6 (1) | 102.7 (4) | 4.2 (a) | 6.5 (a) | 14.8 (3) | 15.2 (a) | 19.9 (3) | 5.4 (2) | 4.0 (2) | 3.8 (1) | 4.4 (a) |

BW: Body weight
HT: Stature
UAC: Upper Arm Circumference
FUAC: Flexed UAC
T: Triceps Fatfold
SS: Subscapular Fatfold
SI: Suprailiac Fatfold
C: Calf Fatfold

in parentheses
percentile channels
1: $\leq$3rd
2: >3rd $\leq$10th
3: >10th $\leq$25th
4: >25th $\leq$50th
5: >50th $\leq$75th
(a), Cuban standards not available

nourished or only constitutionally heavy or thin ?

The subjects we have selected for the study were otherwise healthy children. Growth and development were within the expected range for their age and sex; they had chronic disease and routine laboratory studies showed no abnormality.

Among the overweight children, the familiar incidence of overweight or "heavy constitution" was as follows

*(a)* Parents and one or more siblings, 2 subjects (Nos 1 and 4)

*(b)* Both parents, 2 subjects (Nos 5 and 8)

*(c)* One or more siblings, 2 subjects (Nos 7 and 13)

*(d)* One parent, 4 subjects (Nos 2, 3, 10 and 11)

*(e)* No parent or sibling, 2 subjects (Nos 9 and 12).

Thus, eleven subjects had at least one close relative with overweight or "heavy constitution". As these relatives were not examined and we have been informed only by the child's parents, it was not possible to establish which of them were actually

TABLE IIb

Anthropometric indices in 7 underweight (supposedly undernourished) children

| Subject No. | BW/HT % | FW kg | %BF | LBW kg | AKS | E/P | Somatotype components | | | SDD |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1st | 2nd | 3rd | |
| 1 | 78.8 | 0.254 (1) | 2.02 (1) | 12.45 (3) | 1.11 (3) | 1.490 (2) | 1.5 | 4.0 | 4.0 | 7.95 |
| 2 | 81.5 | 0.882 (1) | 7.22 (1) | 11.32 (2) | 1.18 (4) | 1.450 (2) | 1.5 | 4.5 | 3.0 | 5.41 |
| 3 | 76.9 | 0.527 (1) | 4.43 (1) | 11.37 (1) | 1.13 (3) | 1.323 (1) | 1.5 | 4.0 | 3.5 | 6.96 |
| 4 | 78.7 | 0.301 (1) | 2.47 (1) | 11.90 (3) | 1.12 (3) | 1.455 (2) | 1.5 | 4.0 | 4.0 | 7.95 |
| 5 | 80.7 | 0.609 (1) | 4.97 (1) | 12.09 (2) | 1.13 (3) | 1.419 (2) | 1.5 | 4.0 | 3.5 | 6.96 |
| 6 | 80.9 | 0.421 (1) | 3.16 (1) | 12.88 (3) | 1.12 (3) | 1.277 (1) | 1.5 | 4.5 | 4.0 | 7.07 |
| 7 | 79.3 | 0.537 (1) | 4.30 (1) | 12.06 (2) | 1.11 (3) | 1.396 (2) | 1.5 | 4.5 | 3.5 | 6.11 |

BW/HT: Body Weight for Stature
FW: Body weight in fat
%BF: Body fat percent
LBW: Lean Body weight
AKS: AKS Index
E/P: Energy/Protein Index
SDD: Somatotype dispersion distance

in parentheses:
percentile channels
1: $\leq$3rd
2: $>$3rd $\leq$10th
3: $>$10th $\leq$25th
4: $>$25th $\leq$50th

obese. Nevertheless, the association of overweight in parents and siblings with overweight in the subjects studied was evident, but no differences could be detected between those overweight children we have classified as obese and those considered non-obese.

Among underweights, the information obtained from parents was less precise regarding the siblings. "Thin constitution" was present in both parents in subjects Nos 1 and 5; in one parent in subjects Nos 3, 4, 6 and 7; and subject No. 2 had no thin parents.

Though the probability of being obese or lean increases with the incidence of obesity or leanness in the kinship [20], the same familiar incidence can be expected for "heavy" or "light" constitution. Hence, unless the familiar incidence of obesity or undernutrition could fully be distinguished from the familiar incidence of heavy or light constitution, this aspect cannot be considered a reliable indicator for assessing malnutrition.

The score system was based upon criteria accepted as suitable for nutritional assessment, though some of them are not used commonly. The categorization of these criteria into three groups, each one with a different value in the score, took into

TABLE IIc

Selected criteria for classification of seven underweight children as undernourished

| Criteria considered positive of undernutrition | | Subject, No. | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Body Weight under 10th percentile | (1) | × | × | × | × | × | × | × |
| Upper Arm Circumference under 10th percentile | (1) | × | × | × | × | × | × | — |
| Calf Circumference under 10th percentile | (1) | — | × | — | × | × | × | — |
| Body Weight for Stature under 90% | (1) | × | × | × | × | × | × | × |
| Body Weight for Stature under 80% | (1) | × | — | × | × | — | — | × |
| Triceps Fatfold under 10th percentile | (2) | × | × | × | × | × | × | × |
| Subscapular Fatfold under 10th percentile | (2) | × | × | × | × | × | × | × |
| Suprailiac Fatfold under 10th percentile | (2) | × | × | × | — | × | × | × |
| Body Weight in Fat under 10th percentile | (2) | × | × | × | × | × | × | × |
| Body Fat percent under 10th percentile | (2) | × | × | × | × | × | × | × |
| Lean Body Weight under 10th percentile | (3) | — | × | × | — | × | — | × |
| AKS Index under 10th percentile | (3) | — | — | — | — | — | — | — |
| E/P Index under 10th percentile | (3) | × | × | × | × | × | × | × |
| Mesomorphy (2nd component) $>4.0$ | (3) | — | — | — | — | — | — | — |
| Somatotype Dispersion Distance $\geq 7.00$ | (3) | × | — | — | × | — | × | — |
| Total score | | 20 | 20 | 20 | 19 | 20 | 20 | 19 |
| Classified as undernourished | | — | — | — | — | — | — | — |

Number of points given to each criterion appear in parentheses

account the possibilities of each criterion for detecting changes in body composition. Therefore, we grouped in the one-point category such measurements or indices which only appraise variations in whole body mass; the limitations of BW for age, BW/HT and UAC, had been discussed elsewhere [6, 21, 30, 36, 37]. Calf circumference has been used in the diagnosis of undernutrition as well as thigh circumference [44]. Those however accept similar limitations as UAC.

Fatfolds were grouped in the two-point category. T fatfold above the 85th centile has been considered a suitable criterion of obesity [19], but with a low correspondence with BW for age [18]. SS and SI fatfolds seem

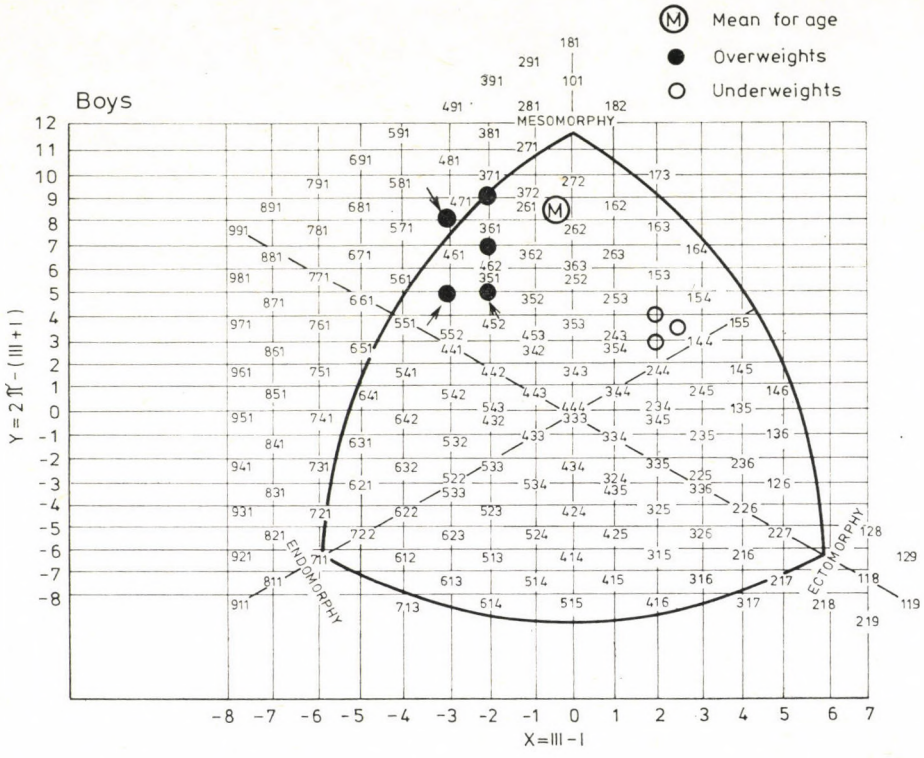



FIG. 1. Five overweight and three underweight boys were plotted in the somatochart. The mean for age and sex is included. The arrows point to the three overweight boys who were classified as obese according to the score

less sensitive to environmental changes than limb fatfolds [10]. In Cuba, Esquivel and Vassallo [15], correlating BW with fatfolds found that the highest "r" value was obtained with SS.

Though most common forms of undernutrition are accompanied by a lack of total energy which has its expression in a decrease of subcutaneous body fat, in undernutrition the decrease of LBM is the most specific feature [27, 28, 29, 36, 40].

The three-point group includes new indices.

Obesity is defined as an increase of FW, and this increase can be measured by determining %BF. The limitations of these two indicators are in the accuracy of the method employed for determining FW [12]. Our experience with Dugdale and Griffiths's regression equations [12] was fairly satisfactory and we believe that they provide a useful tool for nutritional assessment. FW as well as %BF were, however, included in the two-point group when evaluating undernutrition; the cause has been explained above: the decrease of body fat is

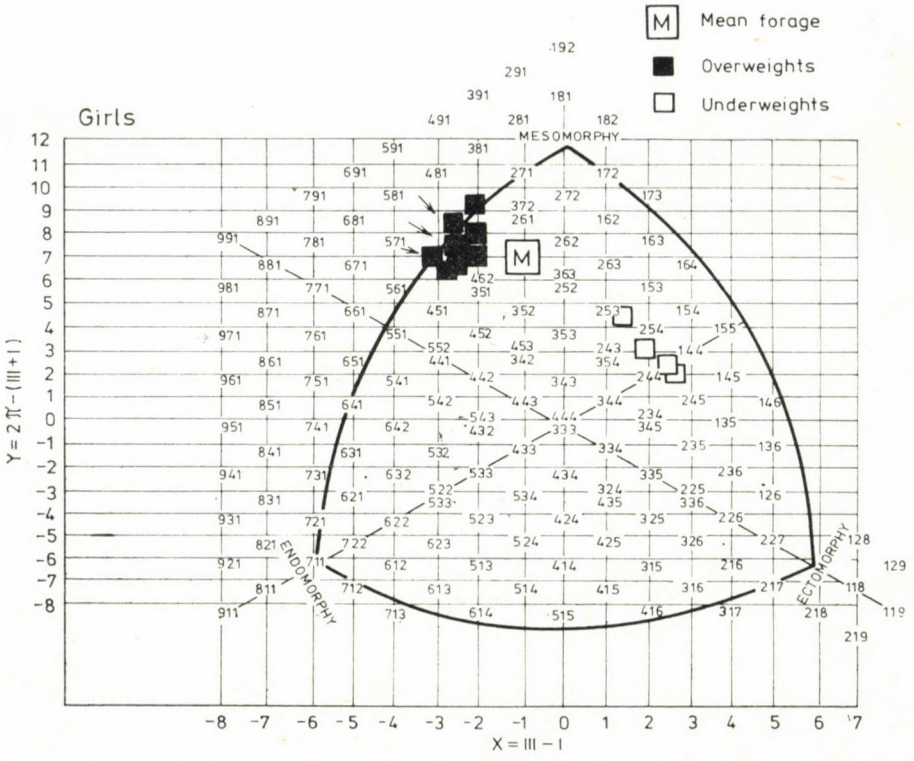



FIG. 2. Eight overweight and four underweight girls were plotted in the somatochart. The mean for age and sex is included. The arrows point to the three overweight girls who were classified as obese according to the score

not the most outstanding feature in undernutrition in contrast with the loss of LBW which rapidly increases during nutritional recovery [33].

Therefore, LBW has been included in the third category. Its only limitation is that it is greatly influenced by the stature, a fact that has been overcome by the introduction of the AKS (Aktiver Körpersubstanz-Index) [42]. This index expresses LBW in kg of fat-free mass per $cm^3$ of total body mass and avoids the variations determined by differences in height. Originally designed for use in athletes, the AKS has been introduced successfully in nutritional assessment of children [5, 8] with the only difference that the original description determines LBW by calculating FW by Par'zková's regression equations for ten fatfolds [32] and we obtained FW by Dugdale and Griffiths's equations for BW, HT and two fatfolds.

Somatotyping is another new method having been tested by us. Its first component measures adiposity and high ratings for endomorphy should be consistent with the diagnosis of obesity. In a previous study, the

mean value for the first component in five-year old healthy children was 1.71 for boys, and 2.49 for girls [7]. This indicator was positive in four of the five children with scores of 20 or more, and only two of the eight subjects had a score under 20.

As we obtained high ratings for mesomorphy in healthy children [7], a rating of 4 (around two standard deviations below the mean; 5.88 for boys and 5.48 for girls) was considered the cut-off point. Four of the seven subjects showed a second component of 4 and none was below that figure.

The Somatotype Dispersion Distance (SDD) [34] shows how far from the means for age and sex are the somatotype ratings for a given individual. In a previous study the Somatotype Dispersion Index (SDI), which is the mean dispersion of the ratings of reference children, was 2.18 for boys, and 1.85 for girls. In the present study we established high cut-off points for SDD considering the great variations existing among individuals in body build and body constitution. In overweight subjects none below a score of 20 was beyond the cut-off point and, conversely, four of the five children classified as obese were positive for this indicator. In underweights only three subjects were positive.

The usefulness of the Energy/Protein Index in assessing obesity [4] and both main forms of undernutrition has been considered in previous reports. The only five overweight subjects with E/P above the 90th percentile were just those with a score of 20 or above. On the other hand, all subjects showed E/P figures under the 10th percentile. If we state that none of the seven subjects was undernourished, this would be contradictory to our previous statement that an E/P below the 10th percentile is an indicator of undernutrition [2, 3]. As a possible explanation, the seven subjects studied were lean, with a low degree of adiposity but conserving their fat-free mass. This means a decrease in the E/P numerator without a change in the denominator, yielding low values for the ratio. If we take the 3rd percentile of E/P as the cut-off points, only two subjects were positive by this criterion. Nevertheless, this raises the question of the discriminative value of E/P in the kind of subjects we have considered in this study.

As to the correspondence among the different indicators, in overweights the indicators of the first group were consistently coincident; in the second group SS and SI were not always coincident with T. Esquivel and Vassallo [14] reported a tendency of T to be at a higher percentile channel than BW and other fatfolds, a finding also reported by Garn et al [18]. In the third category FW, %BF and E/P were also coincident. There was no coincidence between the first component and SDD. The discriminative power of the indicators of group three was decisive in the classification of the subjects.

In underweight children, indicators of the first group were coincident but not with the same consistency. Fat-

folds were coincident and this points to the high degree of leanness of the subjects. The coincidence between FW and %BF contrasted with the difference found between LBW and AKS. The circumstance that all the subjects showed an AKS Index above the 10th percentile, meaning that there was no actual impairment of LBW, was of great significance in the definition that these underweight subjects were not actually undernourished. AKS was also coincident with mesomorphy ratings showing the close relationship between the second component and fat-free mass development.

The wide range found in SDD, the same as it happened with the overweights, could be related to the underlying genetic influence in the features of body build which determine a basic somatotype. Nutritional disturbances influence the phenotype but the basic morphological patterns were comparatively stable [11, 35].

In this paper we have selected several anthropometric criteria with the purpose of establishing a quantification of different features which usually accompany malnutrition. Of course, there are many other indicators available and the present selection was made according to our own experience. The result can be improved by including new criteria or excluding some of the present ones. Though the scoring systems are always arbitrary, we followed a systematization based upon the theoretical ability of each criterion to express the variations of body components.

It is evident that the different anthropometric criteria of malnutrition may yield widely different estimations of the prevalence of malnutrition and different age-specific prevalence patterns [38]. This is also valid for individual assessment. We agree with Trowbridge [38] in that malnutrition cannot be considered a single homogeneous entity which should be measured by a given anthropometric indicator. As different indicators give different estimates of malnutrition, score systems combining several of these indicators, one for obesity and another for undernutrition, will be useful, especially when the diagnosis is doubtful.

## Acknowledgements

We are indebted to Prof. Sofia León, from the Higher Institute of Physical Education, for valuable advice regarding the AKS Index; and to the Centre of Cybernetics Applied to Medicine, for mathematical processing of data.

## References

1. Amador M, Bacallao J, Hermelo M Fernandez R, Tolon C: Indice Energía/Proteina: su utilidad en el diagnóstico de distintas formas de mala nutrición. Rev Cubana Med Trop 28:127, 1976
2. Amador M: Energy/Protein Index: A new approach to the assessment of the nutritional status. Ph. D. Thesis, Havana and Budapest 1978
3. Amador M, Bacallao J, Flores P: Indice Energía/Proteina: nueva validación de su aplicabilidad en evaluación nutricional. Rev Cubana Med Trop 32:11, 1980
4. Amador M, Gonzalez ME, Hermelo M: Energy/Protein Index: Its usefulness assessing obesity. Anthropol Közl 25:3, 1981
5. Amador M, Gonzalez ME, Cordova L, Perez N: Diagnosing and misdiagnosing

malnutrition. Acta Paediatr Acad Sci Hung 23. 1982
6. Amador M, Rodriguez C, Gonzalez ME, Bacallao J: Assessing obesity with body weight and height. Acta Paediatr Acad Sci Hung 23. 1982
7. Amador M, Rodriguez C, Gonzalez ME: Somatotyping as a tool for nutritional assessment in preschool children. Anthropol Közl 26:1983
8. Amador M, Canetti S, Cordova L: Indices antropométricos para la evaluación nutricional: Valores en niños sanos de cinco años de edad. Rev Cubana Pediatr 55:1983
9. Berndt J, Tiesler G: Vergleich anthropometrischer Verfahren zur Beurteilung der "body composition" bei Kindern im Grundschulalter. Gesundh-Wes 40:339, 1978
10. Bogin B, Macvean RB: Nutritional and biological determinants of body fat patterning in urban Guatemalan children. Hum Biol 53:259, 1981
11. Dobzhansky T: Mankind Evolving. Yale University Press, New Haven CT 1962
12. Dugdale AE, Griffiths M: Estimating fat body mass from anthropometric data. Am J Clin Nutr 32:2400, 1979
13. Edwards DA, Hammond WH, Healy MJ, Tanner JM, Whitehouse RH: Design and accuracy of calipers for measuring subcutaneous tissue thickness. Br J Nutr 9:133, 1955
14. Esquivel M, Vassallo J: Grasa subcutánea y estado nutricional (I). Rev Cubana Pediatr 53:274, 1981
15. Esquivel M, Vassallo J: Grasa subcutánea y estado nutricional (II). Rev Cubana Pediatr 54:1982
16. Eveleth PB, Tanner JM: World-wide Variation in Human Growth. Cambridge University Press, Cambridge 1976
17. Eveleth PB: Differences between populations in body shape of children and adolescents. Am J Phys Anthropol 49:373, 1978
18. Garn SM, Clark DC, Guire KE: Growth, body composition and development of obese and lean children. In: Childhood Obesity, ed. Wynick M, Wiley, New York 1975, pp 23–47
19. Garn SM: The measurement of obesity. Ecol Food Nutr. 1:333, 1972
20. Garn SM, Bailey SM, Solomon MA, Hopkins PJ; Effect of remaining family members on fatness prediction. Am J Clin Nutr 34:148, 1981
21. Habicht JP, Yarbrough C, Martorell R: Anthropometric field methods; Criteria for selection. In: Human Nutrition, Vol. 2, Nutrition and Growth. eds Jelliffe DB, Jelliffe EFP, Plenum Press, New York 1979
22. Habicht JP: Some characteristics of indicators of nutritional status for use in screening and surveillance. Am J Clin Nutr 33:531, 1980
23. Heath BH, Carter JEL: A modified somatotype method. Am J Phys Anthropol 27:57, 1967
24. Hermelo MP, Amador M, Bacallao J: Nutritional assessment of infants and preschool children using two different anthropometric criteria of classification. Acta Paediatr Acad Sci Hung 20:35, 1979
25. Jelliffe DB: Assessment of the Nutritional Status of the Community. WHO Monograph Series No 53, Geneva 1977, pp 77.
26. Jordan JR: Desarrollo Humano en Cuba. Editorial Científico-Técnica, La Habana 1979, pp 101–210
27. Kerpel-Fronius E, Frank K: Einige Besonderheiten der Körperzusammensetzung und Wasserverteilung bei der Säuglingsatrophie. Ann Paediatr 173:321, 1949
28. Kerpel-Fronius E, Varga F, Vönöczky J, Kun K: Relation of $O_2$ consumption to circulation in different stages of infantile malnutrition. Pediatrics 7:623, 1951
29. Kerpel-Fronius E: Physiologie pathologique des états de dénutrition. Jour Paris Pédiatr Paris 1975, pp 179–189
30. Margo G: Assessing malnutrition with the mid-arm circumference. Am J Clin Nutr 30:835, 1977
31. Ounsted MK, Simmons CD: Infant feeding, growth and development. Curr Med Res Opin 4:60, 1976
32. Pařízková J: Total body fat and skinfold thickness in children. Metabolism 10:749, 1961
33. Reeds PJ, Jackson AA, Picou D, Poulter N: Muscle mass and composition in malnourished infants and children and changes seen after recovery. Pediatr Res 12:613, 1978
34. Ross WD, Hebbelinck M, Wilson BD: Somatotype in sport and the performing arts. Medicina dello Sport 26:314, 1973
35. Seltzer CC, Mayer J: Body build and obesity. Who are the obese? JAMA 189:677, 1964
36. Sloane N, Latham MC: Nutritional anthropometry in the identification of malnutrition in childhood. Environ Child Hlth 17:98, 1971
37. Sykes PA: Errors arising through using the Harvard tables and percentage levels of median weight for age in

assessing nutritional status. Arch Dis Child 52:391, 1977
38. Trowbridge FL: Anthropometric criteria in malnutrition. Lancet 2:589, 1979
39. Trowbridge FL, Staehling N: Sensitivity and specificity of arm circumference indicators in identifying malnourished children. Am J Clin Nutr 32:687, 1979
40. Waterlow JC: The assessment of marginal protein malnutrition. Proc Nutr Soc 22:66, 1963
41. Weiner JS, Lourie JA: Human Biology: A Guide to Field Methods. International Biologic Programme, Handbook No 9, Blackwell Scientific Publications, Oxford 1969
42. Wutscherk H: Der Einfluss der aktiven Körpersubstanz auf die Leistungen in verschiedenen Sportarten. Wiss Z DHFK Leipzig, 12, 1970, pp 33—67
43. Zabaleta AN, Malina RM: Growth, fatness and leanness in Mexican-American children. Am J Clin Nutr 33:2008, 1980
44. Zeitlin M: The derivation of a reference standard for maximum thigh circumference of preschool children aged 0–5 years. Hum Biol 51:11, 1979

*Received 21 December 1982*

Prof M Amador MD, PhD
Hospital Pediatrico "William Soler"
Ave San Francisco 10112
La Habana 8, Cuba

*Acta Paediatrica Hungarica, 24 (3), pp 247–253 (1983)*

# Effect of parenteral allopurinol treatment in critically ill children in need of intensive care*

D Boda, I Németh

Department of Paediatrics, University Medical School, Szeged, Hungary

Intravenous allopurinol was administered in a dose of 5–10 mg/kg daily with continuous control of the blood level of the drug and its active metabolite in 12 infants or children in critical condition resulting from various illnesses. Only one died of the patients who were all in shock and whose state stagnated or progressed in spite of the usual intensive therapy. The importance of hyperuricaemia before treatment is emphasized as this is a common characteristic of hypoxic states and through urate nephropathy it further aggravates the course of the illness. Allopurinol may exert its beneficial effect not only by decreasing hyperuricaemia, but also by preventing the loss of purines from the hypoxic cells of the ischaemic tissues by inhibition of xanthine oxidase and/or diminishing the cytotoxic superoxide radical production, the source of which is xanthine oxidase.

In hypoxic conditions of different origin, purine metabolism is shifted to a catabolic direction. By the degradation of high energy phosphates (ATP, ADP, AMP) oxipurines (hypoxanthine, xanthine) and uric acid are accumulated. In man this accumulation manifests with extreme hyperuricaemia accompanied by enhanced excretion of uric acid [4, 13, 18]. Uric acid precipitated in the kidneys may cause renal damage, the so-called urate nephropathy, aggravating further the basic illness [2, 18]. Moreover, although the organism is capable of the reutilization of hypoxanthine, the increased uric acid production and excretion lead to an irreversible purine loss and the extent of this loss may be a decisive factor in the outcome of shock [10, 13].

The protective effect of allopurinol (Ap) against tissue ischaemia and consecutive hypoxia have already been proved in animal experiments from different aspects [1, 3, 4, 5, 6, 19, 20]. Our micromethod [14] measuring the blood level of Ap and of its active metabolite, the easily cumulative alloxanthine, allowed us regularly to control the effective drug concentration in the treated patients and, in the case of a decline of renal function, to adjust the dose.

Aware of all these facts, we considered it permissible to give a complementary Ap treatment to the patients who, in spite of the fact that they had had the usual intensive therapy, were still in a critical state or their illness progressed. In this paper our observations have been summarized.

* Supported by the State Office for Technical Development

## Patients

Twelve infants and children were treated with adjuvant Ap. Their age and diagnoses are seen in Table I. The criteria of Ap treatment were the presence of at least one of the following conditions:

*1.* acute renal failure, if from the presence of extreme hyperuricaemia urate nephropathy was considered to be the underlying cause of the illness; or

*2.* a critically severe condition, if there was no improvement in spite of intensive treatment; or

*3.* under intensive treatment if a rapid progression of the disease was observed with a dubious prognosis.

## Methods

A solution of sodium Ap and mannitol, prepared according to the method of Kann et al, [11] was infused intravenously at a slow rate in a dose of 5–10 mg/kg/day.

The blood level of the drug and of its active metabolite was determined by our own method using the xanthinoxidase inhibition by serum Ap and alloxanthine [14]. The therapeutic effect of the drug was indicated by the decrease in serum uric acid concentration as determined by our own method, which is a modification of Morin's procedure based on the specific potassium ferricyanide oxidation of uric acid [15]. Serum creatinine concentration was measured with Jaffe's modified method, urea-N determination was done with the spectrometric reaction after urease decomposition worked out by Berthelot. Acid-base parameters were examined by Astrup's method.

## Results

Table I contains the most important clinical data, the applied therapy, the serum uric acid level before and during Ap administration, the value of the active drug concentration in blood and the changes that occurred in the patient's condition. Of the twelve critically severe cases only one patient died (No. 1). He had an acute lymphoid leukaemia and necropsy showed urate infarction in the kidneys. In all the other cases an improvement of the condition or a lack of its progression was observed.

The serum uric acid level and the serum Ap concentration were controlled regularly. Before the Ap treatment serum uric acid level was below 590 μmol/l [10 mg/dl] in one case, while all the other patients displayed extreme hyperuricaemia. Parenteral Ap administration resulted in an effective blood level of the drug exerting an inhibitory effect on uric acid synthesis, and as a result the serum uric acid level decreased in all cases. If there was a pronounced damage of renal function, the high blood Ap level decreased very slowly after treatment (patients Nos 1, 3, 4).

Side effects that might be considered a consequence of Ap were never observed.

## Discussion

Allopurinol is a potent inhibitor of the enzyme xanthine oxidase catabolizing the transformation hypoxanthine–xanthine–uric acid, and thus diminishes the serum uric acid concentration and the excretion of uric acid.

The blood Ap level of the patients was regularly controlled during treat-

ment and the dose of the drug was adjusted daily so that it produced an effective drug level which did not yet cause side effects. The effective Ap level was between 30 and 60 μmol/l [4–8 μg/ml]. According to the literature, toxic symptoms only occur when the concentration surpasses 182 μmol/l [25 μg/ml] [1, 14]. Such a level was measured in patient No 1 who received doses of 20 mg/kg daily at the beginning, and as he had renal failure, the drug had accumulated, mainly in the form of its active metabolite.

The beneficial effect of Ap is certainly connected with its protection against tissue ischaemia and consecutive hypoxia. In dogs in haemorrhagic shock, Crowell et al. applied Ap pretreatment to decrease the hyperuricaemia due to the enhanced catabolism of purine nucleotides and observed an improved survival. They found a close correlation between the irreversibility of the shock and the loss of purine from the cells [5]. In Baker's view Ap by itself did not increase the survival rate of dogs in haemorrhagic shock; better results were obtained when Ap was combined with hypoxanthine, adenine, inosine and α-ketoglutarate [1]. In similar experiments Hopkins et al. observed an increased level of hepatic adenosine nucleotides after Ap treatment [9]. Stanley reported an increased coronary and aortic flow during Ap administration in experimental myocardial ischaemia of dogs [19]. In a series of transplantation experiments in different animal species, when examining the purine content of ischaemic kidneys, a more and more pronounced decrease of the tissue adenine nucleotides was observed in increasingly longer periods of ischaemia and the less the purine loss, the better was the post-ischaemic renal function [4, 6, 20].

These results cannot be applied directly to a part of the human body or to the hypoxic human organism. It seems however that the shifting of purine metabolism to a catabolic direction is a general consequence of anoxia and in man, too, the synthesis of ATP depends on the oxygen supply of the tissues and on mitochondrial oxidative phosphorylation. This means that hypoxia causes by all means a decrease of the de novo purine synthesis [10].

Recent examinations have directly proved that the biochemical effect of Ap is due not only to the protection against or the moderation of hyperuricaemia. As a consequence of the inhibition of xanthine oxidase, purine degradation stops at the level of hypoxanthine. Hypoxanthine is a substrate of the hypoxanthine-guanine-phosphoribosyl transferase (HGPRT) enzyme that transforms the purine base into intracellular purine mononucleotides. Purine loss is diminished due to reutilization. There is direct evidence that the primary effect of Ap treatment consists of the "hypoxanthine salvage pathway", i.e. the pathway of reutilization which decreases the de novo purine synthesis requiring much energy [7]. As a result, less energy is sufficient to keep the purine pool at the appro-

TABLE I

Patients treated with parenteral allopurinol (Ap): their clinical data, other therapies applied, time of treatment and dosage, changes in clinical state and some characteristic laboratory parameters

| No.<br>Age | Diagnosis | Clinical state | Other therapies | Ap treatment and its effect on serum uric acid (SU) level | Results |
|---|---|---|---|---|---|
| 1<br>11 years | Leukaemia<br>(acute lymphoid)<br>Urate nephropathy<br>Uraemia | Haemorrhage,<br>haematemesis,<br>unconsciousness,<br>uraemia, anuria<br>desperate<br>condition | Cytostatics,<br>transfusion | SU1: 1630 μmol/l<br>D: 5–20 mg/kg for<br>3 days<br>t: 48 h<br>SU2: 970 μmol/l<br>Ap: 216 μmol/l | Diuresis starts, but there is a further increase in urea-N. 6 days later the patient dies. Necropsy: leukaemia, urate infarction in kidneys |
| 2<br>JE-1.<br>3 years | Combustion<br>2nd degree<br>60% body surface | Shock, unconsciousness,<br>gastroatony | Infusions,<br>plasma expanders | SU1: 345 μmol/l<br>D: 10 mg/kg for<br>3 days<br>t: 24 h<br>SU2: 173 μmol/l<br>Ap: 25.7 μmol/l | Rapid improvement by next day. Recovery in two weeks |
| 3<br>12 years | Anaerobic sepsis<br>(leptospirosis?)<br>Pericarditis<br>Acute renal<br>failure with<br>shock | Unconsciousness,<br>haemorrhage,<br>critical state | Antibiotics,<br>transfusion,<br>peritoneal<br>dialysis | SU1: 1261 μmol/l<br>D: 7.5–10 mg/kg for<br>2 days<br>t: 96 h<br>SU2: 756 μmol/l<br>Ap: 48.5 μmol/l | The critical state did not progress, but notable improvement took two weeks |
| 4<br>1 year | Hyperparathy-<br>roidism<br>Renal failure | apathy, anuria,<br>cannot be nourished | Peritoneal<br>dialysis | SU1: 803 μmol/l<br>D: 10 mg/kg for<br>2 days<br>t: 120 h<br>SU2: 434 μmol/l<br>Ap: 92 μmol/l | Gradual improvement of renal function |
| 5<br>7 months | Empyema | Severe hypoxia,<br>septicotoxic state,<br>pulse 220/min,<br>acid haematin residue<br>in stomach | Antibiotics<br>digoxin treat-<br>ment,<br>oxygen therapy,<br>thoracocentesis | SU1: 720 μmol/l<br>D: 7.5–10 mg/kg for<br>two days<br>t: 48 h<br>SU2: 357 μmol/l<br>Ap: 64.7 μmol/l | Considerable improvement by next day |

| | | | | | |
|---|---|---|---|---|---|
| 6<br>7 months | Encephalitis, anuria | Unconsciousness, extreme acidosis, hyperpyrexia, respiratory arrest, critical state | Respiratory treatment, peritoneal dialysis | SU1: 1707 μmol/l<br>D: 5–10 mg/kg for 3 days<br>t: 48 h<br>SU2: 1175 μmol/l<br>Ap: 73.5 μmol/l | Improvement, reappearance of spontaneous breathing, gradual recovery |
| 7<br>6 weeks | Pneumocystosis | Critical state, acid haematin in stomach, dyspnoea, respiratory arrest | Resuscitation, artificial breathing, respiratory treatment antibiotics | SU1: 1296 μmol/l<br>D: 5 mg/kg for 1 day<br>t: 12 h<br>SU2: 928 μmol/l<br>Ap: 47.0 μmol/l | Slight improvement by next day, gradual recovery |
| 8<br>6 weeks | Pneumonia, renal hypoplasia | Unconsciousness, hypotonicity, acid haematin in stomach, acidosis | Antibiotics, peritoneal dialysis | SU1: 732 μmol/l<br>D: 5 mg/kg 3×6 h<br>t: 48 h<br>SU2: 489 μmol/l<br>Ap: 44.9 μmol/l | Slow, gradual improvement, after critical azotaemia |
| 9<br>8 months | Meckel's diverticulum, post-operative state | Severe shock, peritonitis | Antibiotics, peritoneal dialysis | SU1: 1225 μmol/l<br>D: 7.5 mg/kg for 3 days<br>t: 24 h<br>SU2: 571 μmol/l<br>Ap: 47.8 μmol/l | Improvement. Recovery in two weeks |
| 10<br>4 years | Waterhouse-Friderichsen syndrome, meningococcus sepsis | Foudroyant progression, desperate state, unconsciousness | Antibiotics, corticoids, heparin, peritoneal dialysis | SU1: 654 μmol/l<br>D: 5–10 mg/kg for 3 days<br>t: 48 h<br>SU2: 256 μmol/l<br>Ap: 45.6 μmol/l | In 48 h the patient regains consciousness, recovery |
| 11<br>2 years | Acute haemolytic anaemia, DIC | Critical condition, unconsciousness | Transfusion, prednisolone | SU1: 806 μmol/l<br>D: 5 mg/kg for 1 day<br>t: 24 h<br>SU2: 256 μmol/l<br>Ap: 48.5 μmol/l | No renal failure occurs. The patient regains consciousness the next day. In two weeks, recovery |
| 12<br>1.5 years | Combustion 2nd degree 40% body surface renal infailure, shock | In spite of the solution of hypovolemia persisting acute shock, acid haematin in gastric fluid, somnolent, anuria | Peritoneal dialysis | SU1: 767 μmol/l<br>D: 5–10 mg/kg for 3 days<br>t: 48 h<br>SU2: 541 μmol/l<br>Ap: 80.9 μmol/l | Considerable improvement in one day. Abundant diuresis in 36 h. Uninterrupted recovery |

priate level. These results justify to apply Ap treatment in hypoxic conditions or its combination with cytotoxic or immunosuppressive drugs because it gives protection against the deleterious effects that may result from the inhibition of purine synthesis [7].

More recent evidence indicates that the superoxide radical ($O_{2-}$), an unstable and cytotoxic form of molecular oxygen, is primarily responsible for the increased capillary permeability in the ischaemic bowel and the source of superoxide radicals produced in intestinal ischaemia is the enzyme xanthine oxidase [8]. Indeed the results of Parks et al [16] using superoxide dismutase and allopurinol proved that the xanthine oxidase inhibition provides almost the same degree of protection of the mucosa from ischaemic injury as that afforded by superoxide dismutase. Therefore, the superoxide radical mechanism is a likely explanation of the ischaemic injury, since treatment with superoxide dismutase alone would not prevent the irreversible loss of purine, yet clearly protects the tissue.

Manzke and Dorner [12] observed the effect of 7–10 mg/kg/day Ap on oxygen transport by the red blood cells. These showed an increase in both ATP and 2,3-diphosphoglycerate together with a shift to the right of the oxygen dissociation curve which resulted in a 5% increase in tissue desaturation at a mean central venous oxygen pressure of 5.3 kPa (40 mmHg).

Considering our own results, although Ap was applied in critical situations and except for a leukaemic patient all cases showed improvement, it cannot be claimed for certain that intravenous Ap is an effective therapy in shock. There was no control group and thus no comparison was possible but it seems reasonable to complete the traditional shock therapy with Ap infusion. Of course, a definite answer will have to await further investigations.

Oral administration of Ap would have been of no avail in our cases in whom absorption was uncertain and some could not be nourished. The parenteral Ap preparation applied has been examined in detail by several authors. In an advanced stage of malignant haematological disorders it was found effective and harmless in the preventive treatment of urate nephropathy when applied for several days [11].

## References

1. Baker CH: Protection against irreversible haemorrhagic shock by allopurinol. Proc Soc Exp Biol 141:694, 1972
2. Boda D, Pénzes P, Gecse Á, Streitman K, Zsilinszky E, Karády I: Uric acid nephropathy in shocked rats after blocking uricase activity with triazine compounds. Can J Physiol Pharmacol 51:496, 1973
3. Chatterjee SN, Berne TV: Protective effect of allopurinol in renal ischemia. Amer J Surg 131:658, 1976
4. Cowsert MK, Carrier O, Crowell JW: The effect of hemorrhagic shock on blood uric acid levels. Can J Physiol Pharmacol 44:861, 1966
5. Crowell JW, Jones CE, Smith EE: Effect of allopurinol on hemorrhagic shock. Am J Physiol 216:744, 1969
6. Cunningham SK, Keaveny TV, Fitzgerald P: Effect of allopurinol on tissue ATP, ADP and AMP concentration in

renal ischaemia. Brit J Surg 61:562, 1974
7. Edwards LN, Recker D, Airozo D, Fox JH: Enhanced purine salvage during allopurinol therapy: An important pharmacological property in human. J Lab Clin Med 98:673, 1981
8. Granger DN, Rutili G, McCord JM: Superoxide radicals in feline intestinal ischemia. Gastroenterology 81:22, 1981
9. Hopkins RW, Abraham J, Simeone FA, Damewood CA: Effect of allopurinol on hepatic adenosine nucleotides in hemorrhagic shock. J Surg Res 19:381, 1975
10. Jensen MH, Brinklov MM, Lillquist K: Urinary loss of oxipurines in hypoxic premature neonates. Biol Neonate 38:40, 1980
11. Kann HE, Wells JH, Galleli JF, Schein PS, Conney DA, Smith ER, Seegmiller JE, Carbone PP: The development and use of an intravenous preparation of allopurinol. Amer J Med Sci 256:531, 1968
12. Manzke H, Dörner K: Effect of allopurinol on erythrocyte ATP and 2,3-diphosphoglycerate levels and haemoglobin oxygen affinity in man. Arch Clin Pharmacol Ther 3:107, 1975
13. Manzke H, Dörner K, Grünitz J: Urinary hypoxanthine, xanthine and uric acid excretion in newborn infants with perinatal complications. Acta Paediatr Scand 66:713, 1977
14. Németh I, Boda D: A method for determination of the inhibition of xanthine oxidase activity in plasma during allopurinol treatment Eur J Clin Pharmacol 13:423, 1978
15. Németh I, Boda D: Determination of urate concentration by ultraviolet light absorbance change on oxidation with alkaline ferricyanide. Clin Chim Acta 113:223, 1981
16. Parks DA, Bulkley GB, Granger DN, Hamilton SR, McCord JM: Ischemic injury in the cat small intestine: Role of superoxide radicals. Gastroenterology 82:9, 1982
17. Passwell J, Boichis H, Cohen BE: Hyperuricemic nephropathy. Am J Dis Child 120:154, 1970
18. Raivio KO: Neonatal hyperuricemia. J Pediatr 88:625, 1976
19. Stanley EL: Allopurinol, a generalized coronary vasodilator. Circulation 43–44: 229, 1971
20. Vasko KA, De Wall RA, Riley AM: Effect of allopurinol in renal ischemia. Surgery 71:787, 1972

*Received December 9, 1982*

Prof D Boda MD
P. O. Box 471
H-6701 Szeged, Hungary

*Acta Paediatrica Hungarica, 24 (3), pp 255–261 (1983)*

# Late effects of therapy in children previously treated for leukaemia or malignant tumour

D Schuler, Gabriella Kardos, Rozália Koós, Alaine Polcz, G Gács, T Révész

Second Department of Paediatrics, Semmelweis University Medical School, Budapest, Hungary

The late sequelae of leukaemia and tumour therapy are discussed. The most important and/or the most frequent are neuro-psychologic disturbances, deformities of the bones, the decreased reproduction capacity and the second tumours. Because of the rapidly growing number of cured patients a better knowledge of the occurrence, aetiology, prophylaxis and rehabilitation of these changes is needed.

The improving survival rate of children with malignant disease, especially ALL, non-Hodgkin lymphoma and Wilms tumour resulted in a gradual increase in the number of cured patients. Hence the recognition of late effects of irradiation and chemotherapy, their reduction and the rehabilitation of these patients is now of great importance. This is also shown by the data of the American Late Effect Study Group presented in 1979: of 290 patients 166 (57%) had late effects and 106 (64%) of the 166 patients had clinically significant symptoms [14].

In the present paper the late sequelae of leukaemia therapy will be discussed not taking into consideration the permanent changes due to the serious infections of children suffering from malignant disease. The late side effects of the therapy of malignant solid tumours in children will be mentioned only briefly.

## Materials and Methods

STH and TSH determination was performed after the i.v. administration of TRH and the infusion of l-arginine. The TSH-level was determined by the Byk–Mallinckordt kit, while STH by radioimmunoassay. The metopiron test was used for examination of the hypophyseal-adrenal function [21].

The psychological tests used in the evaluation were the Wechsler Intelligence Scale for Children modified for Hungarian standards and the "World Test", where the children could choose objects from 250 pieces to construct their world [22].

Cytogenetic examinations were made in short time cultures of the peripheral blood evaluated by conventional Giemsa staining, further Giemsa-trypsin banding and Hoechst–Giemsa staining after BrdU incorporation [23].

Abbreviations: ALL = Acute lymphoblastic leukaemia; STH = Somatotropic hormone; TSH = Thyroid stimulating hormone; TRH = Thyreotropine releasing hormone; CT = Computerized tomography; IQ = Intelligence quotient; MTX = Methotrexate; ACTH = Adrenocorticotropic hormone; LH = Luteinizing hormone; FSH = Follicle stimulating hormone; GH = Growth hormone

TABLE I

| Age at onset of disease years | No. | Verbal | | IQ performance | | Full scale | |
|---|---|---|---|---|---|---|---|
| | | m | SD | m | SD | m | SD |
| 1–14 | 24 | 111.88 | 10.52 | 106.33 | 10.89 | 110.25 | 11.26 |
| >6 | 9 | 110.89 | 12.72 | 115.0 | 14.07 | 114.33 | 13.37 |
| <6 | 15 | 112.47 | 9.45 | 101.13 | 10.66 | 107.89 | 8.29 |
| CNS | | | | | | | |
| 2400 R | 15 | 113.53 | 7.97 | 107.4 | 13.17 | 111.86 | 9.15 |
| >2400 R | 9 | 109.11 | 14.08 | 104.56 | 14.84 | 107.56 | 14.38 |

## RESULTS AND DISCUSSION

There is considerable controversy on the neurologic sequelae of leukaemia. Some authors [28, 31] reported no alterations, others found after several years of methotrexate therapy and prophylactic cranial irradiation cerebral necrosis and gliosis, which caused encephalopathy and mental deficiency [12]. Peylan-Ramu et al [18] found by CT in 25–30% of the cases periventricular dilatation, cortical atrophy and white matter changes, which was confirmed by Clausen and Pedersen [4] in a prospective study. The clinical symptoms found by German authors [8, 32] were a good cognitive function, but a decreased speed test and concentration ability, especially in mathematics. The distress of neuromotor function: coordination, postural reactions by closed eyes, were more expressed in children treated before 6 years of age. We found a normal IQ in long surviving leukaemic patients and a slightly decreased performance in those whose disease began before 6 years of age (Table I). The prospective study of the IQ scores and cognitive functions made by Meadows et al [15] in ALL children treated with cranial irradiation is different from our observations. They found a reduction in overall IQ score, learning capacity and academic performance. This was more expressed in younger children and in those, whose original IQ was higher than in the others (Table II). The full manifestation of these alterations was at 3 or more years after the irradiation. Meadows and Evans [12] suppose that irradiation enhances the intracerebral absorption of methotrexate. The discrepancy between the results of different investigators could be explained by several factors. *(i)* Therapy was

TABLE II

Changes in IQ by initial IQ [15]

| IQ range | No. of children | Test 3-test 1 (Average change) |
|---|---|---|
| 110–132 | 6 | −23.5 |
| 86–109 | 12 | −8 |

not the same. In some protocols the total quantity of methotrexate administered intrathecally during the treatment was quite high, while we gave all in all 5 doses and of these only 2 after irradiation. This means a total dose of 60 mg/m² MTX while e.g. 132 mg is recommended for standard risk children and 252 mg for high risk cases in the latest Memphis Protocol. It is, however, known that the higher cumulative dose of methotrexate and its administration after irradiation of the brain increases the likelihood of neurotoxicity [11]. *(ii)* The fractionation of irradiation, further the age dependent thickness and density of the cranial bones are also different. *(iii)* The tests used for the examination of these children were also different in the studies.

The psychological study of children 3.5 or more years after the irradiation [22] revealed severe emotional problems: decreased interest in the environment, anxiety, disturbed self image, isolation, and decreased motivation (Table III). Many psychological problems were found in the families of these patients; inconsequent education, problems in marital connections, psychological disturbances in the sibs and isolation of the family (Table IV). All these problems were markedly reduced by psychologic care of the patients and their families (psychotherapy, creative activity, music therapy, education, social care).

TABLE III

Effect of psychological care in per cent of total number of patients

| Patient groups | No. of cases | Anxiety | Disturbed self-image | Slowing of movements | Fear of death | Isolation |
|---|---|---|---|---|---|---|
| Leukaemia | | | | | | |
| No psychological care | 25 | 100 | 92 | 60 | 64 | 62 |
| Psychological care | 34 | 38 | 42 | 20 | 15 | 23 |
| Control | 24 | 21 | 2 | 8 | 4 | 21 |

TABLE IV

Psychologic problems in the families of long surviving leukaemic children (per cent)

| Group | No. of families | Inconsequent education | Disturbed matrimonial connections | Psychological problems of siblings | Narrowing of motivation | Isolation of family |
|---|---|---|---|---|---|---|
| No psychological care | 25 | 92 | 79 | 73 | 49 | 60 |
| Psychological care | 34 | 64 | 24 | 21 | 12 | 19 |
| Controls | 20 | 37 | 25 | 18 | 19 | 24 |

There are controversies also concerning the endocrinological effect of leukaemia and tumour therapy. After irradiation for tumours of the central nervous system excluding those of the adenohypophysis, the eye and middle ear and including in the field of radiotherapy the hypothalamo-pituitary region, isolated growth hormone deficiency, short stature, in some cases deficiency of TSH, ACTH and gonadotropins, even panhypopituitarism could be observed with a delayed onset [17, 19]. The dose of irradiation in acute leukaemia of children is substantially less than that for solid tumours. Most authors observed, however, a progressive fall of growth hormone response with increasing time after the prophylactic irradiation [20, 25], while other authors [7, 21, 30] found normal growth and normal STH, TSH, ACTH, LH and FSH levels. Normal height and a normal reaction to arginine provocation of GH secretion was observed by Dickinson et al [6], too. The peaks of growth hormone after arginine infusion were, however, somewhat lower in our study than in the controls in spite of the normal growth of children (Figs 1, 2).

The gonadal functions as well as the health of the offsprings seem to be normal after leukaemia therapy. Shalet et al [26], however, found the mean tubular fertility index = percentage of seminiferous tubules containing spermatogonia to be 51%. In contrast, these figures after combination chemotherapy for Hodgkin's disease are disastrous [27, 33].

Males usually have a normal progression of pubertal development, however, the FSH values were higher and all were azoospermic after an interval of 2.4 to 8 years after completion of treatment. Thus it seems that tubular cells are more sensitive to MOPP or MVPP therapy than the Leydig cells. Females may have amenorrhoea [3], but about 40%

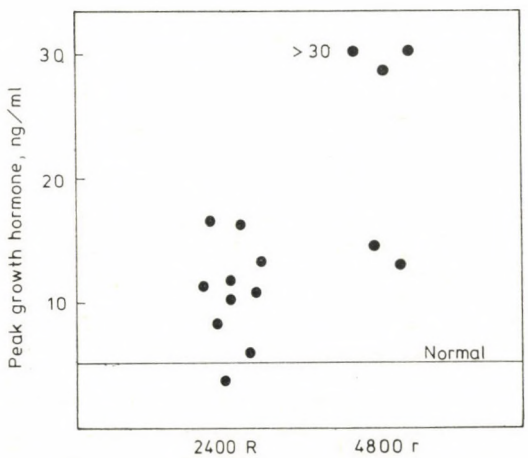



FIG. 1. Growth hormone levels after prophylactic irradiation of the head

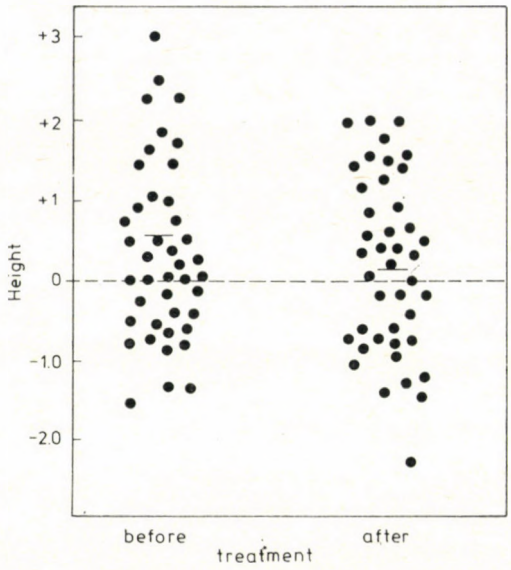



FIG. 2. Height of children before and after treatment of leukaemia

have regular menstrual cycles with evidence of ovulation in some of them. In lymphoma with irradiation of the abdomen the later sterility could be prevented by previous oophoropexis in 75% of the patients [5].

The chromosome aberrations observable several years after leukaemia therapy were studied by some authors in order to determine the long term effects on the chromosomes of such a treatment by mutagenic cytotoxic drugs. Miller et al. [16] found aberrations in four of seven children with ALL, three deletions, one balanced translocation and one inversion. In our own study four aberrations were found in the 12 examined patients [23]. The difference between our patients and the controls was not significant. In the post-treatment group of patients with Wilms tumour an almost two-fold occurrence of stable aberrations was found by Miller et al [16], which underlines the role of radiotherapy in the aetiology of these rearrangements. The frequency of sister chromatid exchange is also normal according to our examinations [23] but the number of 2nd cycle cells was always lower in the treated children, than in the controls. Hence we suppose that the mean cell cycle time of the posttreatment patients is different from the controls. This may be due to a change in lymphocyte subclass distribution or selection of cells with a different cell cycle time or purely a bias due to individual variations. Further studies are needed to prove this supposition and to evaluate its significance.

The frequency of second tumours is increased after complex therapy of the primary tumour [2, 29, 13]. According to several authors, beyond

ten years from diagnosis the most important causes of morbidity and mortality are second primary neoplasms [10, 13, 24]. The occurrence of a second malignancy in Hodgkin's disease was 270 in a follow up study of 1553 patients [1], while in a previous publication only 100 was calculated [5]. Whether an increased susceptibility or a somatic mutation induced by the complex therapy was responsible for the phenomenon is an open question. According to the preliminary results of our studies an increased number of chromosome mutations could be induced in vitro by a chemical mutagen in leukaemic patients being in full remission.

As far as solid tumours are concerned there are still other late effects, which are only listed here. These are,

*1)* local bone growth impairment and scoliosis after bone (i.e. spinal) irradiation especially in children under 6 years of age;

*2)* local lesions after irradiation of the brain, spinal cord and peripheral nerves;

*3)* pulmonary fibrosis;

*4)* renal damage and hypertension [9];

*5)* chronic cystitis and contracted bladder;

*6)* damage of the gastrointestinal tract, liver and pancreas.

## References


1. Boivin JF, Hutchison GB: Leukemia and other cancers after radiotherapy and chemotherapy for Hodgkin's disease. J Nat Cancer Inst 67:751, 1981
2. Canellos GP, De Vita VT, Arseneau JC, Whang-Beng J, Johnson REI: Second malignancies complicating Hodgkin's disease in remission. Lancet 1:947, 1975
3. Chapman RM, Sutcliffe SB, Malpas JS: Cytotoxic-induced ovarian failure in women with Hodgkin's disease. JAMA 242:1877, 1979
4. Clausen N, Pedersen H.: The development of cerebral CT changes during treatment of acute lymphocytic leukemia in childhood. Neuroradiology 22:79, 1981.
5. Delbrück H, Teilet F, Andrieu JM, Schmitt G, Bayle O, Wetter O: Langzeitkomplikationen bei Patienten mit malignen Lymphomen nach Chemo- und/oder Strahlentherapie. Dtsch Med Wochenschr 103:789, 1978
6. Dickinson WP, Berry DH, Dickinson L, Irvin M, Schedevie H, Fiser RH, Elder MJ: Differential effects of cranial radiation on growth hormone respose to arginine and insulin infusion. J Pediatr 92:854, 1978
7. Fisher JN, Aur RJA: Endocrine assessment in childhood acute lymphocytic leukemia. Cancer 49:145, 1982
8. Gutjahr P, Waither B: IQ and cognitive function in long-term survivors of childhood acute lymphocytic leukaemia. Lancet 2:1278, 1981
9. Koskimies O: Arterial hypertension developing 10 years after radiotherapy for Wilm's tumour. Br Med J 285:996, 1982
10. Li FP, Myers HH, Heise HW, Jaffe N: The course of five-year survivors of cancer in childhood. J Pediatr 93:185, 1978
11. McIntosh S, Aspnes GT: Encephalopathy following CNS prophylaxis in childhood lymphoblastic leukemia. Pediatrics 52:612, 1973
12. Meadows AT, Evans AE: Effects of chemotherapy on the central nervous system. A study of parenteral methotrexate in long-term survivors of leukemia and lymphoma in childhood. Cancer 37:1079, 1976
13. Meadows AT, D'Angio GJ, Mike V, Banfi A, Harris C, Jenkin RDT, Schwartz A: Patterns of second malignant neoplasms in children. Cancer 40;1903, 1977
14. Meadows A, Krejmas N: Sequelae of therapy in 300 survivors of childhood cancer. XI. Meeting of the SIOP Lisboa, Sept 1979
15. Meadows AT, Massari DJ, Fergusson J, Gordon J, Littman P, Moss K: Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. Lancet 2:1015, 1981

16. Miller RC, Hill RB, Nichols WW, Meadows AT: Acute and long-term cytogenetic effects of childhood cancer chemotherapy and radiotherapy. Cancer Res 38:3241, 1978
17. Perry-Keene DA, Conelly JF, Young RA, Wettenhall HNB, Martin FIR: Hypothalamic hypopituitarism following external radiotherapy for tumours distant from the adenohypophysis. Clin Endocrinol 5:373, 1976
18. Peylan-Ramu N, Poplack DG, Pizzo PA, Adoruato BT: Abnormal CT scans of the brain in asymptomatic children with acute lymphocytic leukemia after prophylactic treatment of the central nervous system with radiation and intrathecal chemotherapy. N Engl J Med 298:815, 1978
19. Richards GE, Wara WM, Grumbach MM, Kaplan SL, Sheline GE, Conte F: Delayed onset of hypopituitarism: sequelae of therapeutic irradiation of central nervous system, eye, and middle ear tumors. J Pediatr 89:553, 1976
20. Schiliro G, Russo A, Sciotto A, Distefano G, Vigo R: Radiotherapy and growth hormone deficiency. Lancet 2:1031, 1976
21. Schuler D, Gács G, Révész T, Koós R, Keleti J: Hypophysenfunktion und Wachstum bei Kindern unter Leukämiebehandlung. Monatsschr Kinderheilkd 128:773, 1980
22. Schuler D, Polcz A, Révész T, Koós R, Bakos M, Gál N: Psychological late effects of leukemia in children and their prevention. Med Pediatr Oncol 9:191, 1981
23. Schuler D, Szollár J, Koós R, Szakmári É, Bogáthy B: The investigation of late cytogenetic effects in children with acute leukaemia in long remission and off all chemotherapy. Hum Genet 56:339, 1981
24. Schwartz AD, Lee H, Baum ES: Leukemia in children with Wilms tumor. Pediatr 87:377, 1975
25. Shalet SM, Beardwell CG, Morris-Jones PH, Pearson D: Growth hormone deficiency after treatment of acute leukaemia in children. Arch Dis Child 51:489, 1976
26. Shalet, SM, Hann IM, Lendon M, Morris Jones PH, Beardwell CG: Testicular function after combination chemotherapy in childhood for acute lymphoblastic leukaemia. Arch Dis Child 56:275, 1981
27. Sherins RJ, Olweny CLM, Ziegler JL: Gynecomastia and gonadal dysfunction in adolescent boys treated with combination chemotherapy for Hodgkin's disease. N Engl J Med 299:12, 1978
28. Soni SS, Marten GW, Pitner SE, Duenas DA, Powazek M: Effects of central nervous system irradiation on neuropsychologic functioning of children with acute lymphoblastic leukemia. N Engl J Med 293:113, 1975
29. Stott H, Fox W, Girling DJ, Stephens RJ, Galton DAG: Acute leukaemia after busulphan. Br Med J 2:1513, 1977
30. Swift PGF, Kearney PJ, Dalton RG, Bullimore JA, Mott MG, Savage DCL: Growth and hormonal status of children treated for acute lymphoblastic leukaemia. Arch Dis Child 53:890, 1978
31. Verzosa MS, Aur RJA, Simone JV, Hustu O, Pinkel DP: Five years after central nervous system irradiation of children with leukemia. Int J Radiat Oncol Biol Phys 1:209, 1976
32. Walther B, Gutjahr P, Beron G: Therapiebegleitende und überdauernde neurologische und neuropsychologische Diagnostik bei akuter lymphoblastischer Leukämie im Kindesalter. Klin Pädiatr 193:177, 1981
33. Whitehead E, Shalet SM, Morris Jones PH, Beardwell DG, Deakin DP: Gonadal function after combination chemotherapy for Hodgkin's disease in childhood. Arch Dis Child 47:287, 1982

*Received 19 December 1982*

Prof D Schuler
Tűzoltó u. 7
H-1094 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (3), pp 263–267 (1983)*

# Elevated risk of osteoarticular complications in children with acute Brucella melitensis infection

ELI SHAHAR,[1] ZOHAR BARZILAY,[1] ISAAC SHOHET,[1] GIDEON ALTMAN,[2] BERNARD E COHEN[1]

[1] Department of Paediatrics B, and [2] Microbiology Laboratory, Chaim Sheba Medical Center, Tel-Hashomer, Sackler School of Medicine, Tel-Aviv University, Israel

Infection with brucella microorganisms is considered uncommon in the paediatric age group. We report nine paediatric patients between the ages of 8 to 17 years with acute *Brucella melitensis* infection, who presented with spiking fever, night sweats, anorexia and malaise for 5 to 60 days prior to diagnosis. Four patients developed various osteoarticular complications: migratory arthralgia, hydroarthrosis of the knees, arthritis and osteomyelitis. Therapy with tetracyclines alone or in combination with streptomycin resulted in complete recovery in eight children. This combination failed in one patient who developed severe osteoarticular disease successfully responding to rifampicin. Since infection of bone and joints leads to irreversible damage, early recognition and immediate management are crucial for recovery. Rifampicin might be of benefit in children with severe osteoarticular complications when the traditional anti-brucella regimen fails.

The genus brucella is usually an intra-cellular Gram-negative bacillus infecting the reticuloendothelial system. It causes disease in animals which may be transmitted to humans through direct contact or by ingestion of contaminated by-products. The common symptoms of acute brucellosis include spiking fever, night sweats, anorexia and malaise. Multisystem organ involvement mainly including the cardiovascular, nervous, osteoarticular, and genito-urinary systems is an often described phenomenon in adult patients. However, brucellosis does not always have a common clinical pattern and various manifestations may resemble other infectious diseases.

Brucellosis occurs infrequently during childhood and few reports deal with it in the paediatric age group [1–3]. To date the frequency and clinical significance of osteoarticular complications in children with acute brucella infection is still debated. We report herein nine children with acute *Brucella melitensis* infection of which four had osteoarticular complications. The anti-brucella regimen in such patients will be discussed.

## CLINICAL DATA

The diagnosis of brucellosis was based on accepted clinical, biochemical, and serological criteria [6], in nine children admitted during the last 20 years. They were

TABLE I

Clinical and laboratory data of paediatric patients with brucellosis

| Case | Age years | Sex | Duration of illness | Blood cultures | Agglutination antibodies | Management | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | 8 | F | 14 days | *Br melitensis* ×1 | 1 : 10 240 | Tetr; 24 days | Cured |
| 2 | 17 | F | not recorded | Negative | 1 : 640 | Tetr; Strep; 21 days | Cured |
| 3 | 12 | M | 5 days | *Br melitensis* ×1 | 1 : 1280 | Tetr; 10 days | Cured |
| 4 | 14 | M | 14 days | *Br melitensis* ×3 | Tetr; Strep; 1 : 10 210 | 10 days | Cured |
| 5 | 8 | M | 21 days | *Br melitensis* | 1 : 10 240 | Tetr; 14 days | Cured |
| 6 | 10 | F | 1 month | *Br melitensis* ×2 | 1 : 1280 | Tetr; 21 days | Cured |
| 7 | 14 | M | 2 months | *Br melitensis* ×3 | 1 : 640 | Tetr + Strep; 2 months | Cured |
| 8 | 11 | F | 1 month | No data | 1 : 10 240 | Tetr + Strep; 14 days | Cured |
| 9 | 14 | F | 14 days | Negative | 1 : 1280 | Tetr + Strep | Relapse after 8 days; Recovered following rifampicin therapy |

Abbreviations: Tetr — tetracyclines, Strep — streptomycin

admitted following an acute illness with high-grade fever, headaches, night sweats, anorexia and weight loss for five to 60 days before admission to the hospital and the accurate diagnosis. Two patients had spiking fever of the undulant type. A diffuse macular rash was noted in one child (Table I).

*Laboratory data.* Leukopenia was a common symptom ranging from 3300 to 5700 leukocytes per ml with lymphocyte predominance in five patients (44–94%). Three children had a normal differential count. The erythrocyte sedimentation rate was elevated in four children.

*Diagnosis.* Specific blood cultures for brucella were obtained in eight of nine patients. In six patients the culture taken immediately after admission was positive. All patients had elevated agglutination titres of 1 : 320 to 1 : 10,240 which increased within one week after admission. (A titre higher than 1 : 180 is indicative of active disease.) The source of infection could be attributed to unpasteurized sheep and goat milk or by-products in 5 patients.

*Osteoarticular manifestations and management.* Patient No. 5 had migratory arthralgia on admission. Patient No. 2 developed mild arthritis of the right sacro-iliac joint. Patient No. 7 who had migratory arthralgias during the prodromal period subsequently developed arthritis of the right knee and hydroarthrosis of both knees. On the traditional anti-brucella regimen using tetracyclines at a dose of 25 mg/kg/day with I. M. streptomycin at a dose of 20 mg/kg/day, these manifestations gradually subsided in these three children and they became completely asyptomatic. Patient No. 9, a 14-year-old girl, had evidence of infection of the right hip and sacro-iliac joints as well as of the lumbar vertebrae on hospitalization. Al-

TABLE II

Osteoarticular manifestations in children with brucellosis

| Case No. | Clinical Data |
|---|---|
| 2 | Arthritis — Rt sacro-iliac joint |
| 5 | Arthralgia — migratory |
| 7 | Arthralgia |
| | Arthritis — Rt knee |
| | Hydroarthrosis — both knees |
| 9 | Arthritis — Rt hip joint |
| | Rt sacro-iliac joint |
| | Rt shoulder joint |
| | Infection of lumbar vertebrae |
| | Osteomyelitis — Rt humeral head |

though she initially responded to tetracyclines and streptomycin, she developed arthritis of the right shoulder and osteomyelitis of the humerus eight days after initiation of the regimen. Complete recovery was achieved in this patient following additional therapy with oral rifampicin at a dose of 900 mg/day (20 mg/kg/day) for 21 days. On follow-up examination two years later she was found completely asymptomatic (Table II).

*Outcome of patients without osteoarticular disease.* The children made a complete recovery following the administration of oral tetracyclines for 10–24 days with additional intramuscular streptomycin in two of these patients. No relapse was detected in any patient in the present series.

## DISCUSSION

Brucellosis has been considered uncommon during childhood in western countries. Bothwell et al. reported only 17 paediatric patients during the years 1940–1957 [1]. Out of 160 cases of brucellosis in the United States during 1978 only 16 were children [4]. Street et al. [3] reported nine children during the spring of 1973 and stressed the rarity of the disease. A survey of brucellosis in Israel [5], however, detected 42 (24%) of 287 cases under the age of 14 years, indicating that brucellosis was common in children living in the Middle East which is an endemic area.

The question why brucellosis is infrequent in children remains unclarified since the common use of milk and its by-products by children make them more likely to be infected by brucella species. The scarcity of childhood brucellosis has been attributed to a low rate of suspicion while other diseases during childhood may resemble the clinical features of brucella infection [2]. It was also speculated that in contrast to adults the disease in children may have a self-limited course [6], although many

sub-clinical and mild illnesses occur in adults. In Israel infections with *Brucelta melitensis* occur; this is the most virulent strain among brucella organisms and has been associated with acute infection. Those infected with *Brucella abortus* strains, which is common in western countries, may be mildly ill or even asymptomatic [6].

Osteoarticular involvement has been extensively reviewed in adult patients with acute brucella infection [7, 8]. McCullough [9] considered osteoarticular manifestations to be common in childhood brucellosis. Other authors, however, have not verified this observation, reporting a very low rate of joint and bone complications [1, 3]. Four children in this series experienced almost all bone and joint complications of *Brucella melitensis* infection: migratory arthralgia, hydroarthrosis of knees, arthritis of right hip and sacro-iliac joints, and osteomyelitis of the lumbar vertebrae. The course was complicated in one patient with right shoulder arthritis and osteomyelitis of the humerus. The frequent occurrence of osteoarticular complications presented in this series raises the need of its rapid diagnosis and aggressive treatment since brucellosis in bone and joints may cause irreversible damage.

The recommended antimicrobial regimen for patients with acute brucellosis is a combination of oral tetracyclines given for three weeks or longer with intramuscular injections of streptomycin for 7–14 days [10, 11]. Such a regimen resulted in a very low rate of relapses such as 0.9% in a series of 157 patients [10]. In a series of eight children given tetracyclines for 21 days and streptomycin for 14 days, no relapses were recorded [3]. Eight of nine children in the present series rapidly responded to tetracyclines alone or in combination with streptomycin after 10 to 24 days of treatment. Brucella organisms are sometimes protected from these antimicrobial agents due to their intracellular location [12]. This was demonstrated in one of our patients who developed severe bone and joint disease while receiving doxycycline and streptomycin. Additional therapy with rifampicin at a dose of 20 mg/kg daily for 21 days resulted in complete recovery. Since rifampicin acts as an intracellular bactericidal agent [13], it may be of benefit in severe brucella infections especially those with bone and joint disease when the traditional regimen fails. A recent report using rifampicin in children with acute brucellosis has supported this view [14].

## References

1. Bothwell PW: Brucellosis in children. Arch Dis Child 37:628, 1962
2. Wallis PE: Brucellosis in children. Br Med J 1:617, 1957
3. Strett L, Grant WW, Alva JD: Brucellosis in childhood. Pediatrics 55:416, 1975
4. Center for disease control: Brucellosis surveillance: Annual summary 1978, Public Health Service, Atlanta 1978
5. Brucellosis in Israel: 1962–1974. Center for brucella surveillance, Biological Institue, Nes-Ziona, Israel
6. Spink WW: Nature of Brucellosis. University of Minnesota Press, Minneapolis 1956

7. Rotes-Querol J: Osteoarticular sites of brucellosis. Ann Rheumat Dis 16:63, 1957
8. Kelly PJ, Martin WJ, Schirger A, Weed LA: Brucellosis of bones and joints. JAMA 174:347, 1960
9. McCullough NB: Symposium of unusual infections in childhood. Pediatr Clin North Am 2:73, 1955
10. Buchanan TM, Faber LC, Feldman RA: Brucellosis in the United States 1962–1972. Medicine 53:403, 1974
11. Pfischner WCE, Ishak KG, Neptune EN, Fox SM, Farid Z, Nor el Din G: Brucellosis in Egypt: A review of experiences with 228 cases. Am J Med 22:915, 1957
12. Spink WW, Bradely GN: Persistent parasitism in experimental brucellosis: Attempts to eliminate brucella with long-term tetracycline therapy. J Lab Clin Med 55:535, 1960
13. Philippon AM, Plommet MG, Kazmierzack A, Marly JL, Nevot PA: Rifampin in the treatment of experimental brucellosis in mice and guinea pigs. J Infect Dis 136:482, 1977
14. Llorens-Terol J, Busquetes RM: Brucellosis treatment with rifampicin. Arch Dis Child 55:486, 1980

*Received 15 February 1983*

E Shahar MD
Department of Pediatrics B
Chaim Sheba Medical Center
Tel-Hashomer 62621, Israel

*Acta Paediatrica Hungarica, 24 (3), pp 269—279 (1983)*

# Dermatoglyphics in Saethre-Chotzen syndrome: a family study

LIANE BORBOLLA, IBIS MENÉNDEZ

Department of Cytogenetics, Paediatric Hospital "William Soler", Havana, Cuba

The dermatoglyphic findings in a Cuban family with the Saethre-Chotzen syndrome are reported. The family consisted of the parents who were first cousins and their three children. A new classification of zygodactylous patterns was used. Characteristic dermatoglyphic patterns which appeared in these cases were representative of the syndrome.

Dermatoglyphics also helped to discover minor expressions of syndactyly and showed that all the members of the family had zygodactylous patterns on palms and soles.

Craniosynostosis as part of genetically determined syndromes is often associated with limb deformities, especially with syndactylism. Perez Comas [8] differentiated the following varieties of acrocephalosyndactyly: Apert syndrome, Pfeiffer syndrome, Summitt syndrome, Saethre—Chotzen syndrome and two types with polysyndactyly: Carpenter syndrome and Sakati—Nyhan—Tisdale syndrome. Dermatoglyphics have a diagnostic value in such syndromes; when there is a malformation of the hand or foot, dermatoglyphics are abnormal even when the morphologic defect is not easily perceived.

In this paper, distinctive dermatoglyphic features found in a family of five members with the Saethre—Chotzen syndrome are reported. This entity was first described by Saethre [10] in a mother and her two daughters, and a year later by Chotzen [4] in a father and his two sons. The principal abnormalities of the entity are craniosynostosis, asymmetry of skull and facies, hypertelorism, maxillary hypoplasia, deviation of nasal septum, shallow orbits, ear deformities, clinodactyly, brachydactyly, single palmar crease and soft tissue syndactyly usually of second-third fingers and/or third-fourth toes. The diagnostic usefulness of a dermatoglyphic study in these disorders will be discussed.

## MATERIALS AND METHODS

Dermatoglyphics of the hands and soles were taken by an ink method of five members of a Cuban family with the Saethre–Chotzen syndrome. The family consisted of the propositus, a two-year-old boy who had cranial deformity, his eight-year-old sister, his six-year-old brother, his 29-year-old father and the 30-year-old mother. The

parents were first cousins. In all the cases, a clinical and radiological study was made. The more important clinical findings were, craniosynostosis in the propositus and his sister (Cases 1 and 2), palpable cranial sutures in these children and the brother (Case 3); hypertelorism and malformed ears in all. Ear crus extended from the root of the helix across the concha in the children, but not in the parents. All except the father (Case 4) had a high forehead, deviation of the nasal septum and the mother (Case 5), an aquiline nose. Maxillary hypoplasia was seen in all except the father, prognathism in Cases 2 and 5, facial asymmetry in Cases 1, 2 and 5, shallow orbits in the mother and the children. The propositus and his brother had clinodactyly of the fifth finger on both sides. The sister had a short but not curved fifth finger on both hands with a single digital flexion crease. Brachydactyly of the fourth and fifth toes was present in Cases 2, 3 and 4. The toes were close together and a hallux valgus was seen in all the cases. The propositus and his sister had an equivalent of simian crease on one hand and the former had a Sydney line on the left hand and also cryptorchidism. Intelligence was normal in all.

Syndactyly was classified as slight when there was only an excess of membrane between the fingers or toes, mild when the web reached the 1st interphalangeal joint, moderate when it attained the 2nd interphalangeal joint, severe when it involved the tips of fingers or toes and total if the syndactyly was cutaneous and osseous. Based on this classification, the propositus had a moderate syndactyly of the right 2–3 fingers and a mild bilateral syndactyly of the 2–3 toes. The sister had a moderate bilateral syndactyly of fingers 4–5 and severe syndactyly of the right 2–3 toes. The brother had severe syndactyly of the right toes 2–3 and a moderate one of the same toes on the left side. He and the father had no syndactyly of the fingers, but a moderate bilateral one of the toes 2–3. The mother had no syndactyly.

For the classification of dermatoglyphic patterns on hands and feet, determination of the finger pattern intensity index, the main-line index, the terminations of the main-lines on palms and the modal types of main-line D, the method of Cummins and Midlo [5] was used. The modal types of main-line A were analysed following the criteria of these authors with a variant: apart from the modal types of main-line A 1, 3 and 5, a modal type 11 was included to describe the exit of this line in the 11, 12 and 13 positions. For the modal types of main-line C and for the position of the axial triradius, the methods of Plato [9] and Walker [11] were consulted.

Our classification [3] of syndactylous patterns, based on the study of dermatoglyphics of 42 patients with different varieties and grades of finger fusion was used. Nine distinctive pattern types had been established, but in this family only some of them were seen and only these will be commented. Type 1 is an interdigital triradius [5, 7] replacing the two normal adjacent subdigital triradii which had disappeared. Type 2 is a more proximally situated interdigital triradius which involves two or more digits and with the proximal radiant adopting a course similar to a main-line. Type 3 is only seen in severe and total forms of syndactyly. In the midpoint, where the tips of fingers and toes are fusioned, a triradius of the two closely joined finger or toe patterns (a loop and a loop, a whorl and a loop or two whorls) is missing, and only one remains with its proximal triradius extending proximally in a slightly diagonal line. Type 4 is characterized by the absence of triradii and only a band of transversal ridges cross the united digits and the web. Type 5 is a combination of type 1 and type 2; type 6 is the association of type 2 and 3 and type 7, the combination of type 2 and 4. Slight syndactyly is associated with types 1 and 5, mild syndactyly with types 1, 2 and 5; moderate forms are observed with types 1, 2, 4, 5 and 7, severe and total syndactyly

TABLE I

Dermatoglyphics of the hands of the five patients

| Case No. | Digital patterns 1 | 2 | 3 | 4 | 5 | PII | FRC | TFRC | Atd angle | position of t | Th/I | Hy | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 L | U | U | U | U | U | 5 | 38 | 71 | — | 11% t | O | $A^u$ | O | O | cd |
| R | U | U | U | U | R | 5 | 33 | | — | 12% t | O | $A^u$ | ab<br>a′ | O | cd |
| 2 L | W | R | U | U | R | 6 | 56 | 100 | — | 19% t′ | O | $A^u/A^c$ | O | L | cd |
| R | W | U | U | U | R | 6 | 44 | | — | 20% t′<br>29% t′<br>38% t′ | O | $W/A^c$ | O | L | c′<br>cd<br>c′ |
| 3 L | W | U | W | W | W | 9 | 87 | 165 | 38° | 16% t′ | O | $L^r/A^c$ | O | bc | O |
| R | W | W | U | W | W | 9 | 78 | | 34° | 10% t | O | $A^u$ | O | O | O |
| 4 L | W | A | U | U | U | 5 | 70 | 135 | 34°<br>63° | 11% t<br>49% t″ | O | W | O | O | O |
| R | U | U | U | U | U | 5 | 65 | | 40°<br>64° | 13% t<br>47% t″ | O | $L^u$ | O | O | L |
| 5 L | W | R | A | U | W | 6 | 32 | 57 | 34° | 19% t′ | O | $A^u/A^c$ | O | O | L |
| R | W | A | U | U | W | 6 | 25 | | 35° | 16% t′ | O | $A^u/A^c$ | O | L | O |

PII, pattern intensity index; FRC, finger ridge count; TFRC, total finger ridge count; Th/I, thenar area; HY, hypothenar area; 12, 13, 14 interdigital spaces Nos II, III, IV; U, ulnar loop; R, radial loop; A, arch; W, whorl; O, open field; $A^u$, ulnar arch; $A^c$, carpal arch; $L^r$, radial loop; $L^u$, ulnar loop; L, loop; ab, abc, cd, interdigital triradii; a, c, interdigital triradii situated more proximally; t, axial triradius

with types 2, 5, 6 and 3, 5, 6. The types 8 and 9 of our classification [3] are present in very special varieties of syndactyly and will not be discussed here.

The configurations of the toes were examined with the magnifying lens because it is difficult to evaluate them on prints.

## Results

Distribution of patterns on all the fingers showed a preponderance of ulnar loops (54%) and whorls (30%) with a low proportion of arches (6%) and a higher number of radial loops (10%) than in our control series [2] (Table I). An important fact was that the radial loops were located in the 5th finger in two cases. This pattern is never observed in this finger in the normal population. The pattern intensity index was within normal limits. The finger ridge count for each hand and the total finger ridge count were low in the propositus and his mother as compared to normal values and it was due to the presence of small loops and whorls. Cases 2 and 4 had lower counts than the mean value of normal controls [2] but within the normal range. They also had small patterns and all the radial loops had low counts.

On the palms high values for the atd angle were found in the father. In Cases 1 and 2 it was not possible to measure it, because they had no sub-digital triradius d. There was a high distal position t' or t'' of the axial triradius in all the cases, except in the propositus. The hypothenar area displayed a seam whorl on the right palm of Case 2 and Case 4 had an ulnar loop on the right and a whorl on the left side. These figures have low frequencies in the general population. True patterns were not seen in the thenar/I and II interdigital areas in all the patients. An open loop at the third interdigital space was present on both sides of Case 2 and on the right palm of Case 5. An open loop was at the fourth interdigital space of the right palm of Case 4 and of the left palm of Case 5.

On the palms the a—b ridge count gave low values in all the cases except in the father (Table II). The b—c ridge count was low in two patients (Cases 2 and 4) and normal in the mother (Case 5). The b—c ridge count for normal controls is on the left hand $27.76 \pm 5.92$ and $28.60 \pm 5.80$; and on the right hand $28.51 \pm 5.59$ and $29.09 \pm 5.97$. The c—d ridge count was low in the mother.

The modal type 5 of main line A was seen in three patients. The modal type of main line C was absent in the right palm of Case 3 and proximal in the left palm of the father. The main line index showed transversality of the ridges in Cases 3 and 4. The propositus had in one hand an equivalent of simian crease (transitional type) and in the other hand a Sydney line. His sister had also an equivalent of simian crease in the left palm.

As shown in Table III, on the toes the fibular loop (66%) predominated; whorls (14%) were located principally in the first toe (8%). Arches (18%) were found in the fifth toe and

TABLE II

Dermatoglyphics on the hands of the five patients

| Case No. | | a–b ridge count | b–c ridge count | c–d ridge count | Modal types of the main lines | | | MLI | Commins formula | Simian crease | Sydney line |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | A | C | D | | | | |
| 1 | L | 20 | — | — | 5 | — | — | — | Oid0.5″5′ | — | × |
| — | R | — | — | — | — | — | — | — | Oid0.5″ | trans. | — |
| 2 | L | 35 | 18 | — | 5 | — | — | — | Oid0.5″.5″. | trans | — |
| — | R | 28 | 20 | — | 5 | — | — | — | Oid0.5″.5″. | — | — |
| 3 | L | — | — | — | 11 | — | 11 | 13 | 11.Oid0.12. | — | — |
| — | R | 37 | — | — | 3 | absent | 11 | 9 | 11.0.7.3. | — | — |
| 4 | L | 49 | 21 | 34 | 5 | proximal | 11 | 11 | 11.X.7.5′. | — | — |
| — | R | 47 | 20 | 37 | 5 | ulnar | 9 | 10 | 10.7.6.5′. | — | — |
| 5 | L | 32 | 35 | 16 | 3 | ulnar | 7 | 6 | 8.7.3.3. | — | — |
| — | R | 26 | 36 | 22 | 3 | radial | 9 | 7 | 9.9.5′.3. | — | — |

MLI, main line index; Simian crease trans, simian crease transitional

TABLE III

Dermatoglyphics on the soles of the five patients

| Case No. | | Patterns on toes | | | | | Patterns on soles | | | | Zygodactylous triradii | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | Th/I hallucal | $I_2$ | $I_3$ | $I_4$ | $I_2$ | $I_4$ |
| 1 | L | $L^f$ | $L^f$ | $L^f$ | $L^f$ | A | T | O | O | O | a′ | |
| | R | $L^f$ | $L^f$ | $L^f$ | T | A | $L^t$ | O | O | O | a′ | |
| 2 | L | W | $L^f$ | $L^f$ | $L^f$ | A | $L^d$ | O | O | O | — | d′ |
| | R | W | $L^t$ | $L^f$ | $L^f$ | A | $L^d$ | O | O | O | ab a′ | d′ |
| 3 | L | W | W | W | $L^f$ | $L^f$ | $L^d$ | O | $L^p$ | O | a′ | d′ |
| | R | W | W | $L^f$ | $L^f$ | $L^f$ | $L^d$ | O | $L^p$ | O | ab a′ | d′ |
| 4 | L | $L^f$ | $L^f$ | $L^f$ | $L^f$ | A | $L^d$ | O | $V^p$ | O | ab a′ | d′ |
| | R | $L^f$ | $L^f$ | $L^f$ | $L^f$ | A | W | O | $L^p$ | O | ab a′ | d′ |
| 5 | L | $L^f$ | $L^f$ | $L^f$ | $L^f$ | A | $L^d$ | O | O | O | — | — |
| | R | $L^f$ | $L^f$ | $L^f$ | $L^f$ | A | $L^d$ | O | O | O | — | — |

$L^f$, Fibular loop; $L^p$, proximal loop, $L^d$, distal loop, $L^t$, tibial loop; T, tented arch; A, arch; W, whorl; O, open field; $V^p$, proximal curved vestige; ab, interdigital triradius; d, interdigital triradius; a, interdigital triradius situated more proximally

a tented arch was on the fourth right toe of the propositus. A tibial loop was observed on the second right toe of the sister. On the hallucal/I area, distal loops were present in 4 cases, in this area the propositus had a tented arch on the left and a tibial loop on the right. In this region the father had a distal loop on the left and a whorl on the right hand. There were few figures in the interdigital areas. Case 3 had a proximal loop in the third interdigital space, the father in the same area besides the same pattern on the right and on the left side a proximal vestigial loop. This paucity of the interdigital patterns was due to the presence of interdigital triradii

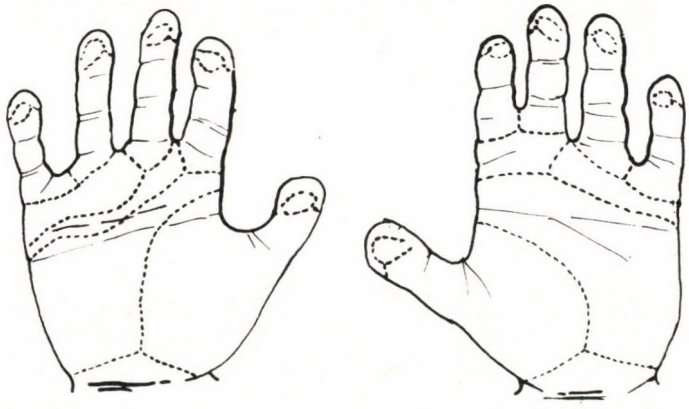


FIG. 1. Diagram of dermatoglyphics in Case 1, the propositus. Note the zygodactylous pattern types of our classification, bilateral pattern type 1 in the fourth interdigital space and pattern type 5 in the right second interdigital area

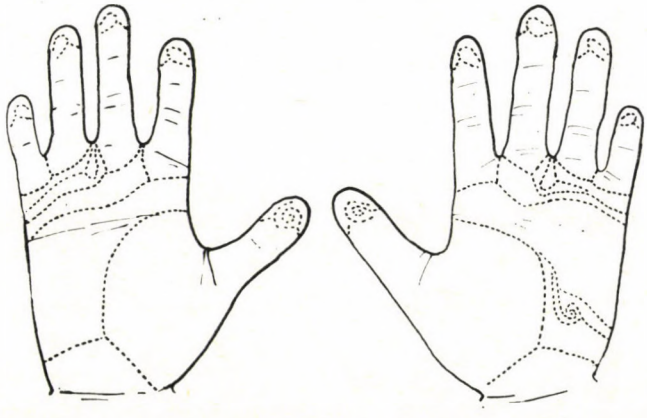


FIG. 2. Dermatoglyphics of the sister (Case 2). Zygodactylous pattern type 5 in the fourth interdigital space of both palms, with a whorl in the right hypothenar area

in 4/5 cases, seventeen in number. No triradius p was found in the family.

The propositus had on both hands a zygodactylous pattern type 1 in the fourth interdigital space, and pattern type 5 in the second right interdigital space (Fig 1). In both palms of his sister pattern type 5 was observed in the fourth interdigital area (Fig 2). The brother had a type 1 pattern in the left third interdigital space (Fig. 3) Figures 4 and 5 showed that the father and mother had no syndactylic triradii in the palms.

On the soles of both feet the propositus had a type 2 pattern in the second interdigital space (Fig 6). The sister showed a type 2 pattern in the fourth interdigital space of both

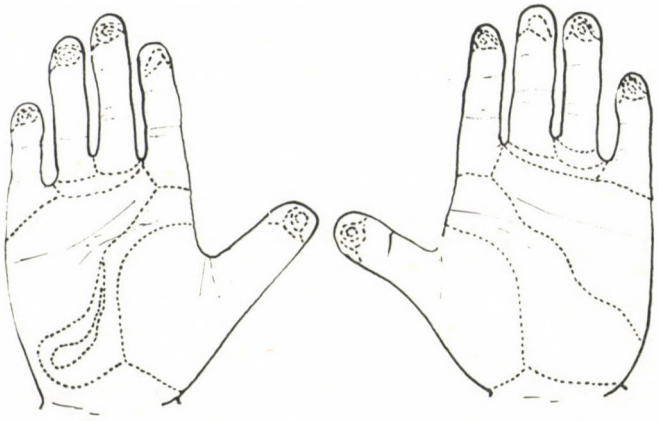


FIG. 3. Dermatoglyphics of the brother (Case 3). Syndactylous pattern type 1 in the third left interdigital space. Modal type absent of main line C on the right

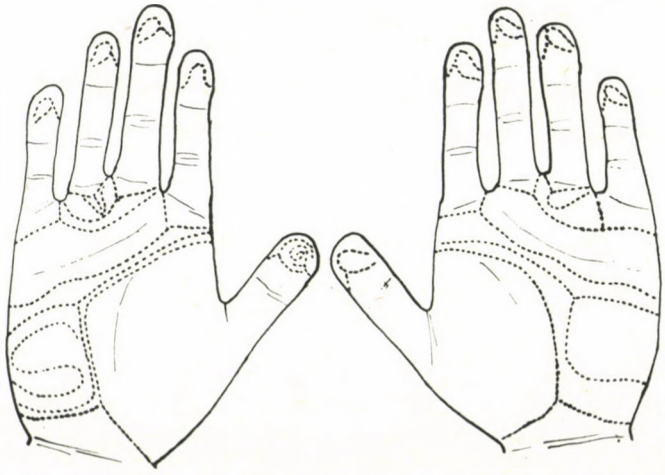


FIG. 4. Dermatoglyphics of the father (Case 4). High distal position of the axial triradius, hypothenar figures on both palms, modal type proximal of main line C on the left hand

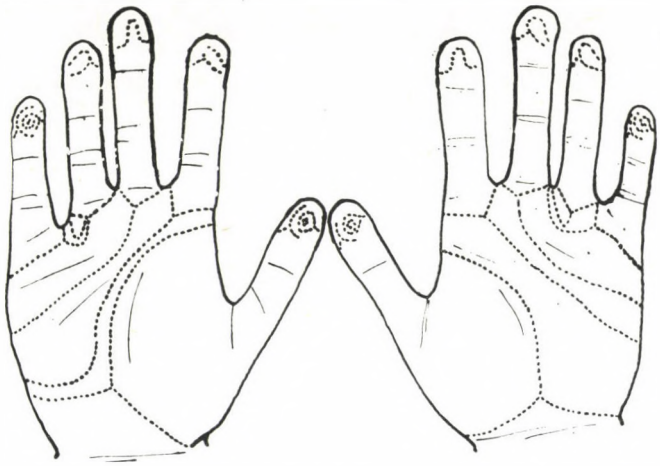


FIG. 5. Dermatoglyphics of the mother (Case 5). No zygodactylous patterns are present, but there is an a–b ridge count and also a c–d ridge count with low values

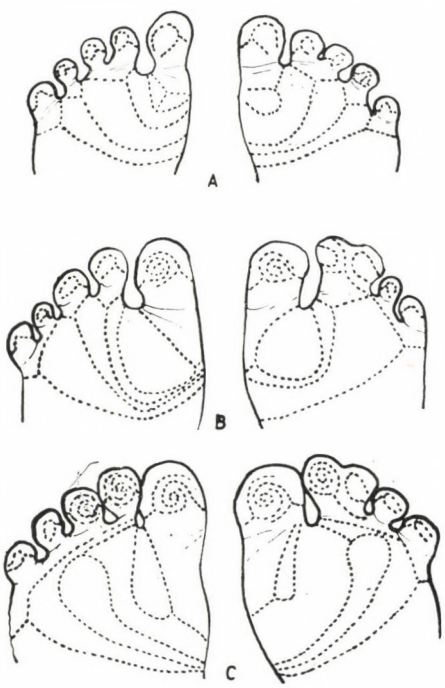



FIG. 6. Dermatoglyphics of the feet of the three children. *a* The propositus shows a bilateral zygodactylous pattern type 2 in the 2nd interdigital space. *b* The sister (Case 2) has syndactylous pattern types 2 in both fourth interdigital spaces and pattern type 6 in the right second interdigital area. *c* The brother (Case 3) has on his left sole a type 2 pattern in the 2nd interdigital space and type 2 pattern in the 4th interdigital space. On the right sole, pattern type 6 in the 2nd interdigital space and pattern type 2 in the 4th interdigital area

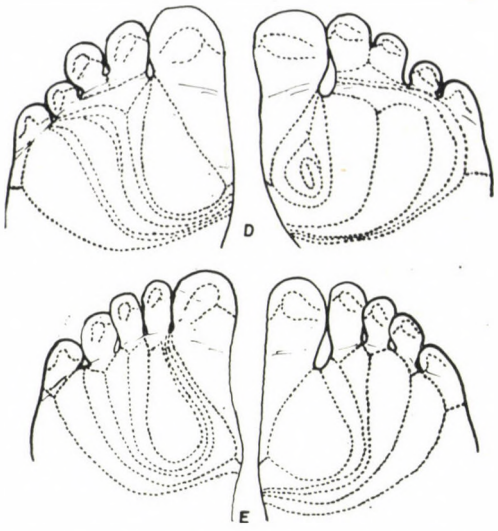



FIG. 7. *d* Dermatoglyphics of the father (Case 4). Syndactylous pattern type 5 in both second interdigital spaces. *e* Dermatoglyphics of the mother (Case 5), all the sub-digital triradii are present on the soles

soles and a type 6 pattern in the right second interdigital space (Fig 6). Type 2 patterns were present in the second and fourth interdigital spaces on the left sole of the brother (Fig 6) and he had on the right side a type 6 pattern in the second interdigital space and a pattern type 2 in the fourth.

The father had on both soles a type 5 pattern in the second interdigital space and a type 2 pattern in the fourth interdigital areas (Fig 7).

No zygodactylous configurations were seen on the soles of the mother (Fig 7).

## DISCUSSION

Characteristic dermatoglyphic abnormalities were observed in this family with Saethre—Chotzen syndrome, *viz.*

1. Low finger ridge count due to reduction of finger pattern size
2. High frequency of radial loops on fingers and of fibular loops on toes, with a radial loop located on the fifth finger
3. Distal displacement of the axial triradius in either, the t' or the t'' position
4. Figures in the hypothenar area
5. Simian crease or equivalent and Sydney line
6. Transversality of the distal ridges of the palm
7. Absence of the p triradius on the soles
8. Typical zygodactylous patterns on the palm and sole.

Our classification of syndactylous patterns helps to determine and appreciate the syndactyly and the grades of severity of this defect. In this family, syndactyly was more

marked in the feet than in the hands, but the peculiar dermatoglyphic abnormalities permit the diagnosis of low grades of the malformation.

Clinically, there was only syndactyly of the right fingers 2–3 of the propositus and of the fingers 4–5 on both hands of his sister. Dermatoglyphic pattern type 1, in the fourth interdigital space in both hands of Case 1 and in the third interdigital space in the left hand of the brother allowed to diagnose syndactyly between fingers 4–5 and fingers 3–4.

The low values of the a–b ridge count in Cases 1, 2, 3 and 5 and the low b–c count in Cases 2 and 4 and the low values of the c–d ridge count in Case 5 could be interpreted as a minor expression of syndactyly [5]. It then became apparent that the whole family had syndactyly on the hands and that practically all the fingers were involved: fingers 2–3 in the propositus, his sister, brother and mother; fingers 3–4 of the father and the brother of the propositus; fingers 4–5 of the propositus, his sister and mother. It was the same on the feet where there was obvious syndactyly of toes 2–3 of the sister and the brother of the patient. The father and the propositus had only mild syndactyly of the same toes. Dermatoglyphic patterns of the soles revealed syndactyly of toes 4–5 in the father, the sister and the brother of the propositus. These same cases had also brachydactyly of toes 4–5, and it would be better to classify the defect as brachysyndactyly of the 4th and 5th toes. Only toes 3–4 were unaffected and the mother had no zygodactylous patterns on the feet.

The dermatoglyphic findings in these patients were in agreement with those reported in the literature [8]: low finger ridge count, high number of arches, high number of hypothenar patterns and simian crease. Our patients had few arches on the fingers and toes but they had small loops and whorls, and these small patterns should be interpreted as transitional forms which tend to be arches. It has to be stressed that the zygodaytylous pattern is indispensable in the diagnostics of the Saethre—Chotzen syndrome.

Aue—Hauser [1] published a classification of plantar zygodactylous triradii in a normal population of 500 males. Zygodactylous triradii were classified as strong, medium and weak expressions. In her classification, only our types 1 and 2 were considered but these forms were seen in a normal population whereas the patterns described by us were observed in abnormal cases.

The great variability of expression of the dominant gene in this family where the parents were first cousins and affected like their children, has been demonstrated by the great number and different varieties of the zygodactylous configurations.

## References

1. Aue-Hauser G: Plantar zygodactylous triradii and corresponding patterns. Am J Phys Anthropol 51:45, 1979
2. Borbolla L, Guerra D, Rodriguez J, Delgado A: Estudio dermatoglifico com-

parativo en controles. Rev Cubana Pediatr 49:253, 1977
3. Borbolla L: A classification of abnormal dermatoglyphic patterns in syndactyly of the hand of 42 patients. In press
4. Chotzen F: Eine eigenartige familiäre Entwicklungsstörung. (Akrocephalosyndactylie, Disostosis craniofacialis und Hypertelorismus). Monatschr Kinderheilkd 55:97, 1932
5. Cummins H, Midlo C: Fingerprints, Palms and Soles. Blakiston, Philadelphia 1943
6. Pantke OA, Cohen MM, Witkop CJ, Feingold M, Schaumann B, Plantke HC, Gorlin RJ: The Saethre-Chotzen syndrome. Birth Defects 11 (2):190, 1975
7. Penrose LD, Loesch D: Dermatoglyphic sole patterns: a new attempt at classification. Hum Biol 41:427, 1969
8. Perez Comas A; Craniosinostosis Genética Craniofacial. C Salinas ed OPS, Washington DC 1979
9. Plato CC: Polymorphism of the C line with a new classification of the C line terminations. Am J Phys Anthropol 33:413, 1970
10. Saethre H: Ein Beitrag zum Turmschädelproblem (Pathogenese, Erblichkeit und Symptomatologie). Dtsch Z. Nervenheilkd 117:553, 1931
11. Walker NF: The use of dermal configurations in diagnosis of mongolism. Pediatr Clin North Am 5:531, 1958

*Received December 21, 1982*

Prof Liane Borbolla MD DSc
William Soler Pediatric Hospital
San Francisco 10112,
La Habana 8, Cuba

*Acta Paediatrica Hungarica, 24 (3), pp 281—285 (1983)*

# Effect of drugs used in obstetrics on the constriction by oxygen of the ductus arteriosus of the rabbit fetus*

E Endreffy, D Boda

Department of Paediatrics, University Medical School, Szeged, Hungary

The tone of the ductus arteriosus of the rabbit fetus near term constricted by oxygen ($P_{O_2}$ = 20 kPa) was relaxed reversibly by the drugs chlorpromazine, promethazine, drotaverine, papaverine, diazepam, propanidid, isoxsuprine, pethidine, 5-ethyl-5-(1-methyl-propyl) 2-thiobarbituric acid, and furosemide. Ethyl alcohol, on the other hand, caused constriction of the fetal ductus arteriosus. These drugs if used in obstetrics may disturb the newborn's adaptation to extrauterine life by inhibiting the postnatal closure of the ductus arteriosus. On the other hand, the constrictive effect of alcohol may adversely affect the fetus. The results make it necessary to investigate the effect of the drugs applied during the perinatal period on the adaptation of newborns to extrauterine life.

The process of the constriction and closure of the ductus arteriosus (DA) shortly after birth has been given much attention in the literature. An important factor is the postnatal rise of oxygen tension in the newborn's blood [11, 16], but vasoactive materials (epinephrine, norepinephrine, histamine, bradykinin, serotonin, prostaglandins, etc.) released after birth also contribute to the effect [16].

The aim of the present examination was to investigate the influence of drugs used during delivery on the tone of the rabbit fetus DA constricted by oxygen in a perfusion system in vitro.

## Materials and Methods

145 examinations were done on the DA of 56 fetuses delivered by Caesarean section from 37 hybrid pregnant rabbits at term. An in vitro perfusion system at 37 °C was used according to the method of Kovalčik [11]. The concentration of the constituents of the perfusion solution was NaCl, 118; KCl, 4.7; $CaCl_2$, 2.0; MgCl, 1.2; glucose, 4.5; and TRIS, 5.0 mmol/l. The pH of the solution was set to 7.4 by HCl. The perfusion solution was equilibrated with room air and $N_2$. Comparing the results obtained in a parallel examination with Tyrode solution, the response controlled with oxygen containing 5% $CO_2$ and with $N_2$ containing 5% $CO_2$ compared to the results found in TRIS buffered solution, no difference was observed in the response of the DA.

Perfusion at 16.9 $\pm$ 1.7 ml/min was kept up by a peristaltic pump (Peristaltic miniflow pump type 304 MTA Kutesz). The change in the perfusion pressure was measured by Statham transducer (Physiological pressure transducer P 2306) and recorded by Hellige electromanometer (Ma-88K) and MTA Kutesz 160-W. Functioning of the DA was tested by injecting 10 $\mu$g of norepinephrine into the system.

* Supported by the State Office for Technical Development

In normal cases the drug elicited a contraction. Perfusion by a solution saturated with room air ($Po_2 = 20$ kPa) was followed by constriction, while saturation with $N_2$ caused relaxation and a repeated saturation with room air increased and settled the constriction.

The effect of the drugs on the DA was examined by measuring the change in perfusion pressure caused by the flow of the perfusion solution containing each drug in the appropriate concentration and saturated with room air. In dose-effect curve examinations the perfusion pressure before the test was taken as 100%, and the drug concentration bringing about a 50% change (mostly a decrease) of the perfusion pressure was determined by introducing perfusion solutions containing different concentrations of the drugs. Their mmol/l value was reckoned so as to reach $ED_{50}$.

As test substances the following drugs were used: buphenine HCl (Dilatol®, Troponwerke), isoxsuprine (Isoxsuprine®, Mead Johnson and Co), fenoterol (Partusisten®, Boehringer), diazepam (Seduxen®, Richter), propanidid (Sombrevin®, Richter), furosemide (Furantral®, Polfa), oxytocin (Oxytocin®, Richter), dihydralazine (Nepresol®, Ciba-Geigy), gallamine (Flaxedil®, Spécia), suxamethonium (Succinyl-Asta®), pethidine (Dolargan®, Chinoin),

TABLE I

Effect of drugs used in obstetrics on the constriction by oxygen of the ductus arteriosus (DA) of the rabbit fetus

| Drug | No. of examination (complete dose-effect curve) | Smallest effective concentration (mol/l)* | $ED_{50}$ mol** $\bar{X} \pm SD$ | Observed effect on DA |
|---|---|---|---|---|
| 1. Diazepam | 10 (4) | $7.0\times10^{-7}$ | $6.0 \pm 7.0\times10^{-6}$ | reversible relaxation |
| 2. Pethidine | 11 (2) | $3.5\times10^{-5}$ | $1.8\times10^{-4}$ | reversible relaxation |
| 3. Papaverine | 3 (1) | $2\times10^{-8}$ | $5.2\times10^{-8}$ | reversible relaxation |
| 4. Drotaverine | 9 (3) | $4.6\times10^{-7}$ | $2.2 \pm 1.5\times10^{-6}$ | reversible relaxation |
| 5. Chlorpromazine | 6 (2) | $1.0\times10^{-7}$ | $6.2 \pm 4.0\times10^{-7}$ | reversible relaxation |
| 6. Promethazine | 5 (1) | $6.2\times10^{-7}$ | $1.4\times10^{-6}$ | reversible relaxation |
| 7. Propanidid | 10 (2) | $6.0\times10^{-6}$ | $0.95 \pm 1.0\times10^{-4}$ | reversible relaxation |
| 8. 5-ethyl-5-(1-methyl-propyl)2--thiobarbituric acid | 4 (1) | $5.0\times10^{-5}$ | $4.0\times10^{-4}$ | reversible relaxation |
| 9. Lidocaine | 9 (4) | $2.5\times10^{-4}$ | $5.0 \pm 2.7\times10^{-4}$ | reversible relaxation |
| 10. Furosemide | 7 (2) | $4.8\times10^{-6}$ | $1.2 \pm 0.5\times10^{-5}$ | reversible relaxation |
| 11. Isoxsuprine | 11 (5) | $1.8\times10^{-5}$ | $3.3 \pm 2.0\times10^{-5}$ | reversible relaxation |
| 12. Fenoterol | 15 (—) | $2.6\times10^{-8}$ | — | partly irreversible relaxation |
| 13. Ethyl alcohol | 9 (—) | $3.3\times10^{-3}$ | — | hypertonicity |
| 14. Buphenine | 10 (—) | $6.0\times10^{-7}$—$1.0\times10^{-5}$ | — | no effect in the concentration examined |
| 15. Dihydralazine | 4 (—) | $3.5\times10^{-6}$—$7.0\times10^{-5}$ | — | no effect in the concentration examined |
| 16. Oxytocin | 10 (—) | 0.2E—10E/l | — | no effect in the concentration examined |
| 17. Gallamine | 4 (—) | $9.0\times10^{-6}$—$9.0\times10^{-5}$ | — | no effect in the concentration examined |
| 18 Suxamethonium | 8 (—) | $2.2\times10^{-6}$—$2.7\times10^{-4}$ | — | no effect in the concentration examined |

* In the case of the drugs Nos 14–18 the data show the concentration examined
** $ED_{50}$: drug concentration producing a 50% effect

lidocaine (Lidocain®, EGyT). The examined substances were chlorpromazine (EGyT), promethazine (EGyT), 5-ethyl-5-(1-methyl-propyl), 2-thiobarbituric acid (Chinoin), polioxethene ricinate (Richter), drotaverine (Chinoin), ethyl alcohol, noradrenaline (Richter), phentolamine, atropine sulphate and papaverine.

## Results

Results are shown in Table I. Reversible relaxation of the DA followed the application of diazepam, pethidine, propanidid, 5-ethyl-5(1-methyl-propyl)2-thiobarbituric acid, furosemide, isoxsuprine, papaverine, chlorpromazine and promethazine. Buphenine, oxytocin, dihydralalzine, succinylcholine and gallamine did not cause any change in the tone of the DA.

Constriction of the DA occurred solely under the effect of ethyl alcohol. No dose-effect parallelism could however be found regarding the degree of constriction of the DA and the ethylalcohol concentration. Figure 1 illustrates the above described relaxing action by presenting a recording of the effect of furosemide which caused a dose-dependent, consistently reversible relaxation of the DA constricted by oxygen.

## Discussion

The results showed that preparations widely used in obstetrics during delivery were, in most of the cases, affecting the DA of the rabbit fetus. It is an important question whether these drugs have a similar effect in the human newborn. To answer the question we must know whether these drugs passed through the placenta and, if so, would their concentration found to be active in vitro correspond to that in the newborn's blood.

Of the drugs studied, diazepam [11], 5-ethyl-5(1-methyl-propyl)2-thiobarbituric acid [14] and furosemide [2] are known to pass through the placenta and to result in a fetal blood level higher than the concentration that was found effective in the rabbit fetus. There are data available about the placental transfer of papaverine, drotaverine [12], chlorpromazine [8], promethazine [1] and propanidid [7] and about their blood level after a usual dose. In this case the blood level in the infants was higher than the concentration effective in vitro. Pethidine [6, 15] lidocaine [5, 14], isoxsuprine [4] and fentoterol [18] also penetrate across the placenta; their blood level after a usual dose was lower than their concentration which proved effective in vitro. Ethylalcohol was the only one among the drugs studied that caused a hypertonicity of the DA. Alcohol is known to pass across the placenta rapidly and even blood levels measured in a moderately alcoholic state were higher than the dose effective in vitro [3].

We have no data concerning the sensitivity in vivo of the DA to these drugs but as it is highly sensitive to prostaglandins and indomethacin [10, 17], it will probably react to other drugs in a similar way.

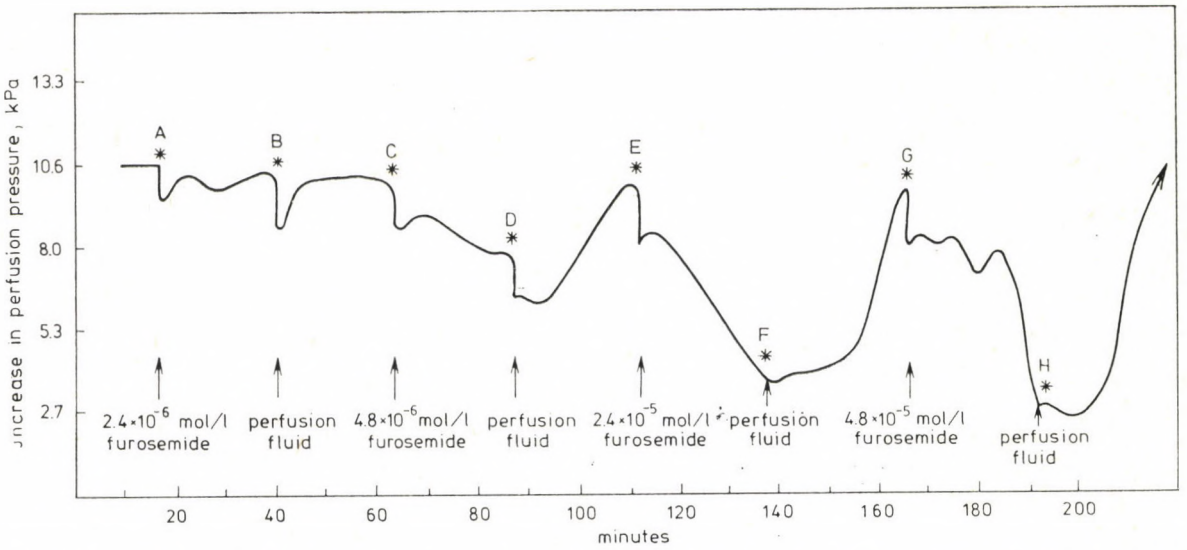



FIG. 1. The effect of furosemide on the DA of the rabbit fetus. Up to *A* perfusion solution saturated with room air ($PO_2$ = 20 kPa). $\overline{AB}$, $\overline{CD}$, $\overline{EF}$ and $\overline{GH}$ sections show DA relaxation on perfusion of solutions of increasing drug concentration. In $\overline{BC}$, $\overline{DE}$, $\overline{FG}$ and $\overline{H}$, administration of drug-free perfusion solution restores the original tone. The short decrease in pressure after change of the perfusion solution was due to technical factors

Most of the examined drugs were found to relax the DA. This effect may disturb the newborn's adaptation to extrauterine life and thus is represents a danger for the newborn, especially in pathological cases.

The hypertonic effect of ethylalcohol on the DA may affect the baby's further development. This possibility will have to be taken into consideration when prescribing infusions containing alcohol for delaying premature delivery.

These observations underline the necessity of further examinations to decide whether the drugs used in obstetrics would influence the closure of the DA of the newborn.

## References


1. Adelman MH, Fisch H, Jacobson E, et al: Studies of promethazine with measurements of concentrations in venous blood fetal cord blood and cerebrospinal fluid. Anesthesiology 19: 93, 1958
2. Beermann BM, Groschinsky-Grind, Fahraeus L, et al: Placental transfer of furosemide. Clin Pharmacol Ther 24: 560, 1978
3. Belinkoff S, Hall OW; Intravenous alcohol during labor. Am J Obstet Gynecol 59:429, 1950
4. Brazy JE, Little V, Grimm J: Isoxsuprine in the perinatal period. II. Relationships between neonatal symptoms, drug exposure, and drug concentration at the time of birth. J Pediatr 98;146, 1981
5. Brown WU, Bell GC, Lurie AO, et al: Newborn blood levels of lidocaine and mepivacaine in the first postnatal day following maternal epidural anesthesia. Anesthesiology 42:698, 1975
6. Cooper LV, Stephen GW, Aggett PJA: Elimination of pethidine and bupivacaine in the newborn. Arch Dis Child 52:638, 1977
7. Doenicke A, Krumey I, Kugler J, Klempa J; Experimental studies of the breakdown of Epontol: determination of propanidid in human serum. Br J Anaesth 40:415, 1968
8. O'Donoghue SE: Distribution of pethidine and chlorpromazine in maternal, foetal and neonatal biological fluids. Nature 229:124, 1971
9. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE: Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med 295:526, 1976
10. Haram K, Bakke OM, Johannessen KH, Lund T; Transplacental passage of diazepam during labour: influence of uterine contractions. Clin Pharmacol Ther 24:590, 1978
11. Kovalčik V: The response of the isolated ductus arteriosus to oxygen and anoxia. J Physiol (Lond) 169:185, 1963
12. Magyar K, Lengyel M, Knoll J: Absorption, distribution and elimination of drotaverine. Acta Physiol Acad Sci Hung 51:401, 1978
13. McMurphy DM, Boreus LO: Studies on the pharmacology of the perfused human fetal ductus arteriosus. Am J Obstet Gynecol 109:937, 1971
14. Mirkin BL: Perinatal Pharmacology and Therapeutics. Academic Press, New York 1976
15. Morrison JC, Whybrew WD, Rosser SI, et al: Metabolites of meperidine in the fetal and maternal serum. Am J Obstet Gynecol 126:997, 1976
16. Moss AJ, Emmanouilides GC, Adams FH, et al: Response of the ductus arteriosus and pulmonary and systemic arterial pressure to changes in oxygen environment in newborn infants. Pediatrics 33:937, 1964
17. Olley PM, Coceani F, Bodach E: E-type prostaglandins: a new emergency therapy for certain cyanotic congenital heart malformations. Circulation 53: 728, 1976
18. Weidinger H: Labour Inhibition. G Fischer Verl, Stuttgart-New York, 1977, p. 47


*Received December 21, 1982*

E Endreffy MD
P. O. Box 471
H-6701 Szeged, Hungary

*Acta Paediatrica Hungarica, 24 (3), pp 287–290 (1983)*

# Renal abscess in infancy

A B Pintér, J Schäfer

Department of Paediatrics, University Medical School, Pécs, Hungary

Renal abscess is a rare occurrence in infancy. Its differentiation from an infected renal cyst may be difficult, especially if a perinephric abscess develops. This report illustrates a hitherto unrecorded unusual presentation of renal abscess as a tumour arising from the left lumbocostal region in an infant.

Renal abscess may be caused by haematogenous spread of infection, local pyelonephritis, renal calculi or underlying obstructive renal disease.

During the last 25 years 23 cases of renal abscess in childhood have been reported in the literature [1, 2, 3, 4, 7, 8, 9, 10, 11]. The patients' age ranged from 13 months to 15 years. Among them there was only one infant and that patient had in addition a congenital nephrotic syndrome. The case to be described probably represents the second infant with a renal abscess.

## Report of a Case

A five months old female infant presented with septicaemia and a protuberant mass in the left lumbocostal region which had started suddenly, two days prior to her admission. Two months earlier she had had pyuria and E. coli bacteriuria. At admission the fairly thin infant was in no apparent distress. In the left abdomen there was a smooth, slightly movable, easily palpable mass (Fig 1, hatched area) and in the left costo-lumbal region a well noticeable protuberance measuring $5 \times 3 \times 1.5$ cm. (Fig. 1, arrow). The overlying skin was not discoloured and showed no inflammatory signs and there was no tenderness or fluctuation. The white blood cell count was 40 000. Erythrocyte sedimentation rate was 100 mm/h. The urinary sediment contained 30–40 white cells but no erythrocytes. There was no pyuria on admission. Urine bacteriology revealed haemolytic *Staphylococcus aureus*. Plain radiographs of the abdomen detected a soft tissue mass displacing the bowel medially. Intravenous pyelography showed a normal right kidney. On the left side the X-ray was suggestive of a tumour arising from the middle part of the kidney. The upper and lower calyces were deformed and displaced cranially and caudally, the middle calyx was not visible (Fig. 2). Thus we had to differentiate between a rapidly growing nephroblastoma and a renal abscess.

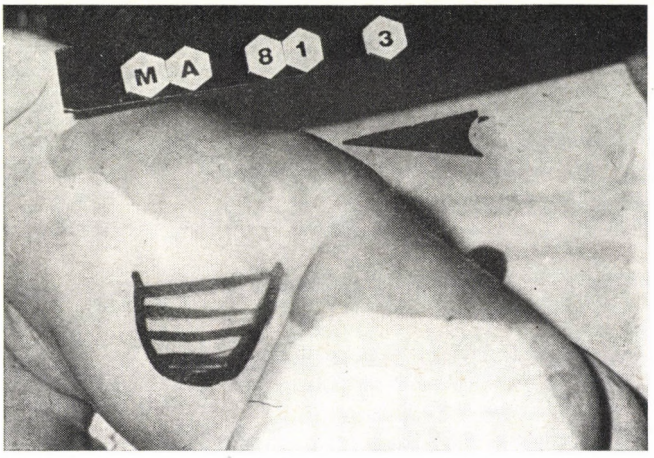



FIG. 1. Mass in the left abdomen (hatched area) and protuberance in the left costo-lumbal region (arrow)

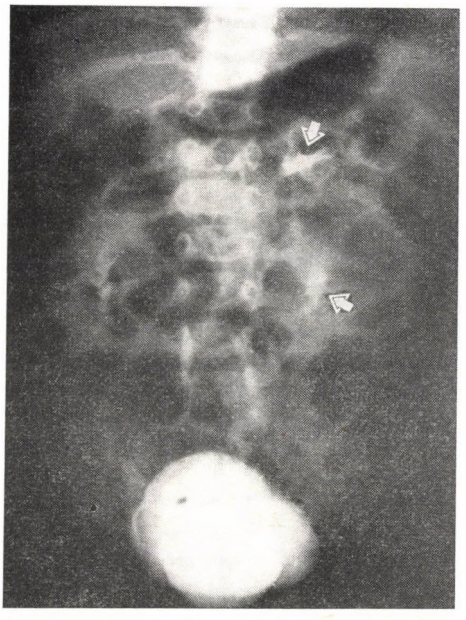


FIG. 2. Intravenous pyelogram on admission: the upper and lower calyces of the left kidney are deformed and displaced cranially and caudally (arrows), the middle calyx is not visible

Under general anaesthesia a needle biopsy was carried out through the lumbocostal mass. From a depth of about 2 cm, thick pus was obtained. An incision was then made at the site of the puncture and about 150 ml of pus was drained. The surface of the kidney could be felt and the tip of the finger could be inserted into a cavity in the renal substance. This

space was drained and from the cultured pus E. coli was obtained. The patient was started on a broad spectrum antibiotic. Intraoperative diagnosis was that of a renal abscess perforating the renal parenchyma and capsule, and appearing as a tumour in the left costolumbal region.

The patient made an uneventful recovery. Intravenous pyelography 2 months and 18 months later revealed an essentially normal collecting system in the left kidney (Fig. 3). The patient is now 2 years old, develops well and seems to be entirely healthy.

## Discussion

Classically, a renal abscess develops 1–8 weeks following a primary skin, respiratory, dental, tonsillar or urinary tract infection [4]. In our case, the previous bacteriuria, pyuria and fever, which had changed after drainage of the abscess, may be regarded as pointing to a urinary infection. There was no sign of a preceding skin lesion which would have explained the staphylococcal finding.

It has been estimated that only one sixth of the cases of renal abscess is diagnosed [4]. One of the causes why they escape diagnosis is that the antibiotics may modify the typical clinical picture and prevent or delay the progression of a renal abscess to a perinephric abscess.

In our patient not only the early age of presentation was unusual but also the appearance of a tumour in the left lumbocostal region, as a hitherto undocumented complication of a renal abscess. In differential

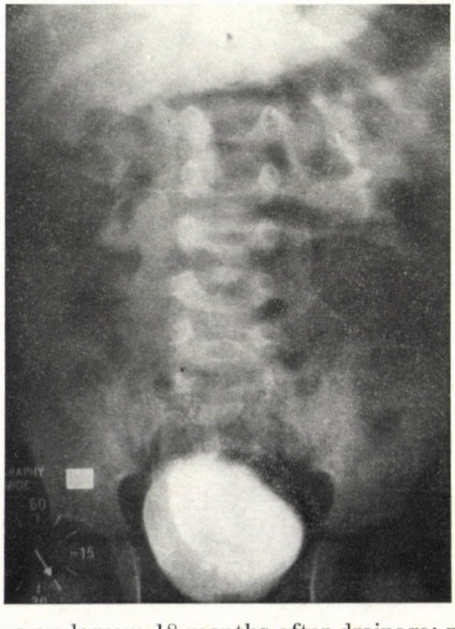


Fig. 3. Intravenous pyelogram 18 months after drainage: normal left kidney

diagnosis, perforation of a suppurating solitary renal cyst should be considered [5].

The treatment of choice of a renal abscess is exploration and drainage. In our case early drainage resulted in rapid recovery which then made a further exploration unnecessary. Recently, Finn et al. [6] have reported on the successful percutaneous management of renal abscesses in adults which supports the non-invasive approach applied by us.

## References

1. Breyen O: Oberer Polabszess der rechten Niere bei einem 12jährigen Mädchen — Angiographische Diagnostik. Z Kinderchir 15:295, 1974
2. Cobb OE: Carbuncle of the kidney. Brit J Urol 38:262, 1966
3. Crawford DB, Rasoulpour M, Dhawan VM Klanber GF, Little HK, McLean RH: Renal carbuncle in a neonate with congenital nephrotic syndrome. J Pediatr 93:78, 1978
4. Fair, WR, Higgins MH: Renal abscess. J Urol 104:179, 1970
5. Finlay DBL, Lowe JS, Kaur K: Perforation of a suppurative solitary renal cyst. Br J Surg 68:585, 1981
6. Finn DJ, Palestrant AM, DeWolf WC: Successful percutaneous management of renal abscess. J Urol 127:425, 1982
7. Moore ChA, Gangai MP: Renal cortical abscess. J Urol 98:303, 1967
8. Rote AR, Bauer SB, Retik AB: Renal abscess in children. J Urol 119:254, 1978
9. Segura JW, Kelalis PP: Localized renal parenchymal infections in children. J Urol 109:1029, 1973
10. Simonowitz DA, Reyes HM: Renal abscess mimicking a Wilms' tumor. J Pediatr Surg 11:269, 1976
11. Timmons JW, Perlmutter AD: Renal abscess: a changing concept. J Urol 115:1976

*Received November 27, 1982*

A Pintér MD
József A u 7
H-7623 Pécs, Hungary

# Book reviews

*Developmental Effects of Prenatal Irradiation.* Edited by H KRIEGER, W SCHMAHL, G KISTNER, FE STIEVE. X + 387 pages with 97 figures and 27 tables. Gustav Fischer Verlag, Stuttgart 1982. Price DM 89,—

This book presents the papers given by a number of experts and specialists, and also the discussions at an international symposium held in Neuherberg near Munich in 1980 under the auspices of the Association of Environmental Research, the Institute of Radiation Hygiene, the German Association for Radiology, and WHO.

The first section dealt with the effects on prenatal development of external radiation and incorporated radionuclides. It has previously been shown by a number of clinical and experimental studies that a teratogenic effect should only be expected from high doses, those above 0.75 Gy. Induction of congenital bone, eye and neurological abnormalities is influenced by the decreasing radiosensitivity during pregnancy and by the fractionation and/or protraction of irradiation. Tne authors agree in that molecular genetic events are not detectable with the usual morphological methods. The second section, entitled Consequences of prenatal radiation exposure, deals with neurological and behavioural disorders induced in utero by irradiation. Estimation of the risk is difficult because of individual variations in radiosensitivity. There are three categories of cells, those with high, medium and low risk in their response to irradiation, as detailed in the third section. Risk estimation should be based on the fact that many chemical agents are crossing the placenta and may increase or change the effect of irradiation. General rules have been worked out for the search for synergistic effects of radiation and chemical substances. The fourth section discusses clinical and epidemiological observations. The reported cases of children with malformations are not convincing as regards the role of prenatal exposure to radiation. More convincing are the papers reporting on normal, healthy children born after the mother had X-ray therapy for cancer. For instance, a child was born to a woman who between the 19th and 27th week of pregnancy had received a total body dose of 680 rad. The offspring now is 27 years old, has an excellent IQ and he is the father of a healthy child. On the other hand, Kneale and Stewart's paper seems to support the hypothesis of leukaemia induction by prenatal irradiation; they assume however that the sequelae are connected with immunological factors.

The book will interest radiologists and experts, mainly paediatricians, who study the genetic risks of radiations.

Judith SZOLLÁR

F VOGEL, AG. MOTULSKY: *Human Genetics*. 2nd printing with corrections. XXVIII + 700 pages with 420 figures and 210 tables. Springer Verlag, Berlin, Heidelberg, New York 1982. Price DM 98,—

It is hardly more than a year ago that I wrote a review about this exceptionally excellent book and appreciated it as a unique example of up-to-date, comprehensive, interesting and complete survey of human genetics. The unusually fast second printing shows that many people have shared my opinion and by now the work has become *the* standard volume of researchers, medical doctors and students wherever you go. All of us find interest in this book, proving that, as the first sentence of its Preface reads "Human genetics provides a theoretical framework for understanding the biology of the human species". In order to exclude self-repetition I shall only quote the titles of the book's 9 chapters. They are,

1. History of human genetics,
2. Human chromosomes,
3. Formal genetics of man,
4. Gene action,
5. Mutation,
6. Population genetics,
7. Human evolution,
8. Genetics and human behaviour, and
9. Practical applications of human genetics and the biological future of mankind.

There is only one point that asks for criticism; I have to mention it on behalf of the owners of the first printing. We do not know what misprints and errors have been corrected and we somehow feel frustrated to have an excellent book without knowing of any errors in it that had to be rectified.

The book is a must to both beginners and advanced experts of medicine and human genetics.

A CZEIZEL

HA KEIM; *The Adolescent Spine*. XV + 254 pages with 366 figures. Springer Verlag, Berlin, Heidelberg, New York 1982. 2nd edition. Price DM 82.—

The first edition of this successful book has been thoroughly revised and enlarged, and two chapters have been added, one on the cervical spine by J. G. MacMurtry and one on the biomechanics of the spine by D. P. Roye, Jr. The author who is associate professor at the New York Orthopaedic Hospital, has practically devoted his life to studying the spine and produced several well-known papers on the subject. His large experience is clearly reflected by this well-edited book which is most useful to medical students, orthopaedic surgeons and also physiotherapists. The many excellent photographs mean a great help in understanding the text.

There are nine chapters in the book. The first describes the complicated development of the spine and its anatomical features, the second its neurology. Chapter 3 discusses the biomechanics. These three chapters occupy little space and limit themselves to the main points. Chapter 4 describes the congenital conditions such as the Klippel–Feil syndrome, spondylolisthesis, diastematomyelia and spina bifida and their treatment. Here we find a useful table for diagnosing the level of the lesion. After a chapter on the benign and malignant tumours there is a new one on traumatic spinal damages including the neurological injuries and the herniated disks and a chapter on the cervical spine with description of basilar impression and malformations of the atlas, among others.

The next four chapters on more than 100 pages are devoted to scoliosis, the most important and most frequent disease of the adolescent spine. The space allotted to it is fully justified by the many unsolved diagnostic and therapeutic points and also by the great advances achieved in the last twenty years. After detailing the classification of special deformities a special chapter describes the clinical and X-ray meth-

ods of examination and screening including the moiré fringe topography, a brilliant method devised more than hundred years ago and revived in our days. It is characteristic of the book that it even reviews the pulmonary physiology of the scoliotic patient. Of the conservative methods, the Milwaukee brace is said to be the most advantageous, having been effective in about 75% of the author's cases. Construction of the brace, its application and evaluation of its effect are also discussed in detail. In addition other types of brace used actually in the USA are described. As to surgical management, after a historical survey advantage is given to the Harrington instrumentation with interior rod. It is said that with this technique the correction of most types of scoliotic deformities has been uniformly rewarding. Total hospital time is less than three weeks and after another three weeks the patients resume normal activities. As another method, electrospinal instrumentation devised by Bobechko in Toronto is described. This method which is still in the experimental stage, was successfully utilized in patients who have curves between 20 and 40 degrees; if they were under 45 degrees, the success rate was about 80%. Finally, a chapter deals with lordosis and kyphosis including Scheuermann's disease, neurofibromatosis and tumours.

Keim's book will certainly be useful to every paediatric orthopaedist.

T Vizkelety

A Peters: *Bewegungsanalysen und Bewegungstherapie im Säuglings- und Kleinkindalter*. 3. Auflage. VIII + 154 Seiten mit 228 Abbildungen. Gustav Fischer Verlag, Stuttgart, New York 1982. Preis DM 28,—

Nach einer kurzen Einleitung in die Entwicklungsphysiologie der Sensomotorik beim Säugling und Kleinkind, werden die verschiedenen Übungen, die zur Rehabilitation benützt werden können, beschrieben. Obwohl diese die neurophysiologischen Kenntnisse der Jahre 1940–50 Jahre widerspiegeln, sind die Übungen grundsätzlich genügend zur Behandlung vieler klinischen Fälle. Dem Entwicklungsalter des Kindes entsprechend gegliedert werden die Übungen mit Hilfe von Zeichnungen dargestellt. Vielleicht hätten hier auch die kongenitalen Bewegungsmuster, als die unentbehrlichen Rehabilitations-Übungsmuster in den ersten 4 Monaten erwähnt werden müssen. Da vom 6–8. Monat an der sensorische Reiz durch Telerezeptoren eine wichtige Rolle bei der zielbestrebten Motilität hat, sollte dieser Einfluß auf die Motorik auch angedeutet werden. Visuelle Reize können z. B. Fehler der posturalen Reaktionen, wie Sitzen, Stehen usw., beeinflussen, so daß man bei älteren Säuglingen und Kleinkindern diese zu rehabilitativen Übungen verwenden kann.

Die beschriebenen Übungen bei den verschiedenen Defekten in Muskeltonus, Bewegungssteuerung und Körperhaltung bieten bei der praktischen Rehabilitation unbedingt eine hervorragende Hilfe. Und wenn man die Beschreibung der phylogenetischen Entwicklung als physiologische Grundlage der Übungen diskutabel betrachtet, — da wir heute die biogenetischen Prinzipien ja anders beurteilen als vor 50 Jahren — soll das keineswegs den Wert der Arbeit beeinflussen oder vermindern.

F Katona

V Steinbicker, J Gedschold, I Göhler: *Das Kind mit Down-Syndrom Ein Ratgeber für Eltern und Erzieher*. 72 Seiten mit 18 Abbildungen und 2 Tabellen. VEB Verlag Volk und Gesundheit, Berlin 1982. Preis M 9,20

Es erscheinen ständig Bücher für die Eltern entwicklungsgestörter Kinder und unter diesen auch solche für Eltern von Down-Kindern. Die Autoren dieses Buches

aus der DDR beschäftigen sich seit zehn Jahren im Rahmen einer Spezialsprechstunde an der Kinderklinik Magdeburg mit Down-Kindern und ihren Familien.

In leicht verständlicher Form werden die Symptome und die häufig zusätzlich vorhandenen Fehlbildungen des Down-Syndroms, ferner die verursachenden Chromosomenveränderungen (Trisomie 21, Translokation, Mosaizismus) beschrieben und an Hand von Fotos veranschaulicht. Die Eigenart der somatischen und psychischen Entwicklung wird kurz angedeutet. Obwohl auf individuelle Unterschiede hingewiesen wird, dürfte die Schilderung der Aussichten der geistigen Entwicklung und der pädagogischen Förderung ein wenig schematisch sein.

Die Autoren sind davon überzeugt, daß die Eltern bei einer eindeutigen Diagnose noch während des Aufenthaltes in der Entbindungsklinik aufrichtig über die wahrgenommene Anomalie, über die Entwicklungsperspektiven und über die Möglichkeiten der Förderung (dieser letzte Aspekt wird von ihnen besonders betont) informiert werden müssen. Da das Buch in erster Linie für Eltern bestimmt ist, hätte man noch mehr auf die Wirkung dieser Mitteilung auf die Eltern (nicht nur auf die Mutter!), auf die dadurch entstehenden Probleme, auf die Selbstverständlichkeit der oft empfundenen negativen Gefühle, Wünsche und auf die eventuelle Notwendigkeit der psychologischen, bzw. psychiatrischen Hilfe eingehen sollen. Die Situation in der Familie und deren Probleme wird auch vom Standpunkt der gesunden Geschwister analysiert.

Zu den Fragen der medizinischen Behandlung wird die sogenannte «Zelltherapie» kritisiert und deren Propagierung als unverantwortlich den Eltern gegenüber gehalten. Die Verfasser betonen, daß im Mittelpunkt aller Behandlungsversuche die frühzeitig begonnene Übungsbehandlung stehen muß. Daneben sind einige Auffälligkeiten korrigierend, symptomatisch medikamentös zu behandeln.

Zur prophylaxe empfiehlt man die genetische Beratung. In den folgenden Fällen wird die pränatale Diagnostik für ratsam gehalten:

— bei Frauen über 40 Jahren

— bei Eltern, die schon ein Kind mit Trisomie 21 haben

— bei gesunden Translokationsträgern.

Die Verfasser heben mehrmals die Wichtigkeit der frühen (womöglich in den ersten Monaten begonnenen) zielgerichteten Förderung hervor. Neben dem Überblick der Voraussetzungen und Prinzipien dieser Förderung und der Erziehung wird an Hand von Beispielen die Anwendung verhaltenstheoretischer Grundsätze zum Erreichen des erwünschten Verhaltens gut illustriert. Konkrete Empfehlungen werden zur Förderung der Selbständigkeit und der Sprachentwicklung geboten. Am ausführlichsten beschäftigt man sich mit der Förderung der Motorik. Auf die anderen Gebiete — wie z. B. das Spiel, die optische Wahrnehmung usw. wird nicht eingegangen.

Die Autoren halten es für wichtig, daß Eltern ihre behinderten Kleinkinder zuhause betreuen Sollen, daß aber gleichzeitig schon im Säuglingsalter eine stundenweise Arbeit mit den Kindern in den Fördergruppen durch Fachleute nicht nur wertvoll ist, sondern auch die Mütter entlastet.

Obwohl die Erziehung der «schulbildungsunfähigen förderungsfähigen» — geistig behinderten — Kinder in der DDR in den Einrichtungen des Gesundheits- und Sozialwesens geschieht, wird in dem Buch sehr wenig über die Arbeit in diesen Fördereinrichtungen und über die Förderung im Schulalter geschrieben.

Wenn auch der Schwerpunkt des Buches in der Frühförderung liegt, hätte man einen kurzen allgemeinen Überblick über die Situation der Erwachsenen mit Down-Syndrom geben sollen.

Marta KEDL

K Zwiener, E Schmidt-Kolmer, L Schoder: *Entwicklungskontrolle in der frühen Kindheit und ihre Bedeutung für die gesundheitliche Betreuung und die Erziehung.* «Hygiene in Kinderkollektiven», Band 7. 287 Seiten mit 53 Abbildungen und 38 Tabellen. VEB Verlag Volk und Gesundheit, Berlin 1982. Preis M 20,40

Das Buch ist die Zusammenfassung und die Ergänzung der teilweise schon mehrmals publizierten Arbeit der Forschungsgruppe des Instituts für Hygiene des Kindes- und Jugendalters zu Berlin und Leipzig. Diesmal wird ihr Verfahren zur periodischen Kontrolle von Leistung und Verhalten bei Kindern von 1 bis 42 Monaten mit der dazu gehörenden Arbeitsanleitung und Dokumentation, mit der theoretischen und methodologischen Grundposition der Erarbeiterung und mit den bei der Standardisierung und Eichung angewendeten Methoden und deren Ergebnisse dargelegt. Die Standardisierung wurde in 74 Kleinkindereinrichtungen aus allen Bezirken der DDR an über 7000 Kindern in den Jahren 1969/75, die Eichung an 4131 Kindern 1977/78 durchgeführt. Die Ergebnisse der Kontrolle des Entwicklungszustandes wurden für jedes Lebensquartal, Lebensjahr und insgesamt dargestellt, und nach Alter, Geschlecht, Körpermeßwerten, Gesundheitszustand, Familienverhältnissen und Erziehungsbedingungen in den Krippen gruppenweise aufgearbeitet, miteinander und mit den Gesamtergebnissen verglichen. Ein von den Mitarbeitern der Kinderneuropsychiatrischen Abteilung der Nervenklinik von Rostock verfaßter Abschnitt ergänzt den Band, der die Ergebnisse der Entwicklungskontrolle von 294 Risikokindern darstellt, die zum Untersuchungszeitpunkt eine Krippeneinrichtung der Stadt Rostock besuchten. Nach der Meinung der Autoren der Methode liefert die Rostocker Arbeitsgruppe einen Beitrag zur Validität und klinischen Effizienz des Entwicklungskontrollverfahrens.

J Falk

*Pädiatrische Immunologie.* Herausgegeben von H-J Blau. 212 Seiten mit 41 Abbildungen und 27 Tabellen. Georg Thieme Verlag, Leipzig 1982. Preis M 61,—

Die Zielsetzung des unter Mitwirkung von fünf Fachwissenschaftlern verfaßten Buches war, aus dem raschen Wissenszuwachs der Immunologie für den klinisch tätigen Kinderarzt ein gut verwendbares Hilfswerk zu bieten. Die Gliederung ist gut, und die Einteilung ist auch vom didaktischen Standpunkt vorteilhaft. Eine Ausnahme dürfte nur das 5. Kapitel über die Immundiagnostik im Kindesalter sein, in dem die immundiagnostischen Methoden und deren Beurteilung, die Klinik der Immunmangelerkrankungen (etwa 16 Seiten) und die Organ- und Systemerkrankungen mit speziellen Reaktionen des Immunsystems zusammengefaßt sind; unter den Letzteren werden die allergischen Erkrankungen behandelt und auf die Methoden zu deren Diagnostik zurückgegriffen. Diese Einteilung verhilft nicht zur Systematisierung der Kenntnisse.

Das Werk gliedert sich in 6 Teile. Im ersten Kapitel finden wir die Grundlagen und Grundbegriffe, Stellung und Aufgaben der pädiatrischen Immunologie und Immunpathologie, Antigene, Antikörper, das Komplementsystem, die Funktion des Immunsystems, Immundefizienz und immunpathologische Reaktionen. Zwei Abschnitte befassen sich kurz — vielleicht zu kurz — mit den wichtigsten Problemen der Transplantation- und Tumorimmunologie. Das 2. Kapitel behandelt die Phylogenese und Ontogenese der Immunantwort. Das 3. Kapitel ist für den Kinderarzt besonders wichtig, da hier der Reifeprozeß der Immunantwort besprochen und mit Hilfe von Tabellen die erwartbare Konzentration der Immunglobuline in den verschiedenen Altersstufen dargestellt wird. (Die Orientierung wird manchmal durch abweichende Angaben verschiedener Autoren gestört.) Kapitel 4 erläutert die Immunprophylaxe, die einzelnen Schutzimpfungen und das 6. Kapitel die Möglichkeiten der Immunthe-

rapie, Immunsuppression und ganz kurz die onkologische Immuntherapie.

Zusammenfassend soll festgestellt werden, daß dem Kinderarzt in Ambulanz und Klinik ein Buch vorgelegt wurde, das fachspezifisches Basiswissen vermittelt und ihm in Diagnostik und Therapie wertvolle Hilfe leisten wird.

E. CSERHÁTI

R HUCH, A HUCH, G ROOTH: *An Atlas of Oxygencardiorespirograms in Newborn Infants.* 257 pages. Wolfe Medical Publications, London 1983. Price £ 25.00

The non-invasive method of following the transcutaneous oxygen tension has aroused great interest in clinical research and therapy in the past decade and has been proved to be an excellent means in the solution of various problems in both obstetrics and neonatology. Exploitation of the range of possibilities the practical utilization of the method has now been described by its inventors, Professors Renate and Albert Huch from the Obstetric Hospital of Zurich University, with Professor Rooth from Uppsala and two of their collaborators. Their results have been acknowledged all over the world.

The book gives an account of the authors' experience with oxygen-cardiograms. The term means a simultaneous recording of the continuous monitoring of respiratory rate, transthoracic impedance, transcutaneous oxygen tension, heart rate in the capillaries of the skin and the „flow" indicating the changes in blood flow within a short time. („Flow" means the amount of electric current needed to maintain the core of the oxygen electrode at a constant temperature. This value depends on the rate of local blood flow.)

The atlas-like book contains 134 original recordings of the possible varieties in newborn infants in the first hours of life with the evaluation of the curves, discussing in detail the influence of the baby's activity, the anaesthesia applied to the mother, the course of delivery, breast feeding, vomiting of the baby, and the cardiorespiratory disturbances as reflected by the oxygen cardiorespirogram recorded by the Hellige Oxygen-Cardiorespirograph equipped with a probe made by Dräger. The accurate illustration of the possible artifacts is essential for a reliable evaluation of the recordings. Besides, the authors discuss their experience with diverse oxygen tests. The material presented in the book is based on the observation of 3000 newborn infants, performed at the Huchs' previous working place, in Marburg, GFR. The recordings give individual examples illustrating each variant while the combined results are evaluated by appropriate statistical methods and discussed in a separate chapter.

The only thing that may disappoint the reader is that no mention is made of the possible use of the method in pathological conditions and situations, but it is true that the authors begin their book by saying that their aim was to describe the various patterns in healthy newborns in the first hours of life. We sincerely hope that another book will soon follow, summarizing the findings in pathological cases. Oxygen-cardiorespirography being widely used, this presentation of the well-known authors' experience will attract the interest of every specialist in perinatology, both by its scientific and practical aspects.

D BODA

*Small Intestine.* Edited by CHADWICK VS and PHILLIPS S. 355 pages. Butterworth Scientific, London 1982. Price L 21

In this book that contains papers from a multinational team of experts and is edited by a senior lecturer of the Postgraduate Medical School in London and the director of the gastroenterology unit of the Mayo Clinic, even the best informed specialist will find some interesting data which were unknown to him. The chapters have appar-

ently been selected so as to present only subjects in which there have been important recent advances. This is clearly seen from the lists of references at the and of every chapter: few of the papers quoted have appeared before the last decade and data published in 1982 are no rarity.

The chapters are centred around five subjects. The first one deals with development, ultrastructure, biochemistry, in vitro methods (mainly small intestinal organ cultures and their technique), small intestinal immune mechanisms and endocrine functions including the recently isolated PHI and PYY in addition to the eight generally known intestinal hormones, and further the motility of the small intestine and the effect of invading microorganisms. The second subject concerns the immunologically related diseases. The first of these shapters deals with some parasites; it is said that the thymus has a central role in the resistance to enteric parasites in mice and rats, and LgA and LgG would also have a role in it, and that the carbohydrate composition of the brush border is affected in trichinelliasis. There is an interesting and detailed review from Algeria of alpha chain disease and a chapter on the intestinal effects of graft-vs-host-disease. Although involvement of the small intestine is a rarity in chronic GVHD, five patients with severe malabsorption have been observed by the authors. Fat excretion amounted to 50–70% in spite of a normal villous architecture and lymphatic blockade and submucosal fibrosis was assumed to have been the responsible factor. The next two chapters deal with the different froms of vasculitis on the basis of case reports, and with atopy of the gut.

Neuroendocrine disorders form the next subject. The first chapter discusses the hormonal diarrhoeas in four patients with Zollinger-Ellison syndrome the authors of the chapter found near the Treitz angle a flow exceeding 3 to 5 times the upper limit of normal; 75% of this was reabsorbed by the small intestine and the rest of the overload by the colon. In mastocytosis, prostaglandin overproduction was found to be an important factor. In endocrine cholera (WDHA syndrome) the source of the diarrhoea was found in the smal intestine. The next two chapters deal with intestinal motility. Infectious agents are the subject of the following two chapters of which the first gives an account of the up to now futile attempts at finding the cytotoxicity-inducing agent in Crohn's disease and ulcerative colitis, and the second chapter presents a review of the enteric pathogens causing acute disease. There is a striking statement here: is it really true that disease and death due to diarrhoea take toll of 500 million children annually in developing countries? The last chapter of the book gives a good review of mostly recent data concerning protein-calorie malnutrition, vitamin and trace element deficiencies and, finally the effects of dietary fibre on the small bowel.

The book will be especially interesting for pathophysiologists and clinicians studying the functions of the small intestine, but practising gastroenterologists will also find it useful.

PV VÉGHELYI

WIEDEMANN HR—GROSS PR—DIBBERN H: *Das charakteristische Syndrom. Ein Atlas für Klinik und Praxis.* 2. Auflage. XXXI 413 Seiten mit 204 Abbildungstafeln. Schattauer-Verlag, Stutgart — New York 1982. Preis DM 154

Wenn man eine Rezension über die »überarbeitete und erweiterte« neue Auflage eines Buches schreibt, muss man meistens flessig nachsehen was eigentlich überarbeitet und was erweitert wurde. Mit dieser 2. Ausgabe hat man keine solche Probleme. Das Format ist viel grösser geworden und das Buch ist mindestens doppelt so dick als seine erste Ausgabe. Anstatt 100 Syndromen enthält nähmlich diese Ausgabe fast 200, und die Seitenzahl beträgt auch das doppelte der vorherigen. Der Untererschied liegt nicht an einer

veränderten Beschreibung der Krankheiten: nach wie vor findet man auf der linken Seite die Beschreibung der Syndrome das an der gegenüberliegenden Seite mit 2 bis 15 charakteristischen Photographien demonstriert wird. Demgegenüber stammt die Erweiterung von einer Fülle neuanfangsnommener Syndromen. Manche davon wie z. B. das Pfeiffersche, das Carpentersche, das Schauthauer-Mariesche Syndrom usw. wurden in die 1. Ausgabe nicht aufgenommen, einige wohl darum, dass sie zu der Zeit noch nicht beschrieben worden sind wie z. B. die mesomele Dysplasie oder das pseudohydrozephale Progeroidsyndrom. Andere sind dagegen nie beschriebene verblüffende Krankheitsbilder wie ein Syndrom von Taubheit. Radiushypoplasie und psychomotorische Entwicklungshemmung, ein anderes das mit ektodermaler Dysplasie, Hypotrichosis mit Pili torti und Syndaktilie einhergeht oder ein Syndrom mit Daumentriphalangie, Thrombozytopathie und Schwerhörigkeit und noch viele Andere. Der Text der Beschreibungen wurde auch sorgfältig überarbeitet und die Referenzien sind bis Mitte 1982 ergänzt. Die Bilde sind demonstrativ, nur hätte vielleicht der Autor einen typischere Kranken mit fazialer Hemiatrophie als das abgebildete Mädchen einfügen und auch bei der gerade durch ihn beschriebenen Thalidomidembryopathie anstatt des jetzigen Bildes eine Tetra-Amelie oder noch eher eine Tetraphokomelie abbilden können.

Das Buch wird jedem Pädiater und Genetiker und allen die sich mit Familienberatung beschäftigen; ein unentbehrliches Nachschlagewerk sein.

PV VÉGHELYI

PRINTED IN HUNGARY
Akadémiai Nyomda, Budapest

# INSTRUCTIONS TO AUTHORS

*Form of manuscript*

Two complete copies of the manuscript including all tables and illustrations should be submitted. Manuscripts should be typed double-spaced with margins at least 4 cm wide. Pages should be numbered consecutively.

Manuscripts should include the title, authors' names and address of the institution where the work was done.

An abstract of not more than 200 words should be supplied typed before the text of the paper.

*Abbreviations* should be spelled out when first used in the text. *Drugs* should be referred to by their WHO code designation (Recommended International Nonproprietary Name); the use of proprietary names is unacceptable.

The *International System of Units* (SI) should be used for all measurements.

*References*

References should be numbered in alphabetical order and only the numbers should appear in the text (in parentheses). The list of references should contain the name and initials of all authors (the use of et al instead of authors' name in the reference list is not accepted); for journal articles the title of the paper, title of the journal abbreviated according to the style used in Index Medicus, volume number, first page number and year of publication; for books the title followed by the publisher and place of publication.

Examples:

Kerpel-Fronius E, Gács GK: Serum insulin values in infants. Acta Paediatr Acad Sci Hung 16:197, 1975

Crosse VM: The Preterm Baby. Churchill Livingstone, Edinburgh and London 1971

Detter JC: Biochemical variation. In: Textbook of Human Genetics, ed. Fraser O, Mayo O, Blackwell Scientific Publications, Oxford 1975, p. 115

*Tables and illustrations*

*Tables* should be comprehensible to the reader without reference to the text. The headings should be typed above the table.

*Figures* should be identified by number and authors' name. The top should be indicated on the back. Their approximate place should be indicated in the text. Captions should be provided on a separate page.

*Proofs and reprints*

Reprints and proofs will be sent to the first author unless otherwise indicated.

A hundred reprints of each paper will be supplied free of charge.

The name and address of the first author should be given after the list of references.

CONTENTS

Effect of lithium carbonate on the bone marrow of patients treated for haematological malignancies. *S Molnár, P Kajtár* ..... 211

Metabolic relations of serum lipids and lipoproteins in diabetic children. *Marta Peja, L Madácsy, L Kassay, Maria Bognár* ..... 217

Assessment of skeletal age in the first year of life on basis of the caput humeri ossification centres. *B Lombay* ..... 221

Testing of two score systems for the diagnosis of malnutrition. *A Amador, C Rodriguez* 231

Effect of parenteral allopurinol treatment in critically ill children in need of intensive care. *D Boda, I Németh* ..... 247

Late effects of therapy in children previously treated for leukaemia or malignant tumour. *D Schuler, Gabriella Kardos, Rozália Koós, Alaine Polcz, G Gács, T Révész* ..... 255

Elevated risk of osteoarticular complications in children with acute *Brucella melitensis* infection. *E Shahar, Z Barzilay, G Altman, I Shohet, BE Cohen* ..... 263

Dermatoglyphics in Saethre-Chotzen syndrome: a family study. *Liane Borbolla, Ibis Menéndez* ..... 269

Effect of drugs used in obstetrics on the constriction by oxygen of the ductus arteriosus of the rabbit fetus. *E Endreffy, D Boda* ..... 281

Renal abscess in infancy. *AB Pintér, J. Schäfer* ..... 287

Book reviews ..... 291

**Index: 26.021**

FORMERLY ACTA PAEDIATRICA ACADEMIAE SCIENTIARUM HUNGARICAE

# Acta Paediatrica Hungarica

VOLUME 24, NUMBER 4, 1983



**Akadémiai Kiadó, Budapest**
ACTA PAEDIATR HUNG HU ISSN 0001-6527

# ACTA PAEDIATRICA

## HUNGARICA

A Quarterly of the Hungarian Academy of Sciences

Editor

P. V. VÉGHELYI


---

*Acta Paediatrica* publishes original reports of studies in paediatrics and borderline fields.


Manuscripts and editorial correspondence should be addressed to

*ACTA PAEDIATRICA HUNGARICA*
Bókay J. u. 53.
H-1083 Budapest
Hungary

*Subscription information*

Orders should be addressed to

KULTURA Foreign Trading Company
P. O. Box 149, Budapest
H-1389

or its representatives

*Acta Paediatrica Hungarica* is published in yearly volumes of four issues by

AKADÉMIAI KIADÓ

Publishing House of the Hungarian Academy of Sciences
Alkotmány u. 21.
H-1054 Budapest

*Acta Paediatrica Hungarica, 24 (4), pp. 299—314 (1983)*

# An orienting diagnostic system in neonatal and infantile neurology

F KATONA

Department of Developmental Neurology and Neurohabilitation,
Paediatric Institute Szabadsághegy, Budapest

A fast orienting diagnostic system was derived from a computerized diagnostic system in order to provide paediatricians and practitioners with a guide how to act in order to detect or exclude symptoms of pre- and perinatal brain damage endangering the normal development of the CNS. Other diseases of the nervous system are also included in the diagnostic system. The system is based on the neurological investigation and follow up of 2000 infants with suspicion of ante and perinatal CNS damage.

Complex diagnostic methods were applied in 2000 neonates and young infants in order to detect pre and perinatal brain lesions. On the basis of this clinical experience 10 diagnostic operative plans were devised. These together form a system containing the most important diagnostic methods and procedures to analyse and substantiate the existence of defects in brain function. A computerized system was developed for data acquisition and analysis to facilitate the diagnosis therapy and follow-up of neonates and young infants suffering from pre or perinatal brain defects. Another important programme of the system was the evaluation of applied therapies and rehabilitative procedures.

During the planning process of the computerized programme a more simple diagnostic system was devised for use without a computer. It serves as a guide to the physician who is not accustomed to deal with special problems in neonatal and infantile neurology. The aim of the system is to help the paediatrician or general practitioner in clinical orientation and investigation. In the presence of suspicious symptoms one should consult the diagnostic and therapeutic plans (ODPs) of the system for evaluation of the symptoms and for orientation concerning their possible correlations.

The system, called Fast Orienting Diagnostic System (FODS). consists of 9 subsystems containing guidelines, informations, suggestions and instructions how to act to obtain an early diagnosis of perinatal brain injury and how to initiate appropriate therapy and habilitation. The FODS informs the paediatrician concerning the most important questions to pose and the activities to fulfil and offers guidelines how to reach the ultimate diagnosis. Each subsystem represents in practice an operative plan in the form of a map containing questions and instructions. By following the guidelines one can proceed from a main question to

subquestions. The subsystems are called Operative Diagnostic Plans (ODP). The nine ODPs reflect the most important structural and functional trends of the maturing human nervous system, and possible pathological alterations produced by various defects such as fetal distress, neonatal hypoxia, etc. In this respect each ODP provides information about the development of all important functions of the central nervous system, and lists various possible defects in them. The ODPs also indicate the necessary steps to be taken to collect further data to the final diagnosis, and give suggestions for therapeutic and neurorehabilitative procedures. Thus, each ODP contains a plan of normal and abnormal developmental gradients in the maturing human nervous system, the symptomatology of possible abnormalities and the methods to detect and treat them if necessary.

The nine ODPs are as follows (Charts of ODPs can be found attached to the back cover).

I. Guide to the aetiology of pre- and perinatal brain injuries.

II. Guide to defects of the developing skull and brain.

III. Guide to defects of the developing spine and vertebral column.

IV. Guide to defects of the cranial nerves V, VII, IX, X, XII, and their central organization with special regard to feeding behaviour.

V. Guide to defects of the cranial nerves II, III, IV, and VI, and their central organization with special regard to early visual behaviour.

VI. Guide to defects of the cochlear portion of cranial nerve VIII and its central organization controlling early auditive behaviour.

VII. Guide to the development of sensorimotor functions and their defects in muscle tonus proportion, motor dynamics, and elementary posture.

VIII. Guide to defects in the development of sleep, alertness, orientation and general behaviour.

IX. Guide to evaluate defects in early mental activity and development of mental faculties as well as communication and social adaptation.

These 9 ODPs together represent a general outline of the structural and functional organization of the maturing nervous system with special regard to its defects, aberrations and pathological development.

## Materials and Methods

### *General structure of ODPs*

Each ODP is a map containing a number of guidelines. The map follows a definite pattern. On the left side we find a summary of the basic structures and functions to be investigated. For example in ODP No. V, from the sentence "Guide to defects of the cranial nerves II, III, IV, and their central organization with special regard to early visual behaviour" a guideline leads to the basic question whether all these functions are normal or abnormal. If any abnormality is found or suspected, the square following the words normal and abnormal must be used. In this case the square following the word abnormal should be marked.

From this square a guideline leads to the next question, "What kind of abnor-

mality?" At this point begins the instructive part of the map. From the main guideline, sub-guidelines lead to operative suggestions; these always indicate the necessity to investigate certain structures or functions, or both. In this case ODP No. V suggests to investigate the fundi, the lens and related structures, the eye movements, the reaction to light and visual orientation, visual behaviour. Along the guideline leading to these main directions we find the methods of the suggested investigations thus the investigation of light sensitivity with a lamp, investigation of the fundi by fundoscopy, investigation of the lens and related structures by fundoscopy, investigation of eye movements by activating the doll's eye symptom, fixation of human face, fixation and the following of objects, and various other procedures. The same and some other methods deal with the next problem, visual attention and behaviour. The guidelines starting from these five suggestions indicate the probability of more than 30 possible defects detectable during the diagnostic procedure. The presence of some of the defects or symptoms may indicate further diagnostic procedures using other methods. For example, abnormal visual orientation and behaviour must be analysed by application of the evoked visual potential method or by polygraphic analysis of the behavioural response to stimulation by light. As the physician follows the guidelines beginning at the left side of the map and proceeds along the arborizing sublines toward the right side, the probability of excluding symptoms and diseases arises, the differential effect increases. The circle around the possible diagnosis becomes narrower and it becomes possible to plan a strategy of the straightforward diagnostic approach by introducing the investigations suggested by the ODP. The arborizing guidelines represent the numerous contacts of the CNS correlating various functions. This mapping helps to connect one defective function to another and arrive at the full symptomatology of a disease. It must, however, be born in mind that the real correlative links between various functions as well as their central organization change in time in the maturing CNS. This is reflected for example in ODP No. V.

The real correlative links between the functions of the maturing CNS change according to the genetic programme of brain development. This is also reflected in ODP No. V.

In this map we find congenital prewired functions such as fixation of the human face, object following, turning towards light, etc. Various steps of the developing spontaneous visual behaviour, and visuomotor function will be encountered as we proceed on the map from left to right.

The maturing nervous system repeatedly reorganizes its vital control activity during development by temporally correlating certain cranial nerves to a distinct function. Such a system is represented by cranial nerves V, VII, IX and XII in order to coordinate sucking, swallowing and breathing. This functional combination offers an opportunity to analyse individual and coordinated performances of the nerves. Defects may readily be detected by the study of feeding. Later, however, new organizational systems arise to regroup the functions of various cranial nerves. For example, vocalization, speech development use the same cranial nerves, the nature of their organization and performance is, however, quite different. If the performance of the nerves is incorrect, dysarthria or other defects may develop, inhibiting normal vocalisation. This may be diagnosed well before this late period of development by analysing feeding behaviour in the first week of life together with crying, facial innervation, etc. In such cases early warning may initiate early therapeutical steps to prevent the integration of early defects in cranial nerve function into the next steps of neurological development.

Each ODP offers at least 3 choices how to begin and proceed with the diagnostical process on the map.

1. One may start with a systematic study of all functions included in the ODP. In this case one should begin to answer all questions one after the other from left to right. One must follow the guidelines proceeding step by step and perform the methods suggested to examine various problems. One is free to form any special individual strategy with the aid of the informations obtained by this procedure. One may go on slowly or may jump fast from the successful application of a method to some special conclusion. Sooner or later the diagnosis will be clear and then the therapeutic and/or neurorehabilitative process suggested by the ODP may begin. This is the analytical approach to the diagnosis.

2. A deductive way is also open. The physician may begin the diagnostic approach by hypothesising a certain diagnosis or opinion on the possible nature of the symptoms and then he may look at the right side of the map for a diagnosis which is nearest to his supposition. To find efficient proofs he has to backtrack all the ways by following the appropriate guiding lines. These are taking him provided his opinion was correct, to specific symptoms characteristic of the supposed diagnosis. The symptoms described in the ODP may or may not be present in the patient. If a similarity can be supposed between the symptoms described in the ODP and present in the patient, then further steps — suggested by the ODP — must be taken to find other symptoms in the patient. Each ODP may be considered a complex equation, which must equally be valid from the right side to the left and vice versa.

3. The third way to use an ODP is less systematic, but this may be the easiest approach. The physician who did find one or more symptoms in the newborn or young infant can look at the map and identify the same symptoms printed out. Now he can follow various guidelines which connect this symptom or symptoms with others. So he will be led to a syndrome, a complex defect which in the map points towards a full diagnosis. An example of the third possibility is that the physician finds a congenital paresis around the right corner of the mouth. He must identify this paresis as an important or an unimportant symptom. The symptom is found in ODP No. IV as a paresis of the cranial nerve VII on the right side. Now one has to follow all guidelines connecting this statement with the other statements reflecting in the functional integrity or defect of other cranial nerves.

Other symptoms mentioned in the ODP are also present, with some of them in the territory of other cranial nerves, the guidelines will indicate interrelations among the symptoms. Thus, a whole syndrome may appear suggesting the necessity of a thorough investigation. The ODP gives indications how to do it, what methods to apply and how to draw conclusions.

## *A short vocabulary of the ODPs*

Each ODP contains notations, suggestions and instructions, questions, connecting guidelines and sub-guidelines. Each ODP is constructed from these items. The notations mark the existence of a certain structure or function and the necessity to investigate it. For example: turricephaly marks the possible existence of a characteristic shape of the skull. This may or may not occur in the given patient. A notation refers in each case to the necessity of looking for something else to observe and to describe it. The word skull in ODP No. I suggests to examine the skull. The words (notations) head and chest circumference contain a suggestion to measure them. Definite suggestions and instructions such as lumbar tap or EEG are usually instructions to undertake certain important investigations, to apply definite methods, or to perform the necessary

therapies and habilitative procedures. The guiding lines connect notations with notations, or notations with instructions. These connections mark the natural, biological links between various functions of the nervous system, mark the links between defective structures and functions forming syndromes, and mark the steps of various diagnostic procedures leading to a temporary or the final diagnosis. These are the baselines of the ODP structures. Each ODP intends to unify the main links in nervous functions and the main diagnostic steps to discover defects in them.

There are altogether 9 ODPs. In the following, summaries are given of each of them. These summarize very briefly the possible defects in a given structural entity such as the skull and the brain (morphology), or in a functional entity as the sensorimotor system of the neonate and the young infant.

### *ODP I. Guide to the aetiology of pre- and perinatal brain injuries*

Brain development can seriously be affected during the embryological and fetal period by various endogenous and exogenous factors. All of them must be considered during consultations with young couples or during the control of pregnancy. According to these data should the labour be planned. Fetal development may be impaired by intrinsic factors such as various diseases of the mother and the father. The most important maternal risk factors are genetic anomalies, bacterial diseases, viral diseases, haemolytic diseases, hormonal disease, malnutrition, chronic heart and circulatory disturbances, renal deficiency, maternal toxicosis, placentar dysfunction, excessive bleeding, habitual abortion, and factors which lead to preterm or postterm birth. Many of these factors can be detected, prevented or treated in time depending on effective pregnant care. For example placentar circulation can be studied in the pregnant woman, biochemical and histological tests may reveal malformations of the fetal nervous system, sonography can detect the arrest of growth of the fetus.

Extrinsic factors such as chemical agents including drugs and physical agents such as irradiation may also act as risk factors. Both intrinsic and extrinsic factors may produce dysmaturity or prematurity, or damage the nervous system of the term neonate. Chronic fetal hypoxia is an extremely dangerous risk factor. Dysmature neonates are apt to develop brain injuries during their fetal life. It is sometimes more advisable to induce labour if there are definite signs of arrested fetal development than to wait and try to carry the pregnancy to term. In a well-equipped and experienced neonatal department the preterm baby can receive all possible help to assure its normal development.

The newborn can sustain brain injury also during labour. Protracted difficult labour, various impairments of the umbilical chord, aberrations in placentar adherence, hydramnios, forceps, vacuum extraction and other factors may play their part. Dysmaturity and prematurity by themselves may, however, be factors predisposing to specific complications which may lead to brain injury. IRDS in the premature may induce

peri- and intraventricular haemorrhage. Fetal distress can influence brain development. Incongruencies in maternal and newborn anatomy may produce head injuries. Neonatal asphyxia in the dysmature is more dangerous owing to lasting oxygen deficiency during fetal life. Hypoxia and intracranial haemorrhage are the most dangerous factors in the genesis of brain injury. A thorough neurologic investigation including EEG is necessary for judging the condition of the neonate, the possible prognosis, and the therapeutical and habilitative measures to be taken. In the case of convulsions, the serum $Na^+$, $K^+$, $Ca^{++}$ and glucose levels should be estimated. All neonates who suffer perinatal injuries of any kind, or who have a history of considerable risk factors should be investigated carefully and controlled regularly later on. The next ODPs will suggest schemes of these examinations to discover all manifest and non-manifest defects of the nervous system [3, 5, 21]. A short summary is given how to investigate the neurologic condition of the neonate, including possible convulsions, and suggestions are given how to cope with them. At the right end of the map indications are found to long term follow-up if events reflected in the guide make it necessary.

*ODP II. Guide to the defects of the developing skull and brain*

As pathological symptoms described in ODPs II–IX may or may not be consequences reflected in ODP I, the latter can be applied to collect the necessary information about the pre- and perinatal history of the infant and to connect the pathologic symptoms with the former events.

The first procedure is a close inspection of the head. In some congenital malformations the skin may be missing in a circumscribed area. Sometimes this is accompanied with a similarly circumscribed defect in the skull and occasionally of the dura. These defects need chronic or operative treatment according to their nature. The form and size of the head is important. Its circumference and that of the chest must be compared and registered for further comparisons. The size and form of the fontanelles, the cranial sutures must be observed and measured. The possibility of macro- or microcephaly must be investigated. One may find varieties in the form of the head such as brachycephaly, scaphocephaly, turricephaly, oxycephaly (acrocephaly) or plagiocephaly. These varieties as well as microcephaly may be part of well defined syndromes as the Apert, Carpenter, Crouson, Greig, Pfeiffer, Russel, Seckel or the Smith-Lemli-Opitz syndrome. Other malformations such as encephalocele may be detected usually in the suboccipital region or at the base of the skull, protruding through a hiatus in the palate. One must carefully observe the vascularization of the head. Occasionally teleangiectasis can be detected which may indicate malformations in the brain vessels. Enriched venous arborization, large head and a peculiar

shape of the frontal curvature may be identified as a sign of hydrocephalus or hydranencephaly.

For further observation of the interior of the cranium, transillumination of the head is necessary. The procedure may reveal the existence of fluid accumulation in the skull. This may be in the subdural space (early subdural effusion with increased protein content, occasionally high ICP) or subarachnoidally (porencephalia, hygroma). Fluid (CSF) may accumulate in the ventricular space and produce hydrocephalus. It often accompanies spina bifida (ODP No. III) or develops as a consequence of perinatal haemorrhage or encephalitis. Hydrocephalus may or may not be occlusive, hypertensive or normotensive. The circulation of CSF must be studied by stain tests. The existence of these malformations or defects must be clarified by neuroradiological procedures (CT, sonography, subdurography, /22/).

The presence of haemorrhage, softening of the cerebral tissue, oedema, porencephalia, watershed infarction, periventricular cavity formation and many other morphological defects can be detected early and followed up by CT and/or sonography. The early diagnosis of these alternations in the brain can be correlated to defects in various functions, for example in sensorimotor function (ODP VIII). The neuromorphologic investigation (neuroradiology) should be correlated to neurophysiologic studies (polygraphy, EEG, evoked potentials). ODP II reflects the applicability of these methods and the necessary steps in therapy if indicated by the investigations. Early chronic subdural effusion, detected by transillumination, neuroradiology, subdural pressure recording and high protein content of the subdural fluid accumulation has to be evacuated to prevent neomembrane formation. Hypertensive hydrocephalus calls for early implantation of an appropriate ventil system, to prevent atrophic changes in the brain. Convulsions necessitate drug treatment. The results of all therapies need careful longitudinal follow-up (indicated in ODPs IV–IX) and early application of appropriate neurohabilitative programmes if necessary.

### *ODP III. Guide to defects of the developing spine and vertebral column*

Development of the vertebral column is determined by a specific genetic programme which includes the natural human specific movements. These motor functions exercise an important influence on the final shape of the vertebral column.

The spinal cord and the spinal column may sustain lesions during birth. Haemorrhages may occur in the epidural space, in the subdural space or in the spinal cord. Fractures of vertebrae may occur during difficult labour.

The integrity of the spinal cord and the vertebral column is often impaired by various congenital malformations. Rachischisis may occur in the form of meningocele, myelo-

meningocele, myelodysplasia. These usually affect the lower part of the vertebral column, but occasionally they are observed at the cervical or upper thoracic level. Diminution in the number of the vertebrae can be detected in the sacrum. The deformity may produce sacral agenesis. The vertebrae may form abnormal contacts and develop continuities for shorter or longer extension as blocks, as in the case of the Klippel-Feil syndrome.

In addition to these local defects, deformities may develop due to other influences. This is the case if the activity of the neck muscles becomes abnormal. A pathologically increased tonus of the neck muscles on one side determines the position of the head. This in turn influences the form of the maturing spinal column. An exaggerated tonus of the neck muscles maintains either a lateralized position of the head or keeps the head in a medial position with upright chin and lower occiput. The former position is called increased asymmetric tonic reaction of the neck, the latter is known as an increased symmetric, tonic neck reaction. Both may be consequences of perinatal brain lesion. The first produces scoliotic changes in the vertebral column, the second gives rise to lordotic changes.

It is important to observe all symptoms which may lead to abnormalities in the development of the vertebral column which is the functional and structural basis of many important body postures such as of the sitting, standing and walking positions [12]. ODP III contains suggestions to the up-to-date diagnosis and treatment of meningomyelocele. Early preoperative diagnosis including early postnatal urodynamics and polygraphy may help the surgeon to consider the operative indication if selection is adopted, and in any case to compare pre- and postoperative states. Early postoperative neurorehabilitation is suggested to prevent further deformities in the structure and function of the lower extremities, the urinary bladder and the rectum. As meningomyelocele is often related to hydrocephalus, these conditions are briefly indicated in ODP III, though hydrocephalus is described in ODP II in detail.

*ODP IV. Guide to defects of the cranial nerves V, VII, IX, X, XII and their central control with special regard to feeding behaviour*

Reactions mediated by the Vth nerve can be studied by activization of the rooting reaction and the stimulation of the cardinal reflex points around the mouth. The function of nerve VII must carefully be studied if an eventual difference in the form of the right and left sides of the face is suspected. Laughing, crying and facial mimics and the technique of suction should be observed. While observing the activities of the baby during suction, the function of the IX and XII nerves should also be studied. Movements of the soft palate and successful swallowing reveal the integrity of nerves IX and X. Paresis

of the VIIth cranial nerve may be central or peripheral and due to some perinatal lesion. Defective sucking and swallowing may also indicate a perinatal lesion of the CNS.

Though the study of each individual cranial nerve is important, it is the investigation of feeding activity and nutritive behaviour which supplies information about the correlation of the nerves which take part in it. The trigeminal nerve acts as the trigger of the feeding reaction and coordinated response movements are mediated through the cranial nerves VII, IX, X and XII. The integrity of coordination between sucking, swallowing and breathing reveals any deficiencies in the nerves which execute these functions. This may be studied by observing breast or bottle feeding. If some defect in the feeding process is suspected, analysis of the feeding behaviour is necessary by polygraphy with simultaneous recording of the orofacial EMG, ECG, breathing, intrabuccal pressure (sucking), intrapharyngeal and intraoesophageal pressure (swallowing). The investigation occasionally detects defective sucking with good swallowing. This is usually due to an impaired coordination in consequence of a cerebral lesion at the supranuclear level over the brain stem. The absence of sucking activity can be a consequence of lesions in the brain stem. To analyse this problem, further investigations are needed. First a measurement of the threshold of the palatopharyngeal muscles to direct electric stimulation should be done. The stimulation of various trigger points in the soft palate and the upper constrictor muscle of the pharynx may reveal a high threshold or the absence of any reaction. In these cases mild or severe defects in the brain stem can be suspected. In the first case direct electrotherapy of the palatopharyngeal muscles followed by intensive feeding trainings is the method of choice. In the latter case no help is available [8, 9].

Sucking can be studied separately by polygraphy. In this case simultaneous EEG recordings should be taken together with orofacial EMG and intrabuccal electromanometry. Exteroceptive light and sound stimulation may reveal the state of consciousness of the infant as well as its orientation towards stimuli. This in turn informs about the plasticity of feeding behaviour.

Early diagnosis of neurological feeding defects is important because such defects may affect the condition of the infant and its future. For instance, the infant's condition can be affected by lung infections while his future by the danger of handicapping the development of speach. The therapies required to combat these factors will beneficially influence the development of vocalization.

### *ODP V. Guide to defects of the cranial nerves II, III, IV, VI, and their central organisation, with special regard to early visual behaviour*

Visual behaviour in the neonate and in the young infant can be studied

by both simple and sophisticated methods. The detection of visual impairment is of paramount importance because the young infant develops contact with the mother, her face, figure and movements partly through the visual system. Defective vision impairs this contact and may lead later to a prolonged defective development of the visuomotor process.

This indicates the necessity of an intensive examination of the visual system. The neonate and the young infant usually turn towards the light. The pupillary reflex may be slow and prolonged in the newborn. Sudden stimulus with bright light activates the startling reaction. In problematic cases this may be analysed by EEG and the activated brain stem potentials.

Vision can be studied effectively by activating rotatory nystagmus, by a rotating striped disk. Fundoscopy may reveal defects in the lens and related structures as well as in the fundi where haemorrhages, retinal defects, malformations can be seen.

The function of the eye muscles is equally important. Brain injuries frequently impair the activity of one or more nerves innervating the eye muscles. Investigations of the doll's eye phenomenon, placement of the infant in upright position and other methods serve to detect defects in the innervation of eye muscles. Detailed analysis of visual behaviour can be performed by the aid of polygraphy. Visual attention and behaviour of the neonate and the young infant can be analysed during an active process such as feeding.

Visual stimulation during feeding usually arrest the feeding process because the stimulus activates orientation and the young infant cannot handle two problems simultaneously. Thus, visual attention can be studied appropriately. Prolonged stimulation produces habituation. The infant first follows the flickering light with closing and opening the eyelids, later closes the eyes and remains quiet during the stimulation. When the stimulation terminates the infant continues to suck. A detailed polygraphic study together with other neuroophthalmologic examinations offers a sound basis to establish an opinion concerning the integrity of the visual system.

In the case of visual impairment due to optic defects or improper eye muscle coordination, visual attention will fail and therapeutic and rehabilitative procedures are needed [4].

*ODP VI. Guide to defects of the cochlear portion of cranial nerve VIII and its central organization controlling early auditive behaviour*

The auditive system of the fetus is responsive to external noises from the 25th—26th gestational week. Hence, the neonate responds well to auditive stimuli. It is imperative to investigate auditive functions in each neonate as early as possible. Impaired auditory function endangers the contact with the environment through this important sensory channel and handicaps the development of speech.

This is the reason why a thorough audiological investigation is necessary in all neonates and young infants.

The auditive behaviour of the young infant is characteristic. The cochleopalpebral reflex must be activated to observe primitive reactions to auditive stimuli. Auditory stimulus according to its intensity produces arousal reaction in the infant; this can be verified by EEG or activated potential analysis. Stronger stimuli activate the startling reaction in its various forms. Active orientation towards auditory stimuli is reflected by intensive movements or their arrest. The effect of the auditory stimulus depends partly on its nature and partly on the condition of the infant before stimulation. If the neonate was in a quiet state of behaviour the reaction is a startling reflex. On the contrary, if the infant was restless or crying, the most probable reaction will be a sudden quietness and reduction of movements. Both responses reflect the integrity of the auditory system. The responses reveal the existence of orientative behaviour toward auditive stimuli.

It is important to distinguish between peripheral and central auditory impairment. The latter is the consequence of brain injury. Its most important representation is the failure of auditive attention. While subjective audiometric studies can define in many cases the nature of the defect, special investigations will be necessary to detect an impaired attention to auditive stimuli. Polygraphic examination of the infant in a state of activity, for example during feeding, can give information in this direction. EEG, EMG of the extremities, ECG, and sucking must be recorded simultaneously. During the feeding process programmed stimulations with various sounds can be undertaken. The nature of the changing behaviour of the infant must be analysed. The normal reaction to the first sound is orientation. If the same initial sound is repeated regularly for a longer time, inhibition occurs and the attentive orientation diminishes. This reaction may supply information on the attentive processes of the brain. Inhibited attention, habituation, is a predisposing function to a novel orientation. This can be observed if some characteristic component of the stimulus is changed. A new frequency of sound serves again as a stimulus to activate orientation.

This and other examinations such as electroencephalography evoked brain stem potential audiometry etc. are necessary to detect an impairment of the auditory system and to introduce early therapy and rehabilitative training [10, 11].

### *ODP VII. Guide to the development of sensorimotor functions and the defects of muscle tonus proportion, motor dynamics and elementary posture*

The motor function of the neonate and the young infant consists of seemingly haphazard movements.

These, however, are only fragments of complicated stereotype elementary motor patterns. The blueprints of

elementary motor patterns can be activated by stimulation of the vestibulo-cerebello-reticular system and various proprioceptors in the extremities. Positioning the infant according to various patterns activates stereotype series of movements of the extremities and the muscles of the spinal column. Chain-reactions develop, such as elementary crawling, sitting, walking and other motor activities.

The defects of motor function may produce a great variety of symptoms. Generalized hypotonicity may develop, giving place later to hypertonicity and extensive spasticity. Latent hemiparesis may occur, masked by a relative immobility of the infant and becoming manifest later when spontaneous movements begin. Neck muscle defects may give rise to forced positions of the head, for example in the lateral direction. This in turn inhibits the maturation of rotatory functions of the trunk, orientation of the head, and the free activity of the upper arm. Hypotonicity of the neck muscles inhibits elevation of the head and handicaps the development of erect posture. In many cases some important muscle groups are hypotonic (neck and spine) while others produce hypertonicity of the extremities. Neither the myotactic reflexes nor spontaneous movements give sufficient information on the nature and place of the defect. Passive movements of the extremities are of no help. Elementary motor patterns, however, contain ample information because of the manifold movements produced by the stimulus-activated nervous system itself. The activating function of the midbrain and the brain stem, the integrating function of the spinal cord can well be analysed by activating the most important elementary patterns.

Early detection of motor defects is important for the sake of early habilitation and rehabilitation [1, 2, 7, 14].

*ODP VIII. Guide to defects in the development of sleep, alertness, orientation and general behaviour*

ODP VIII follows the main gradients of behavioural maturation with special regard to the development of affections, emotions and attention. This ODP reflects important steps in the normal and abnormal development of sleeping and awake behaviour spontaneous and activated attention, contact readiness, infant-mother, mother-infant relation, tendencies to preference, longing, activity and withdrawal. Developing trends in the formation of personality are intimately connected with the maturation of learning, socialisation, and communication. These human faculties are treated in ODP IX. ODPs VIII and IX contain many items of various well-known tests as the Bayley Scales of Infant Development, the Cattell Infant Intelligence Scale, the Denver Developmental Screening Test, the Gesell Developmental Schedules and others. These ODPs, however, differ in several items from all known tests.

The study of sleeping behaviour must include an analysis of the quan-

tity and quality of sleep, the duration of diurnal and nocturnal sleep. The rhythm of sleep, the nature how the infant falls asleep are all important facts. So are the behavioural patterns during the waking state. The level of spontaneous activity must be observed, symptoms such as restlessness, hypermotility, deprivation symptoms including deprivational movements, the motility patterns during alertness are all basic informations.

Signalization towards the environment is beginning at birth. Vocal signalization and signalization with facial muscles and movements should be noted and studied. These are often significant behavioural patterns to activate contact with the environment, principally with the mother. In this respect the number of signals towards the mother, the nature of the contact, the number of daily interactions are all important. When the general behaviour or mental development of the infant is investigated, a study must be dedicated to the activity of the mother and the environment towards the infant. The nature and number of contacts between the environment and the infant should be regarded as bio-social feedbacks acting on the development of social patterns in the baby's behaviour.

The level of socialization is mirrored in the development of feeding behaviour, dressing, maturation of self-reliance, manifestations of will, tolerance of frustrations, emotional maturation. All these can be studied on the manifestation of various acts reflecting the baby's adaptation to social conditions, for example urinary and rectal continence.

The behaviour of the young child among other children, in children's communities, etc., offers data to the physician and psychologist how to act when irregular behaviour is suspected and therapy is considered.

The physician must be aware of the family's relation to the maturing infant. This is especially important if the infant is sick and active aid is required from the family. The mother as the principal person in habilitation including the execution of various sensory and motor trainings, plays the main part in this aid. The physician has to know how the family reacts to the infant's disease, what aid is given to the infant and how the prescribed therapy and habilitative procedures are performed. The control of the baby's maturing behaviour with all its ever multiplying patterns needs a close and good contact between the physician or psychologist and the family.

### *ODP IX. Guide to defects in early mental activity and development of mental faculties, communication and social adaptation*

ODP IX reflects outlines of the maturation of memory, cognition, learning and communication. The development of metacommunication, verbal communication, with the possible main abnormalities during their evolution are stressed. Emerging defects in reasoning, understanding,

interpretation of objects, situations are described in the guide. As mentioned before, the last two ODPs interpret the close correlation in the development of human behaviour, intelligence, learning and adaptive social activities.

The diagnostic approaches in this plan are concentrated on the development of attention, exploration, the maturity of interpretation and studying, the development of conceptual faculties and the utilization of comprehension in daily life. This diagnostic approach begins in early infancy. The readiness of attention and attentive reactions such as orientation, habituation and dyshabituation can be studied as well as in the later months the stability of attention in various situations. Evoked potential and polygraphic studies may inform the physician how the infant proceeds in handling more and more external stimuli simultaneously. Preference behaviour the development of attentive behaviour can be analysed and used to consider possible anomalies.

In the later stages of development, exploration activity of the infant is very informative. The exploration of objects, situations, of the environment and space are important steps in development. All these signs of growing intelligence are deeply connected to the maturation of character. Comprehension and behaviour are inseparable factors mutually influencing each other. Affective behaviour is reflected in utilization of comprehension, for example in problem-solving during play or activity transfer.

The development of conceptual behaviour can be studied by conditioning by non-verbal stimuli and by estimation of the grade of transferability. The comprehension of suggestion or instructions and the capability to express affects, needs, requirements are mile-stones in the development of mental faculties.

The maturation of attentive behaviour is deeply connected to the ability of studying. The comprehension of a task, problem-solving is based on vigility, the stability of attentive behaviour and an inborn need to face and solve situations. Short and long memory can be studied by objective methods as well as the need to stabilize the above mentioned processes with other stimuli. The maturity of verbalization is naturally important in the development of study and comprehension.

The development of special patterns (gradients) influencing comprehension and studying are significant factors of the maturing human conceptual behaviour. The development of visual-motor patterns is especially useful to the physician for discovering early aberrations. One of the first signs of comprehension, problem-solving and attention are object handling and related patterns.

In order to be able to detect anomalies of the development of the mental faculties, the physician must often rely on the family. Data on the developing comprehensiveness and intelligence of the young child must partly be based on family assumptions. The physician must carefully

compair his own observations with the informations received from the family to estimate an eventual abnormality and to indicate further investigations and treatment.

## Discussion

The basic approach to the problem of early diagnosis, prognosis and early therapy as well as habilitation in cases of pre- and perinatal brain injury must be based on thorough neurological studies and close longitudinal control. Early treatment and early habilitation should only be indicated on the basis of a series of detailed neurological examinations. The treatment must concentrate on the source of the discovered neurological defect [17, 18, 20].

Adequate ante- and perinatal care has decreased the danger of brain damage during fetal or infantile age. Neonatal departments feel that nowadays the danger of brain damage is minimal. Rehabilitation centres, paedagogic institutions do not, however, share readily this kind of optimistic view.

The maturing CNS fulfils two basic functions, 1) the direction and control of daily life; 2) the direction and control of its own maturation processes. The first function may be controlled well by modern neonatology even in acute situations. This, however, does not automatically mean that it can always normalize the second function, too.

The 9 ODPs together produce a complete guide: the comprehensive Fast Orienting Diagnostic System. The aim was the illustration of the main interdependent, correlated ontogenetic gradients of the human nervous system, together with normal variations and pathologic alterations. The close interdependence of the 9 ODPs reflects the necessity to investigate the whole patient instead of suspicious symptoms. In all ODPs time was represented as an essential factor in normal and abnormal brain maturation. The initial brain injury (illustrated mainly in ODP I) produces subsequent brain lesions (illustrated in the other ODPs) which create, during time correlated brain maturation various pathological symptoms. There is much to learn about the natural history of cerebral palsy, the development of its partly uniform, partly individual symptomatology. The Fast Orienting Diagnostic System may help to accumulate more data on the correlation of the developing pathological symptoms for early diagnosis, and to objectivate the control of therapeutic and rehabilitative effects.

## Acknowledgement

I am greatly indebted to Dr T. Vámos, Institute of Automation, Hungarian Academy of Sciences, for help and fruitful suggestions.

## References

1. André-Thomas, Saint-Anne Dargassies S.: Études neurologiques sur le nouveau-né et le jeune nourrisson. Masson, Paris 1952
2. Cahuzac M: L'enfant infirme moteur d'origine cérébral. Masson, Paris 1980

3. Calame A, Reymond-Goni I, Maherzi M, Roulet M, Marchand C, Prod'hom LS.: Physiological and neurodevelopmental outcome of high risk newborn infants. Helv Paediatr Acta 31: 287, 1976
4. Cohen LB: Habituation of infant visual attention. In: Tighe TJ (ed.): Lawrence Earlbaum Publishers, Hillsdale, N. J. 1976, pp. 207—238
5. Dubowitz L, Dubowitz V: The Neurologic Assessment of the Preterm and Full-term Newborn Infant. Heinemann, London 1981
6. Hall D: Neonatal neurology. In: Paediatric Neurology, ed. Clifford, Rose F, Blackwell, Oxford 1979
7. Illingworth RS: The development of the infant and young child, normal and abnormal. Churchill Livingstone, London 1970
8. Ingram TTS: Clinical significance of the infantile feeding reflexes. Dev Med Child Neurol 4: 159, 1962
9. Katona F: Neue Methoden in der Säuglingsneurologie und Rehabilitation. Acta Paediatr Acad Sci Hung 15: 67, 1974
10. Katona F: Manual de prevencion y diagnostico precóz de los danos cerebrales. IAMER, Madrid 1982
11. Katona F, Berényi M: Differential reactions and habituation to acoustical and visual stimuli in neonates. Activ Nerv Sup 16: 435, 1974
12. Kostyuk PG: Supraspinal mechanism on spinal level. In: The motor system: neurophysiology and muscle mechanism (Shahani B ed) Elsevier, Amsterdam 1975, pp. 211—234
13. Menkes JH: Textbook of child neurology. Lea and Febiger, Philadelphia 1980
14. Peiper A: Die Eigenart der kindlichen Hirntätigkeit. Thieme, Leipzig 1956
15. Prechtl FRH, Beintema DJ: Die neurologische Untersuchung des reifen Neugeborenen. Georg Thieme, Stuttgart 1976
16. Saint-Anne Dargassies S.: La développement neurologique du nouveau-né a terme et prématuré. Masson, Paris 1974
17. Scherzer AL, Tscharnuter I: Early Diagnosis and Therapy in Cerebral Palsy Marcel Dekker, New York 1982
18. Shortliffe EH: Computer based medical consultations: MYCIN, Elsevier 1976
19. Szolovits P, Pauker SG: Categorical and probabilistic reasoning in medical diagnosis. Artif Intell 11: 115, 1978
20. Thom H: Die infantilen Zerebralparesen. Georg Thieme, Stuttgart 1982
21. Usher RH: Clinical implications of perinatal mortality statistics. Clin Obstet Gynec 14:885, 1971

*Received 27 March 1983*

F Katona MD
Mártonhegyi út 6.
1121 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 315—321 (1983)*

# A new acoustic method for the discrimination of monozygotic and dizygotic twins

G Forrai, G Gordos

District 14 Policlinic for Children, and Institute for Telecommunication Electronics, Polytechnical University, Budapest, Hungary

The close similarity of the voices of consanguineous persons has suggested that there must exist hereditary phonetic parameters. To test this hypothesis, a method for characterizing numerically the similarity or dissimilarity of voices of twins with zygosity previously established by anthropological methods was elaborated. By speech processing and appropriate classification strategy the method has attained the discriminating power of blood-group determination for zygosity. The hereditability of certain physical parameters of the human voice has also been suggested.

Comparison of concordance and discordance for a trait or disease between monozygotic resp. dizygotic twins is a widespread method in human genetic research aiming at the degree of heritability of the trait in question. If concordance within monozygotic twins significantly exceeds that observed in dizygotic twins of the same gender, it may be anticipated that the condition is more under genetic than environmental control.

Therefore, discrimination between monozygous and dizygous twins is of great importance. It can be carried out by morphological examination of the placenta at birth; this method is, however, not practicable with twins of adult age or when data concerning the placenta are no more available. Beside a series of anthropological tests, extensive blood-group determinations are most wide-spread. In zygosity studies, a like-sexed pair of twins is a priori regarded as monozygous as long as any difference in an inherited blood-group trait has not been found. The discriminative power of the method can be increased by using blood-groups as many as possible. Absolute safety in exclusion of dizygosity cannot be achieved. This and the large quantity of blood necessary for extensive blood-group studies lend importance to research into painless methods that can replace blood-group determinations or further increase their discriminating power.

It is well-known that the voice of closely related persons is often confounded, especially over the telephone where the individual nuances are partly lost. This has prompted us to conceive the idea that some parameters of human voice are genetically determined and, if so, monozygous

twins have a higher intra-pair similarity of voice than dizygous like-sexed twins. If this similarity can be quantified and made measurable, a new acoustic method can be elaborated. The hypothesis can be tested by applying the voice-based method to twins whose zygosity has been established by detailed blood-group analysis.

The blood-group studies utilized three erythrocyte membrane systems (ABO system: $A_1$, $A_2$, B, O, $A_1B$, $A_2B$ phenotypes; MN system: M, MN, N phenotypes; Rh system: C, $C^n$, c, D, E, e factors) and two serum protein systems ($H_p$ system: $H_p$ 1–1, 2–1 and 2–2 types; Gm system: Gm/1/factor).

## Materials and Methods

Some years ago an extensive twin study was carried out jointly by ourselves and the Institute of Anthropology, Eötvös Loránd University, Budapest. Within this work the voices of both members of 117 like-sexed adult twin-pairs reading the same text of about one minute duration were recorded (by B. Lubi) on tape.

For zygosity discrimination the methods of speech recognition and speaker identification by machine had to be further developed [2]. All these methods consist of two steps: feature extraction followed by classification. In feature extraction appropriately selected details of the spoken text are characterized numerically. Pitch is one of such numerically characterizable features.

Before describing the traits examined in this study some general comments have to be offered. Feature extraction of speech characteristics is performed all over the world by computerized electronic signal processing. For our present study, however, characteristics that can be measured by autonomous devices of low intelligence and the measurement of which can readily be automated had to be chosen.

Here we give a list of characteristics along with their numerical parameters considered in our study.

An obvious physical trait is pitch (fundamental frequency). Since it is not an absolute characteristic feature of the speaking person but is modulated by the content of speech, word stress, phase of respiration, etc., the mean value of the pitch and its mathematical standard deviation were used as parameters. The degree of "signing", reflected by the standard deviation of the pitch, characterizes a person rather reliably.

The so-called formant frequencies are characteristics widely used in phonetics. Formants arise when tenable voiced sounds (all vocals and the consonants l, m and n) are formed. The air current leaving the lungs and interrupted by the vocal cords at the rate of the fundamental frequency passes the pharyngeal, oral and eventually the nasal cavities and the elements separating them and its spectrum shows characteristic maxima when entering the environmental air. The formant frequencies are defined by these maxima. In our study, each three formants of the vocals "a" and "e" were measured and averaged over their occurrences during the one minute reading.

The so-called plosive consonant transition times [3] were also investigated in the study. The phonation of voiceless burst consonants (e.g. "k") is always followed by a silent interval lasting for some 10 msec only thereafter can the subsequent sound be formed. Research aimed at the identification of anonymous phone callers revealed that this interval, the plosive consonant transition time, is characteristic of the individual. It is determined by the anatomical and physiological properties of the individual by which he or she restores the air pressure having dropped at burst-

ing. For our study, investigation and measurement of the transition time following all word-initial "k" sounds were chosen. Their mean value was calculated for each individual.

Further five parameters are based on the spectral analysis of the so-called monochorus [4, 7]. The monochorus is the electronic addition of a large number of speach segments of the same length but of different content, of the same speaker. In our study, about 5000 segments, each of 50 msec duration, were copied one on top of the other, by a computer. The concept of monochorus was initially based on the subsequently confirmed hypothesis that in the monochorus accidental events (faltering of voice, malphonations, etc.) are mutually extinguished but the stable characteristics are reinforced. The monochorus was subjected to computerized spectral analysis. In the spectrum we detected two hardly distinct peaks, we named these double peaks. It was also observed that at frequencies lower than that of the double peak there is only one further peak while at higher frequencies than that of the double peak there are several. From these latter, only the peak adjacent to the double peak was taken into consideration. We found that the frequencies of the first peak, of both peaks of the double peak, of the peak of the envelope fitted over the double peak and of the third peak are fairly characteristic of the speaking individual.

Thus, a maximum of fourteen parameters were taken into consideration to characterize each individual. It has to be stressed that devices directly measuring these parameters are not available on the market. The most used device in speech analysis is the computer supplemented by an electronic gear capable of storing the speech to be analysed, of carrying out operations and mathematical transformations and of visualizing curves or diagrams derived from the analysed data. The desired operations and mathematical transformations have to be fed into the computer as programmes. Most of our investigations and programme developments were carried out in a computer type PDP 11/40 of Digital Equipment Co., USA [2].

No automatic methods are known which would yield all the parameters listed above. In other words, the computer sometimes stops "hesitantly" and one has to have the programme proceeded by making a decision. Most parameters were determined by such interactive operations. The success of our fully automatic procedure to determine the pitch and the plosive consonant transition time, developed at the Institute of Telecommunication Electronics, Polytechnical University, Budapest, and experience described in the literature give hope that appropriately constructed small devices with a microprocessor small as a heart may make larger computers dispensible, at least in zygosity determination of twins.

Since the measurements of the fundamental frequency and the explosive consonant transition could fully be automated, these parameters were determined for all the 177 twin-pairs participating in the study. The total of all fourteen parameters has been calculated up to now for 16 twin-pairs.

It has to be noted that in addition to these parameters put forward by the general practice of computer processing of speech and by our own experience gathered during this study, several other parameters could be investigated with equal chance for success. The number of parameters is the resultant of two opposed points of view: too many parameters lead to superfluous prolongation of the analytical work. On the other hand, too few parameters may make the result uncertain, by being exposed too much to intra-individual variability caused by incidental events like acute airway disease of the individual or other causes. One of our intentions was to determine the minimum number of parameters necessary for a safe zygosity discrimination.

Having obtained the parameters,we could turn to the classification of the twin-pairs. For this purpose, discriminance analysis and learning algorhythm based on the nearest neighbour principle seemed most appropriate. The procedure needs a complicated mathematical apparatus but it is generally applied and has been described [5, 6]. Therefore, here we restrict ourselves to the most essential steps. Initially all twin-pairs are represented by a set of figures (in mathematical terms: a vector) representing intra-pair differences in terms of the differences of the two individual values of each parameter, e.g. the difference in fundamental frequencies, the difference of standard derivations of the fundamental frequencies, etc. Thereafter each member of this set is multiplied by a member of a set of so-called weighing figures. If the sum of the resulting set of figures is lower than a certain threshold value, this speaks for monozygosity while the opposite case for dizygosity. The elements of the weighing set and the threshold value are determined automatically by the procedure itself. To obtain this, for a sufficient number of twin-pairs not only the characteristic parameters but also the zygosity classification attained by any independent method have to be fed into the computer. From these data the computer so to say learns the weighing set and the threshold value necessary for the right decision, hence the term learning algorhythm.

Finally, the expenses of the acoustic method involving voice recording, computer feeding and calculation time are considerably lower than those of blood-grouping if the expenses of blood sampling and storing, the price of chemicals and devices are taken into consideration.

## Results

Tables I and II illustrate the results obtained in 49 male and 68 female twin-pairs for a single parameter, the intrapair difference of the averages of the fundamental frequencies. Next to these data the result of zygosity

Table I

Intra-pair differences of average fundamental frequencies ($\Delta$F) and zygosity diagnosis based on blood-group determination (Z) in 49 male twin-pairs

| $\Delta$F (Hertz) | Z | $\Delta$F (Hertz) | Z |
|---|---|---|---|
| 0.8 | MZ | 7.9 | MZ |
| 1.1 | MZ | 8 | DZ |
| 1.1 | DZ | 8.2 | DZ |
| 1.2 | MZ | 8.3 | MZ |
| 1.5 | MZ | 8.6 | DZ |
| 1.6 | MZ | 11 | DZ |
| 1.9 | MZ | 11.9 | DZ |
| 1.9 | MZ | 12 | DZ |
| 2 | MZ | 12 | MZ |
| 2.1 | MZ | 14.5 | DZ |
| 2.1 | MZ | 16.6 | DZ |
| 3.1 | MZ | 18 | MZ |
| 3.2 | DZ | 21.6 | DZ |
| 3.4 | MZ | 23.4 | DZ |
| 4.1 | MZ | 23.7 | MZ |
| 4.1 | MZ | 23.8 | DZ |
| 4.5 | MZ | 27.9 | MZ |
| 4.6 | MZ | 30.5 | DZ |
| 5.1 | MZ | 33.5 | MZ |
| 5.7 | MZ | 33.7 | MZ |
| 5.7 | DZ | 38.9 | DZ |
| 5.9 | DZ | 39.1 | DZ |
| 6 | DZ | 52.3 | MZ |
| 6.5 | MZ | 59 | MZ |
| 6.7 | DZ | | |

TABLE II

Intra-pair differences of average fundamental frequencies (ΔF) and zygosity diagnosis based on blodd-group determination (Z) in 68 female twin-pairs

| ΔF (Hertz) | Z | ΔF (Hertz) | Z |
|---|---|---|---|
| 0 | MZ | 12.3 | MZ |
| 0 | MZ | 13 | DZ |
| 0 | MZ | 13.1 | DZ |
| 1.3 | MZ | 14.3 | MZ |
| 2.1 | MZ | 14.7 | DZ |
| 3.6 | MZ | 16.6 | DZ |
| 3.7 | MZ | 16.7 | MZ |
| 3.9 | MZ | 17.4 | DZ |
| 4.1 | MZ | 17.9 | MZ |
| 4.4 | MZ | 18 | DZ |
| 4.7 | MZ | 18.9 | DZ |
| 4.8 | MZ | 19.1 | DZ |
| 4.9 | MZ | 19.2 | DZ |
| 6.1 | MZ | 19.4 | MZ |
| 6.7 | MZ | 19.5 | DZ |
| 7.6 | MZ | 19.6 | MZ |
| 8.1 | MZ | 19.6 | DZ |
| 8.1 | MZ | 19.7 | MZ |
| 9.1 | MZ | 20.5 | MZ |
| 9.5 | MZ | 20.5 | DZ |
| 10 | MZ | 23.1 | DZ |
| 10 | MZ | 25 | MZ |
| 10.1 | DZ | 30.7 | DZ |
| 10.2 | MZ | 30.9 | DZ |
| 10.2 | DZ | 31.2 | DZ |
| 10.9 | MZ | 31.9 | DZ |
| 11.4 | DZ | 32.4 | MZ |
| 11.5 | DZ | 34.9 | DZ |
| 11.6 | DZ | 35.6 | DZ |
| 11.9 | DZ | 38.2 | MZ |
| 12 | MZ | 45.6 | MZ |
| 12 | MZ | 50 | MZ |
| 12 | MZ | 51.3 | DZ |
| 12.2 | MZ | 58.6 | DZ |

classification (monozygotic: MZ, dizygotic: DZ) obtained by previous bloodgrouping is indicated. In case of complete concordance of the two methods the designation MZ should be replaced by DZ at a certain point if the data are placed in the order of increasing intra-pair differences. Since this is not the case and only a trend like that can be seen, it may be concluded that this single parameter is not capable of complete discrimination.

If all 14 parameters are available as in the case of the twin-pairs whose results are illustrated in Table III, there is perfect fit between the zygosity diagnoses obtained independently by the phonetic and the bloodgrouping method. These data formed the input programme fed to the computer. One of the characteristics of the internal operation of this programme is that by a learning algorithm the parameters exert their effect through different weights. Thereby, the jumble of data, perfectly confusing for the human eye, becomes classifiable for the computer.

The next tasks in the development of the study are increasing the number of fully evaluated twin-pairs, from sixteen on one side, and decreasing the number of parameters from fourteen as well as further automatization of the determination of parameters on the other side. Further, there is hope that refined definitions of measurable parameters characteristic of the heritability of human voice may clarify various medical and biological problems.

TABLE III

Parameters of individuals of 16 twin-pairs investigated in terms of fourteen parameters. a twin-pair. Parameter No. IX is

| Serial number of twin-pairs | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Fundamental frequency, | 243.9 | 180 | 227 | 222 | 229 | 177 |
| expected value, I | 227.3 | 198 | 196 | 235 | 179 | 187 |
| Fundamental frequency, | 27.1 | 47 | 17 | 25 | 54 | 19 |
| standard derivation, II | 26.2 | 15 | 24 | 43 | 12 | 12 |
| First formant of "a", | 747.5 | 989 | 703 | 754 | 772 | 797 |
| expected value, III | 767.0 | 929 | 814 | 787 | 707 | 736 |
| Second formant of "a", | 1495.0 | 1339 | 1476 | 1514 | 1467 | 1363 |
| expected value, IV | 1319.5 | 1486 | 1436 | 1495 | 1414 | 1315 |
| Third formant of "a", | 2002 | 2217 | 2179 | 2002 | 2007 | 2115 |
| expected value, V | 2223 | 2352 | 2030 | 2204 | 2070 | 2104 |
| First formant of "e", | 253,5 | 301 | 355 | 292 | 331 | 276 |
| expected value, VI | 526.5 | 365 | 275 | 326 | 451 | 268 |
| Second formant of "e", | 2463.5 | 2054 | 2062 | 2008 | 1984 | 2116 |
| expected value, VII | 2099.5 | 1901 | 1983 | 2040 | 2193 | 2106 |
| Third formant of "e", | 2892 | 2806 | 2915 | 2528 | 2810 | 2990 |
| expected value, VIII | 2626 | 2778 | 2623 | 2611 | 2580 | 2758 |
| Mean of transition time | 28 | 24.0 | 25.0 | 29 | 38.0 | 26.7 |
| in "k", IX | 21.7 | 21.3 | 29.7 | 37 | 28.3 | 23.3 |
| First peak of monochorus, X | 255 | 210 | 245 | 230 | 220 | 200 |
| | 245 | 290 | 220 | 245 | 185 | 200 |
| First peak of the double peak | 420 | 325 | 485 | 445 | 385 | 415 |
| of monochorus, XI | 440 | 470 | 400 | 465 | 335 | 390 |
| Peak of the envelope of the | 445 | 355 | 510 | 480 | 430 | 515 |
| double peak of monochorus, | 475 | 480 | 440 | 480 | 390 | 510 |
| XII | | | | | | |
| Second peak of the double peak | 465 | 370 | 565 | 495 | 450 | 650 |
| of monochorus, XIII | 490 | 520 | 490 | 515 | 415 | 595 |
| Third peak of monochorus, | 710 | 580 | 715 | 740 | 640 | 740 |
| XIV | 745 | 640 | 645 | 730 | 565 | 760 |
| Sex | ♀ | ♀ | ♀ | ♀ | ♀ | ♀ |
| Zygosity, based on blood-group | | | | | | |
| determinations | DZ | DZ | DZ | DZ | DZ | MZ |

Upper and lower entries in a box represent parameters of one and the other member of measured in msec, the rest in Hertz

| 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|
| 202 | 263 | 131 | 141 | 102 | 138 | 126 | 112 | 117 | 131 |
| 206 | 256 | 101 | 153 | 114 | 123 | 175 | 110 | 115 | 133 |
| 23 | 17 | 28 | 55 | 11.3 | 14.7 | 5.1 | 19 | 21 | 4.4 |
| 14 | 8.2 | 7 | 15 | 11.3 | 25.6 | 7.2 | 33 | 38 | 6.1 |
| 889 | 924 | 1001 | 720 | 715 | 702 | 728 | 1124 | 721 | 806 |
| 809 | 745 | 1079 | 1092 | 910 | 1079 | 734 | 741 | 1118 | 897 |
| 1368 | 1493 | 1495 | 1441 | 1573 | 1495 | 1482 | 1306 | 1307 | 1385 |
| 1306 | 1330 | 1313 | 1306 | 1365 | 1345 | 1475 | 1534 | 1391 | 1560 |
| 2120 | 2062 | 2002 | 2423 | 2483 | 2288 | 2327 | 2106 | 2190 | 2496 |
| 2301 | 2234 | 2015 | 2398 | 2483 | 2418 | 2392 | 2626 | 2112 | 2340 |
| 354 | 369 | 286 | 422 | 357 | 312 | 416 | 409 | 520 | 293 |
| 308 | 355 | 539 | 370 | 442 | 286 | 455 | 267 | 429 | 351 |
| 1951 | 1954 | 2047 | 2039 | 2353 | 2164 | 2210 | 1930 | 1904 | 1989 |
| 2032 | 2217 | 1904 | 2080 | 1995 | 1989 | 1976 | 2230 | 2392 | 2333 |
| 3015 | 2640 | 2632 | 2531 | 2912 | 2652 | 2762 | 2743 | 2912 | 2737 |
| 2772 | 2749 | 2528 | 2821 | 2730 | 2600 | 2522 | 2782 | 2525 | 2990 |
| 18.4 | 19.0 | 22.4 | 5.2 | 22.3 | 19.2 | 16 | 14 | 8.7 | 34.5 |
| 21.3 | 19.7 | 35.6 | 11.2 | 34.0 | 26.4 | 17 | 24 | 13.5 | 36.0 |
| 240 | 245 | 145 | 155 | 205 | 270 | 240 | 235 | 225 | 275 |
| 245 | 260 | 220 | 145 | 225 | 145 | 210 | 225 | 245 | 270 |
| 415 | 495 | 270 | 410 | 315 | 395 | 350 | 345 | 395 | 395 |
| 420 | 495 | 325 | 295 | 320 | 245 | 330 | 320 | 415 | 345 |
| 480 | 510 | 305 | 435 | 370 | 420 | 400 | 390 | 445 | 490 |
| 470 | 510 | 385 | 325 | 390 | 290 | 410 | 395 | 445 | 380 |
| 565 | 615 | 340 | 470 | 395 | 465 | 465 | 415 | 510 | 540 |
| 565 | 535 | 470 | 345 | 445 | 370 | 490 | 460 | 510 | 440 |
| 810 | 730 | 490 | 638 | 630 | 640 | 590 | 540 | 610 | 640 |
| 685 | 740 | 570 | 490 | 540 | 535 | 590 | 535 | 585 | 615 |
| ♀ | ♀ | ♂ | ♂ | ♂ | ♂ | ♂ | ♂ | ♂ | ♂ |
| MZ | MZ | DZ | DZ | DZ | DZ | MZ | MZ | MZ | MZ |

## Acknowledgements

In the elaboration of some details of feature extraction and classification much help was furnished by several students of the Polytechnical University, Budapest, especially by Mr. Z. Kormány and Mr. S. Dankó.

## References

1. Andrews HC: Introduction to mathematical techniques in pattern recognition, John Wiley, New York 1972, p 242
2. Dunn HK, White SP: Statistical measurements on conversational speech. J Acous Soc Am 11:278, 1940
3. Gordos G: Recent results in speech processing. Period Polytechn, 24:243, 1980
4. Gordos G: An interactive speech analysis system and its application to the diagnosis of twin-zygosity. Proc Symposium on Speech Acoustics, Budapest 1980, Pp 45
5. Nilsson NJ: Learning machines, McGraw Hill, New York 1965, p 137
6. Takács Gy: Personal communication
7. Tarnóczy T, Radnai J: Eine Möglichkeit automatischer Erkennung von Vokalen. Proc VII. International Congress on Acoustics, Vol 3, Budapest 1971. Pp 61—64

*Received 9 February 1983*

G Forrai MD
Alig u 5
H-1132 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 323—326 (1983)*

# HLA phenotypes in children with Duchenne muscular dystrophy and their gene carrier mothers

Aranka LÁSZLÓ, Gabriella KAISER

Department of Pediatrics, and Blood Transfusion Centre, University Medical School, Szeged, Hungary

Typing of HLA A, B and C locus antigens was carried out and the frequency distribution calculated in 32 hemizygous children affected by DMD, in 11 mothers who were either obligatory gene carriers or had increased CPK activity, and in 222 healthy blood donors. For typing peripheral blood lymphocytes and the standard NIH lymphocytotoxicity test were used. The HLA-B7 antigen had a tendency to be more frequent, being 31% in the group of hemizygous children with DMD as against 13.5% in the control group ($p < 0.04$). In the gene carrier mothers the frequency of HLA–B7 was 36% ($p < 0.12$). In the group of DMD hemizygotes the HLA–Aw24 antigen showed a tendency to higher frequency ($p < 0.05$).

The association between various pathological conditions and the HLA antigens has been the subject of intensive study in the last ten years. We only refer here to the HLA and Disease Registry by Ryder et al. [1] Neither this international register nor the recent literature contain data

TABLE I

Distribution of HLA-antigens in DMD-hemizygotes

| HLA–A antigens | DMD (n=29) HLA–A antigen positivity | | Controls (n=222) HLA–A antigen positivity | | $\chi^2$ | p |
|---|---|---|---|---|---|---|
| | No. | per cent | No. | per cent | | |
| 1 | 4/29 | 13.8 | 49/222 | 22.1 | 0.62 | 0.44 |
| 2 | 13/29 | 43.8 | 110/222 | 49.5 | 0.08 | 0.98 |
| 3 | 10/29 | 34.5 | 43/222 | 19.4 | 2.67 | 0.10 |
| 11 | 2/29 | 6.9 | 33/222 | 14.9 | 0.77 | 0.39 |
| w24 | 9/29 | 31.0 | 32/222 | 14.4 | 4.04 | 0.05 |
| 25 | 1/29 | 3.40 | 19/222 | 8.5 | 0.35 | 0.60 |
| 26 | 5/29 | 17.2 | 24/222 | 10.8 | 0.5 | 0.46 |
| 28 | 3/29 | 10.3 | 22/222 | 9.9 | 0.07 | 0.99 |
| 29 | 3/29 | 10.3 | 11/222 | 4.9 | 0.58 | 0.42 |
| w30 | 1/29 | 3.4 | 7/222 | 3.2 | 0.23 | 0.99 |
| w31 | 1/29 | 3.4 | 6/222 | 2.1 | 0.14 | 0.99 |
| 32 | 1/29 | 3.4 | 13/222 | 5.8 | 0.01 | 0.99 |

TABLE II

Distribution of HLA-B antigens in DMD-hemizygotes

| HLA–B antigens | DMD (n=29) HLA–B antigen positivity | | Controls (n=222) HLA–B antigen positivity | | $\chi^2$ | p |
|---|---|---|---|---|---|---|
| | No. | per cent | No. | per cent | | |
| 5 | 8/29 | 6.9 | 28/222 | 12.6 | 0.35 | 0.59 |
| 7 | 9/29 | 31.0 | 30/222 | 13.5 | 4.74 | *0.04* |
| 8 | 4/29 | 13.8 | 41/222 | 18.5 | 0.13 | 0.72 |
| 12 | 8/29 | 27.6 | 44/222 | 19.8 | 0.53 | 0.46 |
| 13 | 2/29 | 6.9 | 18/222 | 8.1 | 0.02 | 0.99 |
| 14 | 4/29 | 13.8 | 15/222 | 6.7 | 0.95 | 0.32 |
| 15 | 3/29 | 10.3 | 16/222 | 7.2 | 0.05 | 0.99 |
| 17 | 2/29 | 6.9 | 18/222 | 8.1 | 0.02 | 0.99 |
| 18 | 4/29 | 13.8 | 34/222 | 15.3 | 0.004 | 0.99 |
| w21 | 2/29 | 6.9 | 15/222 | 6.7 | 0.13 | 0.99 |
| 27 | 4/29 | 13.8 | 29/222 | 13.1 | 0.03 | 0.99 |
| w35 | 4/29 | 13.8 | 50/222 | 22.5 | 0.7 | 0.41 |
| 38 | 3/29 | 10.3 | 10/222 | 4.5 | 0.79 | 0.36 |
| w39 | 1/29 | 3.4 | 10/222 | 4.5 | 0.05 | 0.99 |
| 37 | 1/29 | 3.4 | — | — | — | — |
| 40 | 4/29 | 13.8 | 31/222 | 13.9 | 0.07 | 0.99 |
| Cw 2 | 4/22 | 18.2 | 16/124 | 12.9 | 0.11 | 0.71 |
| 3 | 4/22 | 18.2 | 18/124 | 14.5 | 0.01 | 0.99 |
| 4 | 2/22 | 9.1 | 38/124 | 30.6 | 3.35 | 0.053 |
| 6 | 1/22 | 4.5 | — | | | |

concerning progressive muscular dystrophy (DMD). Therefore, a study of the question has been performed.

## MATERIALS AND METHODS

Frequency distribution of HLA antigens was studied in 32 hemizygous DMD child patients from 29 families and in 222 healthy blood donors as controls. Eleven mothers were available for examination; they were either obligatory heterozygous gene carriers, or had increased CPK activity. In two families where 2 and 3 children, respectively had DMD, we took into consideration the data of one child for each of these families.

HLA typing of peripheral blood lymphocytes was carried out by the standard NIH lymphocytotoxicity test [3] for 37 HLA antigens of the A, B and partly the C loci. We have omitted from the Tables those antigens which were not represented in the patient population. Evaluation was done by the $\chi^2$ test and Yates correction at the computer centre of Szeged University.

## Results

Table I shows the frequency distribution of HLA–A antigens in the DMD hemizygotes and in the control group. Table II shows the frequency of the HLA–B antigens in the aforementioned groups. It can be seen that the frequency of antigen HLA–B7 had a tendency to be higher than in the controls ($p < 0.04$), and of the HLA–A antigens the HLA–Aw24 had a tendency of being more frequent ($p < 0.05$) than in the controls.

Among the HLA antigens of the DMD gene carrier mothers HLA–A3 and B7 showed a slight tendency to be somewhat more frequent than

Table III

Distribution of HLA-antigens in DMD-gene carriers

| HLA–A antigens | DMD-gene-carriers (n=11) HLA–A antigen positivity | | Controls (n=222) HLA–A antigen positivity | | $\chi^2$ | p |
|---|---|---|---|---|---|---|
| | No. | per cent | No. | per cent | | |
| 1 | 1/11 | 9.1 | 49/222 | 22.1 | 0.42 | 0.55 |
| 2 | 6/11 | 54.5 | 110/222 | 49.5 | 0.0003 | 0.99 |
| 3 | 5/11 | 45.5 | 43/222 | 19.4 | 2.91 | 0.1 |
| w24 | 2/11 | 18.2 | 32/222 | 14.4 | 0.008 | 0.99 |
| 25 | 1/11 | 9.1 | 19/222 | 8.5 | 0.24 | 0.99 |
| 26 | 1/11 | 9.1 | 24/222 | 10.8 | 0.1 | 0.99 |
| 28 | 2/11 | 18.2 | 22/222 | 9.9 | 0.14 | 0.63 |
| 29 | 2/11 | 18.2 | 11/222 | 4.9 | 1.42 | 0.24 |
| 32 | 1/11 | 9.1 | 13/222 | 5.8 | 0.04 | 0.99 |
| HLA–B | | | | | | |
| 7 | 4/11 | 36.4 | 30/222 | 13.5 | 2.75 | 0.12 |
| 12 | 2/11 | 18.2 | 44/222 | 19.8 | 0.06 | 0.99 |
| 13 | 3/11 | 27.3 | 18/222 | 8.1 | 2.65 | 0.09 |
| 15 | 1/11 | 9.1 | 26/222 | 7.2 | 0.13 | 0.99 |
| 17 | 1/11 | 9.1 | 18/222 | 8.1 | 0.2 | 0.99 |
| 18 | 2/11 | 18.2 | 34/222 | 15.3 | 0.03 | 0.99 |
| 27 | 4/11 | 36.4 | 29/222 | 13.1 | 2.96 | 0.11 |
| w35 | 2/11 | 18.2 | 50/222 | 22.5 | 0.001 | 0.99 |
| 40 | 1/11 | 9.1 | 31/222 | 13.9 | 0.00004 | 0.99 |
| 39 | 1/11 | 9.1 | 10/222 | 4.5 | 0.0008 | 0.99 |
| Cw | | | | | | |
| 2 | 3/11 | 27.3 | 16/124 | 12.9 | 0.74 | 0.37 |
| 3 | 1/11 | 9.1 | 18/124 | 14.5 | 0.002 | 0.99 |
| 4 | 2/11 | 18.2 | 38/124 | 30.65 | 0.27 | 0.63 |

usual ($p < 0.1$ and $p < 0.12$ respectively).

Two affected children of different sexes in a family proved to be HLA-identical while lacking the B7 antigen. In two out of three male children of another family the haplotypes inherited from the mother were identical: A3, B7; in the third the maternal haplotype was A25, B18. Their sister who was suspected to be a gene carrier, also possessed the A3, B7 maternal haplotype.

## Discussion

The only investigation into HLA antigen frequency in muscle disease known to us has dealt with neurogenic myopathy and myasthenia gravis [2], finding the antigens A1, B8, and DRw3 more frequent. We have no knowledge of data concerning DMD hemizygotes. In our material, antigen B7 had a tendency to be more frequent and antigen Aw24 to be more frequent, too. In a small group of possible heterozygous gene carrier mothers A2 and B7 had a slight tendency to be more frequent. The frequency of B7 was similar in percentage in the two groups, thus somewhat supporting each other while being not significant in the statistical sense. Further examinations are needed to find out whether these or other HLA antigens might figure as genetic markers in Duchenne muscular dystrophy.

## References

1. Ryder LP, Anderson E, Svejgaard A: HLA and Disease Registry. Copenhagen 1979
2. Szobor A, Gyódi E, Ónody K, Petrányi G, Hollán S: HLA Antigene und geschlechtsbedingte genetische Faktoren bei Myasthenia gravis. Akt Neurol 7:19, 1080
3. Terasaki P: Manual of Tissue Typing Techniques. 4:50, 1972

*Received 10 March 1983*

A László MD
P.O. Box 471
H-6701 Szeged, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 327—329 (1983)*

# Serum alpha-galactosidase activity in children with Duchenne-type muscular dystrophy and in gene carriers

Aranka László, Z Havass

Department of Paediatrics, University Medical School Szeged, Hungary

Serum alpha-galactosidase activity was studied in 21 control children, 15 children with Duchenne muscular dystrophy, and in 8 gene carrier mothers. In both the DMD hemi- and the heterozygous groups a significant increase of alpha-galactosidase activity was demonstrated.

Lack or minimal activity of alpha-galactosidase (AG), which belongs to the group of lysosomal enzymes of serum, is a commonly known genetic feature of Fabry's disease with X-linked heredity [5]. The gene site of AG is located on the long arm of the X-chromosome ($X_q$ 22–24) [9]. The elevated serum level of lysosomal enzymes is indicative of membrane destruction [8].

An attempt has been made to establish whether in Duchenne-type muscular dystrophy (DMD), AG was suitable to characterize the homo- and heterozygous condition of the disease.

## Materials and Methods

AG activity was studied in the sera of 15 hemizygous 5–18-year-old children and 8 gene carrier mothers of families suffering from DMD as well as in 21 children free from genetically determined myopathy, using the fluorimetric method with 4-methyl-umbelliferyl-beta-D-galactopyranoside (Koch–Light Ltd.) as substrate [4].

Enzyme activity is expressed in nmol/ml/h according to the quantity of decomposed substrate. The creatine kinase (CK) level of the DMD patients and their gene carrier mothers is shown in Table I. The clinical severity of DMD was marked with 2–4 points. Two points indicated the patients who had no noticeable difficulty of gait except when walking uphill; those marked with three points had serious difficulty in walking, and those marked with 4 points were unable to walk. We calculated the correlation coefficient between AG activity and CK activity as well as between the degree of clinical severity and the AG level in the group of hemizygotes with DMD and the gene carriers.

## Results

Table I shows the AG level of the control group, that of the DMD patients (hemizygotes), and that of the gene carriers with DMD. The value of serum AG activity was 3.21 nmol/ml/h in the control group; in the group of hemizygotes with DMD the mean activity was 9.99 nmol/ml/h significantly higher than in the control group. The AG level of DMD patients, compared with the degree of clinical severity showed a statistically significant positive correlation. At

TABLE I

Alpha-galactosidase values of DMD patients, DMD gene carriers and controls

| Case No. | DMD patients | | |
|---|---|---|---|
| | Degree of clinical severity | AG nmol/ml/h | CK mU/ml |
| 1 | 3 | 11.9 | 132 |
| 2 | 2 | 5.8 | 756 |
| 3 | 2 | 8.0 | 280 |
| 4 | 2 | 8.3 | 178 |
| 5 | 3 | 14.1 | 74 |
| 6 | 4 | 11.9 | 1000 |
| 7 | 4 | 7.9 | 300 |
| 8 | 3 | 9.3 | 78 |
| 9 | 3 | 8.9 | 340 |
| 10 | 3 | 6.1 | 1000 |
| 11 | 3 | 7.6 | 158 |
| 12 | 2 | 3.9 | 3160 |
| 13 | 3 | 7.7 | 1530 |
| 14 | 4 | 22.6 | 95 |
| 15 | 4 | 16.9 | 268 |

Mean: 9.99
S.D.: ±4.71
$p = 0.0001$
Correlation coefficient between clinical severity and AG: 0.64
$p = 0.0089$
Correlation coefficient between AG and CK: −0.46
$p = 0.08$

the same time, AG activity and CK activity showed a nearly significant correlation in the DMD patients. AG activity of the DMD gene carriers was also significantly increased in comparison with the control group, but 50% of the cases examined showed an overlap; in the remaining 50% a marked increase could be observed.

In the heterozygotes, the CK and AG activities failed to show a significant correlation.

## DISCUSSION

Dennis et al. [2] discussed the use of CK for detecting severe X-linked muscular dystrophy carriers. Nicholson et al. [7] investigated the effect of age on carrier-detection rates with CK: the detection rate with a standard CK assay was 53%, in the daughters of known carriers it was 45% after correction for age. A much higher detection rate, about 90% may be obtained in young carriers and thus seems to be suitable for differentiation between carriers and non-carriers.

There is evidence that in carriers of the relatively benign type of X-linked muscular dystrophy the serum CK level decreases with age [11]. This may also be true, though to a lesser extent, in carriers of DMD [6].

*Table 1 (continued)*

| Case No. | DMD gene carriers | |
|---|---|---|
| | AG nmol/ml/h | CK mU/ml |
| 1 | 4.0 | 223 |
| 2 | 25.5 | 15 |
| 3 | 7.9 | 228 |
| 4 | 15.7 | 40 |
| 5 | 17.4 | 149 |
| 6 | 5.8 | 59 |
| 7 | 6.2 | 56 |
| 8 | 7.2 | 5.9 |

Mean: 11.21
S.D. ±7.52
Correlation coefficient between AG and CK: −0.42
$p = 0.29$
Controls (n=21)
AG, nmol/ml/h
Mean: 3.21
S.D.: ±1.64

Information on the serum CK level of the normal daughters of a consultand might be helpful in counselling [10]. A modification was given of the original density function formula of Emery and Morton for estimating heterozygosity in X-linked DMD [3] which takes into account the CK level in the normal sisters and normal daughters of a suspected carrier in families where there is only one affected male.

As in the literature available we have found no report on AG activity examination in DMD patients, the present report seems to be the first to demonstrate the significant increase in AG activity in the serum of hemizygotes and of possible gene carriers for DMD.

Although a negative correlation was found between CK and AG activity, at the same time the AG activity corresponds better to the degree of clinical severity; there seems to be a positive correlation between them.

It is well-known that the serum CK activity is increased in not more than two thirds of the gene carriers. Thus genetic guidance is difficult since one third of the carriers cannot be detected. Still, investigation of the AG activity may provide further clues concerning the gene carriers.

## References


1. Beutler E, Kuhl W, Matsumoto F, Pangalis G: Acid hydrolases in leukocytes and platelets of normal subjects and in patients with Gaucher's and Fabry's disease. J Exp Med 143:975, 1976
2. Dennis NR, Evans K, Clayton B, Carter CO: Use of creatine kinase for detecting severe X-linked muscular dystrophy carriers. Br Med J 2:577, 1976
3. Emery SEH, Holloway S: Use of normal daughters' and sisters' creatine kinase levels in estimating heterozygosity in Duchenne muscular dystrophy. Hum Hered 27:118, 1977
4. Griffiths PA, Milson JP, Lloyd JB: Plasma acid hydrolase in normal adults and children and in patients with some lysosomal storage diseases. Clin Chim Acta 90:129, 1978
5. Kint JA: Fabry's disease: alfa-galactosidase deficiency. Science 167:1268, 1970
6. Moser H, Vogt J: Follow-up study of serum creatine kinase in carriers of Duchenne muscular dystrophy. Lancet 2:661, 1974
7. Nicholson GA, Pennington RJT, Gardner-Medwin D, Walton JN: Carrier detection in Duchenne muscular dystrophy: assessment of the effect of age on detection-rate with serum creatine-kinase-activity. Lancet 2:692, 1979
8. Rao GJS: Reaction of 4-methyl-umbelliferyl-guanidinobenzoate with proteases in plasma of patients with cystic fibrosis. Enzyme 23:314, 1978
9. Sapiro LJ: X-linked ichthyosis. Int J Dermatol 20:26, 1981
10. Satz M, Frota-Pessoa O, Peres CA: Use of normal daughters' CPK levels in the estimation of heterozygosity risks in X-linked muscular dystrophies. Hum Hered 25:354, 1975
11. Skinner R, Emery AEH, Anderson AJB, Foxall C: The detection of carriers of benign (Becker-type) X-linked muscular dystrophy. J Med Genet 12:131, 1975


*Received 14 December 1982*

A László MD
Pf 471
6701 Szeged, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 331—336 (1983)*

# Antinuclear factor, smooth and striated muscle antibodies in Duchenne-type muscular dystrophy

Aranka László, J Hudák, Éva Szabó, L Varga

Department of Paediatrics, First Department of Medicine, and Department of Dermatology, Szeged University Medical School, Szeged, Hungary

Antinuclear factors and antibodies to smooth and striated muscle were studied by the indirect immune fluorescence method in the sera of 19 children suffering from progressive muscular dystrophy.

In 47% of the patients antinuclear factor positivity, in 65% anti smooth muscle antibody positivity, and in 26% antistriated muscle antibody positivity was found.

Antibody to striated muscle was present in patients with serious advanced dystrophy and in patients unable to walk, while anti-smooth muscle antibody occurred in less serious cases, too. On the basis of the results, it is concluded that in genetically determined progressive muscular dystrophy a secondary autoimmune process develops owing to the degeneration of muscles as the disease progresses.

Duchenne muscular dystrophy (DMD) is a genetically determined, X-bound recessive hereditary myopathy, the primary biochemical defect of which is not known. There is some evidence pointing to a membrane defect, as for instance is the case of muscle tissue, platelets, and erythrocytes [1, 8, 15, 16, 17, 21]. Several authors [20, 24] have investigated the properties of the erythrocyte membrane in DMD patients and obtained conflicting results. Percy and Miller [19] found pathological deformability, Fisher et al. [10] and Lloyd and Nunn [14] increased fragility, Howland [12], Dise et al. [7] increased permeability for the ions K and Ca.

The immunological condition of DMD patients is unclear. As a working hypothesis we assumed that in the genetically determined myopathy the myoglobin which reaches the blood from the disintegrating muscle fibres, would trigger a secondary immunological process.

## Materials and Methods

Examination of the antinuclear factor (ANF) and the antibodies to smooth muscle (SM) and striated muscle (STM) was carried out by the indirect immune fluorescence method (IIF) [4] in the sera of 19 children with DMD and 24 control children free from autoimmune disease and DMD. For determination of antinuclear factor, rat liver and kidney tissue, for determination of antibodies to striated muscle the quadriceps muscle of rats were used as substrate, and for the demonstration of antibodies to smooth muscle the fundus ventriculi of the rat was used. The immune fluorescent kit of Hyland Co., Costa Mesa, Calif. Cat. No.

TABLE I

Anti-nuclear-antibody (ANF), smooth-muscle-antibodies (SMA) and striated-muscle-antibodies (STMA) in control children

| Number | Age, year | ANF | | SMA | | STMA | |
|---|---|---|---|---|---|---|---|
| | | + | − | + | − | + | − |
| 24 | 6.6±2.3 | 1 (4%) | 23 (96%) | 1 (4%) | 23 96%) | 0 (0%) | 24 (100%) |

TABLE II

ANF, SMA and STMA in the serum of Duchenne muscular dystrophy patient

| Case No. | Age, year | ANF | | SMA | | STMA | | Duration of DMD, years |
|---|---|---|---|---|---|---|---|---|
| | | + | − | + | − | + | − | |
| 1 | 13 | + | | + | | ± | | 5 |
| 2 | 11 | + | | ++ | | | − | 4 |
| 3 | 11 | | − | | − | | − | 6* |
| 4 | 8 | + | | | − | | − | 4 |
| 5 | 12 | + | | | − | | − | 4 |
| 6 | 10 | | − | ++ | | ++ | | 5* |
| 7 | 8 | | − | + | | ++ | | 5* |
| 8 | 12 | | − | ++ | | | − | 5 |
| 9 | 9 | | − | + | | ++ | | 6* |
| 10 | 8 | | − | + | | | − | 4** |
| 11 | 12 | | − | + | | ++ | | 8** |
| 12 | 8 | + | | ++ | | | − | 3 |
| 13 | 18 | + | | + | | ++ | | 15* |
| 14 | 2 | | − | | − | | − | 3 |
| 15 | 12 | + | | | − | | − | 4 |
| 16 | 8 | + | | ++ | ± | ± | | 4 |
| 17 | 5 | | − | | − | | − | 2 |
| 18 | 12 | | − | | − | | − | 3 |
| 19 | 5 | + | | ++ | | | − | 1 |

$\bar{x} = 9.94$ n = 9 n = 10 n = 12 n = 7 n = 5 n = 12 $\bar{x} = 4.79$
S.D. = 3.11 47.36% 52.64% 64.5% 35.84% 26.31% 63.16% S. D. = 2.92

| | | |
|---|---|---|
| $\chi^2 = 8.37$ | $\chi^2 = 14.19$ | ±n=2 |
| p < 0.01 | p < 0.01 | 10.53% |
| $K_{coef.}$ −0.01 | $K_{coef.}$ 0.31 | $K_{coef.}$ 0.74 |
| T = 0.081 | T = 1.389 | T = 4.57 |
| p > 0.1 | p > 0.10 | *p = 0.00031* |

*unable to walk
** serious walking difficulty

6–73–00–10 was employed. Cryostat sections 2–4 μm thick were prepared from the organs. The sections were incubated first in serum diluted 1:28, then with FITC-labelled polyvalent antihuman immune globulin conjugate (5E-ShAu–IgGAM–FITS, Human, Budapest) diluted 1:32 at room temperature in a wet chamber. In the periods of incubation and after staining with fluorescein, the preparations were washed with Nairn buffer, and finally a mixture of glycerol and water 1:1 was added and the preparation was covered with a coverglass. Optimum dilution of the serum samples and the fluorescein conjugate was determined by chessboard titration. Evaluation was made with a Zeiss–Fluoval type immune fluorescence microscope (Zeiss–Fluo II. No. 685193, Carl Zeiss, Jena, GDR) with a B-221 g filter as primary filter, and a D-287 g filter as secondary filter.

Unstained preparations and preparations incubated only with fluorescein conjugate were used as controls.

## Results

Table I shows the data of the control group. It can be seen that while ANF and SM positivity was found in 4.17% of the cases, all the serum samples proved negative for anti-STM antibodies. The data for the DMD patients as well as the age of the patients and the period of existence of DMD as reckoned from the appearence of the clinical symptoms are given in Table II. The sera of the diseased children showed ANF positivity in 47.36% (Fig. 1), SM positivity in 65.4% (Fig. 2), and STM positivity in 26.31% (Figs 3 and 4). The percentile incidence of ANF positivity and SM positivity proved significantly higher in the $\chi^2$ test than in the control group. Among the antibodies examined, the correlation coefficient, calculated with the period of existence of DMD showed a significant correlation with the anti-STM antibodies.

## Discussion

Indirect immune fluorescence examination showed that the occurrence of anti-ANF and anti-SM antibodies

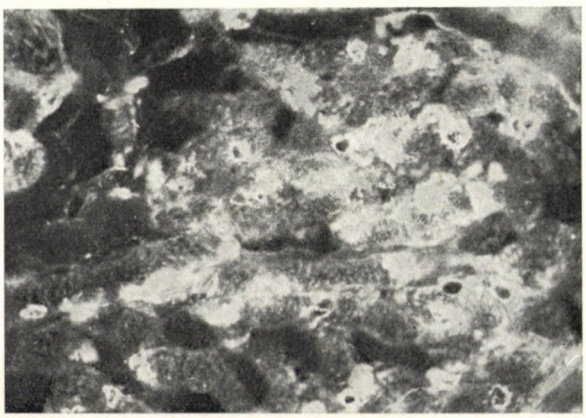


Fig. 1. ANF-indirect immune fluorescence (IIF) of rat lip muscle. ×500

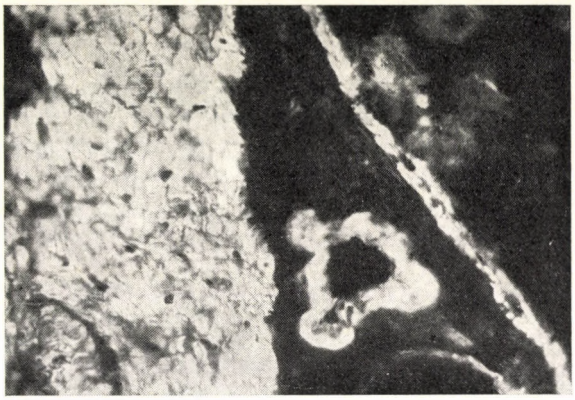


FIG. 2. Smooth muscle IIF positivity in fundus ventriculi of rat. ×500

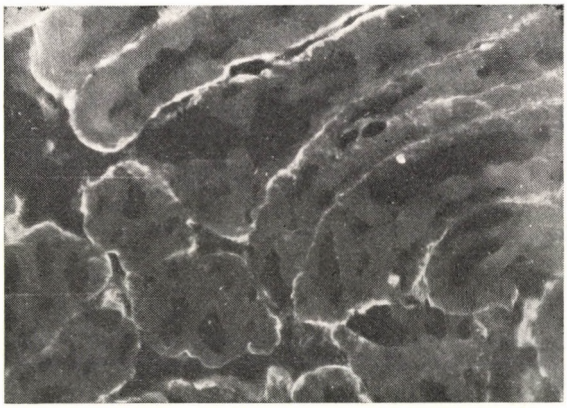


FIG. 3. Striated muscle (sarcolemmal, subsarcolemmal) IIF positivity in sternocleidomastoid muscle of rat. ×500

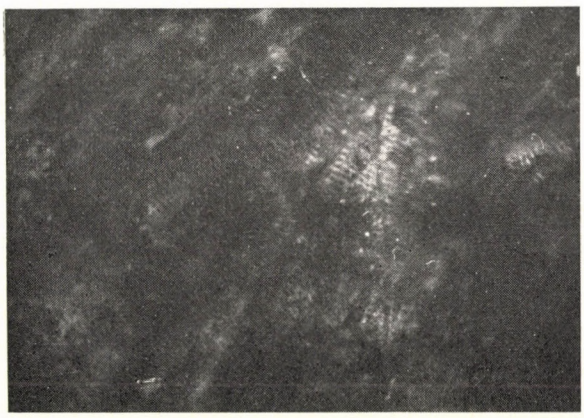


FIG. 4. Striated muscle IIF positivity in rat muscle. ×500

was significantly more frequent in the sera of DMD-patients than in the control group. With progression of the disease, anti-STM circulating antibodies could be demonstrated in the sera of the patients. Persisting SM antibodies can be demonstrated in titres above 1:800 in chronic aggressive hepatitis; temporary low-titre SM occurs in upper respiratory infections [22], acute viral hepatitis [9], infectious mononucleosis [1], and CMV infection [2]. SMA and ANF are pathogenic for lupoid hepatitis.

Anti-striated muscle antibodies occur in titres above 1:60 in myasthenia associated with thymoma, less frequently in polymyositis [13, 18, 23].

Peers et al. [18] testing glycerinated myofibrils by immune fluorescence technique, demonstrated anti-skeletal and heart muscle antibodies in the sera of patients suffering from myasthenia gravis. Inside the muscle they observed a striational reaction. These antibodies are heterogeneous in thymoma; they can be demonstrated also in penicillamine-treated rheumatoid arthritis. Strauss et al. [23] found a complement-fixing globulin fraction bound to striated muscle in the sera of myasthenia gravis patients. The serum of one patient suffering from paroxysmal myoglobinuria also bound the complement. The serum of a patient with acute dermatomyositis produced sarcolemmal fluorescence on skeletal muscle in the presence of guinea pig complement and fluorescein-labelled rabbit anti-guinea-pig complement. Storch [22] emphasized that the cytoplasmic components of skeletal and heart muscle and the subsarcolemmal and sarcoplasmatic reticulum can be regarded as skeletal muscle antagonizing target antigens; biochemically myosin, heavy meromyosin and actin come into consideration as antigens. The antibodies are considerably tissue-specific, but at the same time not species-specific. Antibodies of the SH type reacting to skeletal and heart muscle do not bind complement, while those of the S type react only to skeletal muscle and do bind complement [3]. Caspary et al. [4] detected no statistically significant difference in regard to antimyosin antibodies between the controls and the patients suffering from polymyositis, muscular dystrophy (myotonic dystrophy, facio-scapulohumeral dystrophy, limb-girdle dystrophy) and neurogenic muscle atrophy. Immunoconglutinin was more frequent in the sera of patients with polymyositis and neurogenic muscle-wasting than in the controls, whereas the muscular-dystrophy sera showed no significant variation from the normal. In the absence of evidence for an immunological basis of these disorders, the antibody response is not specific; it rather seems to reflect the indirect effect of a damage to muscle tissue.

The present results seem to prove our assumption that in primarily genetically determined DMD a secondary immunological process develops in connection with the degeneration of the muscles as the disease progresses.

## References


1. Anand S, Emery AEH: Erythrocyte spectrum in Duchenne muscular dystrophy. Clin Chim Acta 117:345, 1981
2. Andersen P, Andersen HK: Smooth-muscle antibodies and other tissue antibodies in cytomegalovirus infection. Clin Exp Immunol 22:22, 1975
3. Beutner EH, Witebsky E, Ricken D, Adler RH: Studies on autoantibodies in myasthenia gravis. JAMA 182:46, 1972
4. Caspary EA, Gubbay SS, Stern GM: Circulating antibodies in polymyositis and other muscle-wasting disorders. Lancet 2:941, 1964
5. Carpenter S, Karpati G: Duchenne muscular dystrophy: plasma membrane loss initiates muscle cell necrosis unless it is repaired. Brain 102:147, 1979
6. Coons AH, Creech HJ, Jones HN, Berliner E: The demonstration of pneumococcal antigen in tissues by the fluorescent antibody. Immunology 45:159, 1970
7. Dise CA, Goodmann DBP, Lake WC, Hodson A, Rasmussen H: Enhanced sensitivity to calcium in Duchenne muscular dystrophy. Biochem Biophys Res Commun 79:1286, 1977
8. Emery AEH: Duchenne muscular dystrophy: Genetic aspects carrier detection and antenatal diagnosis. Br Med Bull 36:187, 1980
9. Farron LJ, Holborow EJ, Johnson GD, Lamb SG, Steward JS, Taylor PE, Zuckerman AJ: Autoantibodies and the associated antigen in acute infective hepatitis. Br Med J 1:693, 1970
10. Fisher ER, Silvestri E, Vester JW, Nolan S, Ahmed U, Danowski TS: Increased erythrocytic osmotic fragility in pseudohypertrophic muscular dystrophy. JAMA 236:955, 1976
11. Holborow EJ, Hemsted EH, Mead SV: Smooth muscle autoantibodies in infectious mononucleosis. Br Med J 3: 323, 1973
12. Howland JL: Abnormal potassium conductance associated with genetic muscular dystrophy. Nature (Lond) 251:724, 1974
13. Irvine WJ, Kalden JR: Muscle in allergic disease: Myasthenia gravis and polymyositis. In: Gell PGH, Coombs RRA, Lachmann PJ eds: Clinical aspects of immunology, 3rd ed. Blackwell Scientific Publications, Oxford 1975
14. Lloyd SJ, Nunn MG: Osmotic fragility of erythrocytes in Duchenne muscular dystrophy. Br Med J 2:252, 1978
15. Lucy JA: Is there a membrane defect in muscle and other cells? Br Med Bull 36:187, 1980
16. Mawatari S, Takayi A, Rowland LP: Adenyl cyclase in normal and pathologic human muscle. Arch Neurol 30:96, 1974
17. Mokri B, Engel AG: Duchenne dystrophy: electron microscopic findings of a basic or early abnormality in the plasma membrane of the muscle fiber Neurology 25:1111, 1975
18. Peers J, McDonald BL, Daekins RL: The reactivity of the antistriational antibodies associated with thymoma and myasthenia gravis. Clin Exp Immunol 27:66, 1977
19. Percy AK, Miller ME: Reduced deformability of erythrocyte membrane from patients with Duchenne muscular dystrophy. Nature (Lond) 25:147, 1975
20. Rowland LP: Biochemistry of muscle membranes in Duchenne muscular dystrophy. Muscle Nerve 3:3, 1980
21. Schmalbruch H: Segmental fibre breakdown and defects of the plasmalemma in diseased human muscles. Acta Neuropathol (Berl) 33:129, 1975
22. Storch W: Immunfluoreszenzfibel. Gustav Fischer Verlag, Jena 1979, p. 122
23. Strauss AJL, Seegal BC, Hsu KC, Burkholder PM, Nastuk WL, Osserman KE: Immunofluorescence demonstration of a muscle binding complement-fixing serum globulin fraction in myasthenia gravis. Proc Soc Exp Biol Med 105:184, 1960
24. Tsung PK, Palek J: Red cell membrane protein phosphorylation in hemolytic anamias and muscular dystrophies. Muscle Nerve 3:55, 1980


*Received 23 November 1982*

A. László MD
P.O. Box 471
7601 Szeged, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 337—341 (1983)*

# Changes in cardiovascular risk factors in diabetic children during a camping holiday

L Barta, A Czinner, Mária Tichy, Magdolna Bedő

First Department of Paediatrics, Semmelweis University Medical School, and Institute of Nutrition, Budapest, Hungary

Diabetic children in a holiday camp were divided into two groups according to physical activity. In the active group a significant elevation of HDL-cholesterol and a highly significant decrease in total/HDL-cholesterol ratio were observed. In the inactive group similar but non-significant changes occurred.

No appreciable changes were observed in the serum albumin level but the fasting FFA level decreased in both groups, more markedly in the active group. Therefore, the FFA/albumin quotient and also body fat percent decreased considerably in the active group while in the inactive group there were no significant changes.

Micro- and macroangiopathy is a well-known complication of diabetes. Hyperlipoproteinaemia [1] caused by high triglyceride and variable cholesterol levels and accompanied by a low high density lipoprotein (HDL) cholesterol level in the plasma [11] is a common finding in juvenile, insulin-dependent diabetes. An important role has been attributed to the deranged lipid and lipoprotein status, especially to the high total/HDL cholesterol quotient in the pathogenesis of atherosclerosis [2, 6, 10, 11].

The angiopathy is also related to well-documented changes in haemostasis, developing by altered functioning of the prostacyclin ($PGI_2$) system. On platelets, $PGI_2$ has an antiaggregatory effect enhanced by albumin and inhibited by free fatty acids (FFA). The FFA/albumin quotient is a good indicator of this process; a high value represents an increased risk of vascular complications [7, 9].

In this study we describe observations on changes of the FFA/albumin and total/HDL cholesterol quotients in diabetic children participating in a holiday camp.

## Materials and Methods

During summer 1982, a three-week holiday camp for diabetic children was organized in Hungary. Of the children 26 (15 boys and 11 girls) were selected for study. Their mean age was $13.22 \pm 1.27$ years. The mean duration of diabetes was $4.32 \pm 2.63$ years. They were on a regulated but flexible diet consisting of 50% carbohydrate, 20% protein and 30% fat; the diet contained saturated and unsaturated fatty acids in the desirable ratio (1:1.76).

Skinfold thickness was measured with Holtain caliper at five different sites of the body's right side in all children on the first and last day of camping. From these values percent body fat content was calculated by the method of Parizkova and Roth [8]. The children were grouped

as active or inactive according to the opinion of the physician and the pedagogue leading the camp. As active, 13 boys and 3 girls were qualified; these children participated in all physical activity programmes offered while 2 boys and 8 girls with much less physical activity were regarded as inactive.

On the first and last mornings of the camping holiday, before the injection of insulin, untreated and heparinized blood samples were taken and immediately transported to the laboratory in a portable refrigerator.

Triglycerides were determined by the method of Laurell, total and HDL-cholesterol enzymatically, FFA by the method of Dole, and albumin by radial immune diffusion. All concentrations were expressed in mmol/l.

From the data the quotients of total/HDL-cholesterol and FFA/albumin were calculated. The mean values obtained for the first and last days were compared by the *t*-test.

## Results

Table I shows the means and standard deviations obtained on the first and last day, separately for the active and the inactive group. As reported earlier [2] no appreciable changes in the level of $HbA_{1c}$ occurred in the course of the holiday. In the majority of cases insulin dosage had to be reduced because of hypoglycaemia. The diet was flexible, and this allowed a certain liberalism. For all children there were days with glycosuria exceeding 20 g/day.

The mean triglyceride level decreased in the active group, the difference was, however, not significant statistically. In the inactive children there was a statistically significant increase ($p < 0.01$). Total cholesterol exhibited a slight, statistically insignificant increase in both groups, a finding expected on the basis of data in the literature, HDL-cholesterol increased in both groups as expected [6, 11]. In the active group this latter change attained the level of high significance ($p < 0.001$) while for the inactive children it remained insignificant. Since a relationship between HDL-cholesterol and physical activity had been shown previously [9, 10], our grouping of the children seemed justified.

Consequently, similar changes were encountered in the total/HDL-cholesterol quotient: an insignificant increase in the inactive and a significant increase ($p < 0.05$) in the active group.

The fasting FFA levels decreased in both groups significantly, the change was, however, more pronounced in the active group ($p < 0.001$) than in the inactive children ($p < 0.05$).

No appreciable changes in serum albumin were observed; a modest increase occurred in the active group. The FFA/albumin quotient exhibited a marked decrease ($p < 0.001$) in the active group while there were no significant changes in the inactive group.

Body fat percent calculated from the skinfold measurements showed no change in the inactive children while in the active group it decreased markedly ($p < 0.001$). This points to a sharp increase in lean body mass in the active group, which may be

TABLE I

Means and standard deviation in the active and inactive group

| | Active | | Inactive | |
|---|---|---|---|---|
| | Before camping | After camping | Before camping | After camping |
| Triglyceride | 1.05 ±0.27 | 0.89±0.30 | 0.96 ±0.17* | 1.42 ±0.59 |
| Total cholesterol | 4.70 ±0.66 | 4.96 ±1.21 | 4.94 ±0.40 | 5.51 ±0.98 |
| HDL-cholesterol | 0.86 ±0.19*** | 1.03 ±0.21 | 0.98 ±0.12 | 1.11 ±0.26 |
| Total/HDL-cholesterol | 5.73 ±1.50** | 4.87 ±1.09 | 5.10 ±0.84 | 5.13 ±1.18 |
| FFA | 0.816±0.156*** | 0.588±0.127 | 0.822±0.141** | 0.662±0.221 |
| Albumin | 0.607±0.059 | 0.636±0.067 | 0.667±0.071 | 0.667±0.083 |
| FFA/albumin | 1.35 ±0.23*** | 0.88 ±0.21 | 1.23 ±0.19 | 0.98 ±0.25 |
| Percent body fat | 24.78 ±4.12*** | 21.87 ±4.43 | 27.03 ±6.39 | 25.69 ±6.93 |

* $p < 0.01$, ** $p < 0.05$, *** $p < 0.001$

ascribed to the physical activity. This too showed that our grouping was adequate.

## DISCUSSION

For the pathogenesis of arteriosclerosis there are two theories. The older hypothesis emphasizes the role of blood lipids and lipoproteins. There are nowadays doubts about the importance of hypertriglyceridaemia while the pathogenetic role of very low density lipoprotein and low density lipoprotein and the protective effect of HDL-cholesterol have been fully established [10, 11]. Therefore, an elevation of the total/HDL-cholesterol ratio is a well-based risk factor predicting angiopathy. The haemostasis hypothesis underlines the role of platelet aggregation, the first step of coagulation provoked by endothelial damage. The process may be influenced by prostaglandins, oxygenated derivatives of arachidonic acid; thromboxane $A_2$ liberated in platelets, promotes aggregation while it is inhibited by prostacyclin ($PGI_2$). Equilibrium between the two compounds is the basis of the regulation of clotting [7].

It has been shown both in vitro [7] and in vivo [4] and in also morphological studies that the catabolism of $PGI_2$ is enhanced by FFA and inhibited by albumin. As a consequence, the FFA/albumin quotient is an appropriate indicator in this respect, and a high value foretells angiological complications [10].

In a previous paper we have described the favourable effect of a holiday camp on the working capacity of diabetic children. The two

quotients improved much in the active group while in the inactive diabetic children total/HDL-cholesterol remained unchanged and only an insignificant improvement ensued in the FFA/albumin quotient.

Unfavourable fasting FFA and cholesterol levels may also be attributed to poor insulin dosage. When insulin doses are adequate, a high level of HDL-cholesterol and albumin reflect a favourable metabolic and vascular situation. Metabolic alterations provoke rapid changes in the FFA and HDL-cholesterol level while serum cholesterol and albumin are less sensitive and follow the changes more sluggishly.

In these children, physical activity increased the level of HDL-cholesterol and reduced the body fat content. The improvement of the total/HDL-cholesterol quotient is attributed exclusively to the favourable changes in HDL-cholesterol.

Favourable changes of the FFA/albumin quotient were encountered in both groups. The more important factor was the decrease in FFA concentration. Here also, the better result was achieved in the active group.

There was a certain parallelism in behaviour between the two quotients. This suggests that the FFA/albumin quotient or, since the serum albumin level remained unchanged, the FFA concentration too is a good indicator of the condition of the diabetic patient.

In the active group a slight decrease in the mean triglyceride level was seen while an insignificant increase occurred in the inactive group. Systematic estimation of the triglyceride levels is of outstanding importance in the management of diabetes. If the insulin action comes short, lipoproteinase activity decreases, thus leading to an increase in the very low density lipoprotein triglyceride level [5]. This explains why we found significantly higher levels in the inactive group.

## References

1. Barta L: Über die Bedeutung der Blutlipoide beim Diabetes mellitus im Kindesalter. Endokrinologie 53:261, 1968
2. Barta L, Molnár M, Tichy M: Camping für Diabetiker und HDL-Cholesterinspiegel. Acta Paediatr Acad Sci Hung 22: 341, 1981
3. Barta L, Pena M, Regöly-Mérei A, Gedeon E: Variacione en la composición corporal y la caposiclad functional de minor diabetica en un campamento de verano. Rev Cubana Pediatr 54: 87, 1982
4. Gjesdal K, Nordoy A, Wang H, Bernstein H, Mjos OD: Effects of fasting on plasma and platelet-full fatty acids and platelet function in healthy males. Thromb Haemost 36: 325, 1976
5. Greenfield M, Kolterman O, Olefsky J, Reaven GM: Mechanism of hypertriglyceridaemia in diabetic patients with fasting hyperglycaemia. Diabetologia 18:441, 1980
6. Koepp P, Hennenberger A: Blutlipide bei Diabetes mellitus juvenilis. Monatschr Kinderheilkd 126:711, 1978
7. Mikhailidis D, Mikhailidis M, Dandona P: Plasma non-esterified fatty acid levels and atherogenesis in diabetes mellitus. Diabetologia 21:499, 1981
8. Parižkova JL, Roth Z: The assessment of depot fat in children from skinfold thickness measurements by Holtain caliper. Hum Biol 44:613, 1972
9. Reinila A: Long term effects of untreated diabetes on arterial wall in rat. Diabetologia 20:205, 1981

10. Sherwin RS, Koivisto V: Keeping in steps: does exercise benefit the diabetic? Diabetologia 20:84, 1981
11. Soltész G, Molnár D, Klujber L, Kardos M: Relationship between metabolic control and plasma lipoprotein level in diabetic children. Acta Paediatr Acad Sci Hung 23:75, 1982

*Received 17 February 1983*

Prof L Barta MD
Bókay J. u. 53
H-1083 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 343—347 (1983)*

# Glucocorticoid receptors in circulating lymphocytes of premature infants and newborns

Teresia KEREPESI, P. ARÁNYI

Department of Paediatrics, University Medical School, Debrecen, and Second Institute of Biochemistry, Semmelweis University Medical School, Budapest

The number and affinity of glucocorticoid receptors in lymphocytes of newborns and prematures were determined by a whole cell $^3$H-dexamethasone binding assay. Mean receptor numbers were, $1758 \pm 245$/cell in cord blood, $2758 \pm 307$/cell in mature newborns and $2025 \pm 485$/cell in prematures. Three of the premature babies died with hyaline membrane disease (HMD). They had not been treated prenatally with dexamethasone and no specific binding was measurable in their lymphocytes, suggesting that the lack of receptors might be one of the causes of HMD

Recently it has been established that several mammalian tissues display a significant number of glucocorticoid receptors [1, 3, 5, 12, 20]. Receptors have been analysed also in a number of diseases [5, 9] and correlations have been found in several cases between receptor number and the clinical outcome [11].

Hyaline membrane disease (HMD) is a major cause of neonatal mortality, especially in premature infants. Glucocorticoids are known to accelerate maturation of the lungs and they have been administered as prenatal therapy in recent years. Since the introduction of this therapy, the frequency and mortality of HMD have significantly been reduced [18].

Our aim was to compare the number of glucocorticoid receptors in peripheral lymphocytes of healthy term newborns, prematures, and of babies suffering from HMD. It was hoped that based on this kind of data, it will be possible to tell in retrospect why prenatal glucocorticoid therapy for the prevention of HMD was successful in some cases, but not in others.

## MATERIALS AND METHODS

### *Patients*

The patients were 20 mature newborns and 20 prematures of $32.7 \pm 2.17$ weeks gestational age. Blood samples were taken from a peripheral vein, sometimes through the umbilical catheter 48–72 h after birth, at 8 o'clock a.m. Clotting was inhibited by heparin. Umbilical blood samples were taken also from ten normal babies delivered without complication. Ten out of the 20 prematures had been treated with steroid in the prenatal period; in this case the mother was given 15 mg of dexamethasone intramuscularly once, $47 \pm 2.3$ h before delivery. The deliveries were vaginal except in two cases where Caesarean section was performed. The 20 newborns were healthy, but of the 20 prematures only 4 were symptom-free. Of the rest, 3 suffered from bronchopneumonia, 4 from HMD I–II, 3 from HMD III–IV,

2 from wet lung syndrome, 1 from hyperviscosity syndrome, and 3 had hyperbilirubinaemia of which 2 needed an exchange transfusion.

The diagnosis of HMD was established on the basis of the clinical signs, X-ray findings, blood gases and the pH [17].

*Chemicals*

(1,2-$^3$H)-dexamethasone (specific activity 1.48 $TB_q$/mol) was obtained from the Radiochemical Centre Amersham, UK, unlabelled dexamethasone from Sigma. All other chemicals were obtained from Reanal, Budapest, Hungary.

*Binding assays*

*Determination of dexamethasone binding in whole cells.* Blood was separated by Ficoll–Uromiro density gradient centrifugation [4], then washed with Hank's medium. Separated lymphocytes, $1-4 \times 10^6$/tube were incubated in Hank's medium containing $^3$H-dexamethasone at different concentrations, at 37 °C for 30 min. The amount of non-specifically bound $^3$H-dexamethasone was determined by incubation in the presence of a 500fold excess of non-labelled dexamethasone. Specific binding was calculated as the difference in radioactivity of samples incubated with and without non-labelled dexamethasone. The number of binding sites per cell was determined using a single saturating concentration of dexamethasone. Dissociation constants were obtained from Scatchard analysis [15] of the data (Fig. 1). The radioactivity was measured with Nuclear Chicago ISOCAP 300 radiospectrofluorometer.

## Results

Receptor number per cell was the lowest, $1758 \pm 245$/cell in, lymphocytes

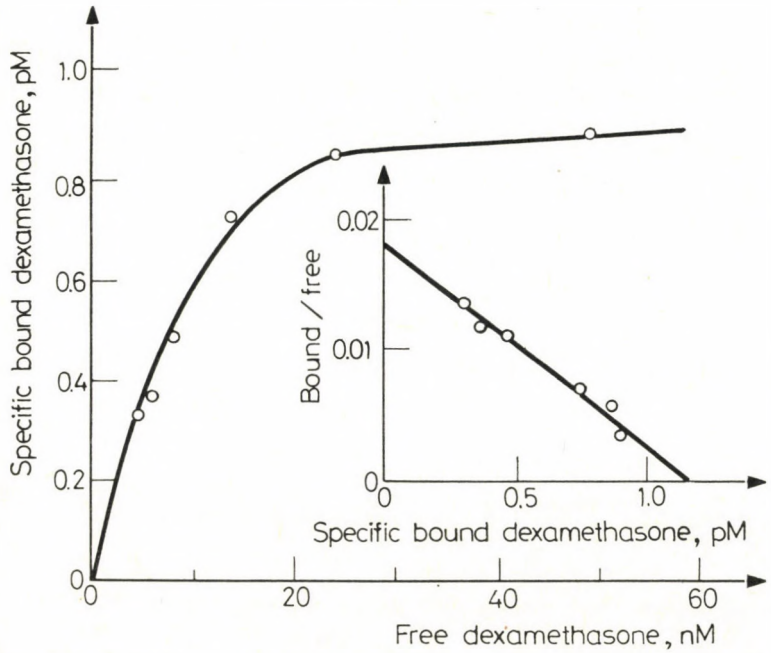



Fig. 1. Determination of dissociation rate constants. Lymphocytes of 4 healthy newborn babies were pooled in order to obtain enough cells for performing saturation analysis. Concentration of dexamethasone varied between 2.5 and 50 nM. The inset shows Scatchard transformation of the data. $K_d = 6.23$ nM

TABLE I

Glucocorticoid receptors in lymphocytes of premature infants

| No* | Sex | Gestational age, weeks | Weight at birth | Diagnosis | Steroid receptors per cell | Mean ± SEM |
|---|---|---|---|---|---|---|
| 1 | M | 35 | 1650 | Bronchopneumonia | 2772 | |
| 2 | F | 34 | 2300 | Hyperbilirubinaemia | 1029 | |
| 3 | F | 33 | 1900 | Bronchopneumonia | 2700 | |
| 4 | M* | 33 | 2005 | HMD III–IV | not measurable | |
| 5 | F | 34 | 1850 | HMD I–II | 2304 | |
| 6 | F | 36 | 2130 | HMD II | 1324 | 1446±386 |
| 7 | F | 34 | 1750 | Prematurity | 1195 | |
| 8 | M* | 31 | 1300 | HMD III–IV twin A | not measurable | |
| 9 | F* | 31 | 1300 | HMD III–IV twin B | not measurable | |
| 10 | F | 36 | 2050 | Prematurity | 3132 | |
| 11 | F | 34 | 1800 | HMD II | 192 | |
| 12 | M | 26–27 | 1300 | HMD II | 734 | |
| 13 | F | 31 | 1550 | Hyperbilirubinaemia | 1122 | |
| 14 | M | 32 | 1950 | Hyperbilirubinaemia | 4874 | |
| 15 | M | 31 | 1600 | Wet lung syndrome | 6528 | |
| 16 | M | 34 | 1950 | Prematurity | 1611 | 2604±726 |
| 17 | M | 36 | 1950 | Bronchopneumonia | 1612 | |
| 18 | F | 28 | 1290 | Prematurity | 907 | |
| 19 | F | 29 | 1440 | Hyperviscosity syndrome | 2600 | |
| 20 | M | 35 | 1850 | Wet lung syndrome | 5860 | |

The number of glucocorticoid receptors in lymphocytes of prematures was determined as described. Nos 1–10: no prenatal steroid administration. Nos 11–20: mothers received 15 mg dexamethasone once 47±2.3 h before delivery. * = died

obtained from the umbilical blood of mature healthy newborns. The mean receptor number of peripheral lymphocytes of mature newborns amounted to 2758±307/cell. The mean receptor number of prematures was 2025±485/cell. Within this, high values were found in babies treated with steroid prenatally: 2604±726/cell, and the lymphocytes of prematures who had not been treated with steroid had only 1446±386 sites/cell. In this latter group specific binding activity was not measurable in 3 cases (Table I). All the three prematures suffered from serious HMD III–IV and died on the 3rd or 4th day of life. Their post mortem findings supported the clinical diagnosis. The mean receptor number in lymphocytes of the 7 prematures, who had not been treated with steroid and survived, was 2064± 256/cell. It was striking that even in babies with steroid therapy a rather low receptor number was observed in three cases. Two of them suffered from HMD II, and one baby was healthy.

## DISCUSSION

Ballard and Ballard [1, 2] and Giannopoulos et al. [7, 8] examined the glucocorticoid binding in fetal lung tissues. The presence of high affinity dexamethasone binding sites has been demonstrated in cytoplasmic extracts

from the lung of fetal rats, guinea pigs, rabbits, further from lungs of normal human neonates, but not in lungs of prematures with HMD. In spite of the success of prenatal glucocorticoid treatment in HMD therapy, it cannot be applied in every case because of maternal contraindications. On the other hand, sometimes serious HMD develops in spite of prenatal maternal steroid administration.

The steroid receptors of the lung of living human newborns or prematures cannot be determined, since no tissue samples can be taken. According to Okret et al. [14] the glucocorticoid receptors in different tissues of the same individual are immunologically similar. Their expression might also be related in certain cases. For this reason we examined glucocorticoid binding in peripheral lymphocytes. A mean receptor number of peripheral lymphocytes of mature healthy newborns was $2758 \pm 307$/cell ($K_d$: $6.23 \times 10^{-9}$M) and a similar number was observed in lymphocytes of premature infants treated prenatally with dexamethasone.

We are not aware of any previous data in the literature on glucocorticoid binding in lymphocytes of newborn and premature infants. According to our results, the receptor content of the lymphocytes of the newborn is slightly lower than that found in adults while their affinity for dexamethasone is about the same [6, 10, 11, 13, 16, 19]. Homo et al. [10] found that the number of steroid receptors and the glucocorticoid sensitivity was dependent on different parameters such as the immunological nature of the cell, the degree of maturation and differentiation, and the stage of proliferation.

We could find no correlation between receptor number and gestational age, birth weight or sex. Ballard and Ballard [2] could not demonstrate specific binding sites in the lungs of prematures who died with HMD. In agreement with this, no specific dexamethasone binding activity could be measured in our three serious HMD cases with fatal outcome. This finding suggests that their lymphocytes either contained no glucocorticoid receptors, or only immature, inactive form. Perhaps a defect in hormone binding may be the cause of the lack of surfactant in the lungs and in turn of the occurrence of HMD. The number of receptors in lymphocytes of the surviving prematures with stage I–II HMD was lower (1131/cell) than that of healthy premature babies or prematures suffering from other diseases.

In our opinion the glucocorticoid binding capacity of lymphocytes may mirror the binding of glucocorticoid in the lung tissue and may possibly be of diagnostic value.

ACKNOWLEDGEMENTS

We are highly indebted to Professors L. Karmazsin and I. Horváth for their continuous interest in this work. Dr. J. Csongor's help in radioactivity determinations is gratefully acknowledged.

## References


1. Ballard PL, Ballard RA: Glucocorticoid receptors and the role of glucocorticoids in fetal lung development. Proc Nat Acad Sci USA 69:2668, 1972
2. Ballard PL, Ballard RA: Cytoplasmic receptor for glucocorticoids in lung of the human fetus and neonate. J Clin Invest 53:477, 1974
3. Ballard PL, Baxter JD, Higgins SJ, Rousseau GG, Tomkins GM: General presence of glucocorticoid receptors in mammalian tissues. Endocrinology 94: 998, 1974
4. Böyum A: Separation of leukocytes from blood and bone marrow. Scand J Clin Lab Invest 21: Suppl. 97, 1968
5. De Sombbre ER: Steroid receptors in breast cancer. New Engl J Med 301:1011, 1979
6. Duval D, Homo F, Thierry C: Glucocorticoid sensitivity of normal lymphocyte populations. In: Glucocorticoid Action and Leukaemia, ed. Bell PA, Borthwick NM, Alpha Omega Publishing Ltd, Cardiff 1979, pp. 143–153
7. Giannopoulos G: Glucocorticoid receptors in lung. I. Specific binding of glucocorticoids to cytoplasmic components of rabbit fetal lung. J Biol Chem 248:3876, 1973
8. Giannopoulos G, Mulay S, Solomon S: Glucocorticoid receptors in lung. II. Specific binding of glucocorticoids to nuclear components of rabbit fetal lung. J Biol Chem 248:5016, 1973
9. Hawkings EF, Hutchens TW, Fligiel S, Horn D, Markland FS: Glucocorticoids and melanoma: receptor properties of dexamethasone sensitive and resistant tumors. J Steroid Biochem 16:673, 1982
10. Homo F, Picard F, Durant S, Gagne D, Simon J, Dardenne M, Duval D: Glucocorticoid receptors and their function in lymphocytes. J Steroid Biochem 12:433, 1980
11. Lippman ME: Glucocorticoid receptors and effects in human lymphoid and leukemic cells. In: Glucocorticoid Hormone Action, ed. Baxter JD, Rousseau GG, Springer Verlag, Berlin 1979, pp. 377–397
12. Munck A, Crabtree GR, Smith KA: Glucocorticoid receptors and actions in rat thymocytes and immunologically stimulated human peripheral lymphocytes. In: Glucocorticoid Hormone Action, ed. Baxter JD, Rousseau GG, Springer Verlag, Berlin 1979, p. 341–355
13. Neifeld JP, Lippman ME, Torney DC: Steroid hormone receptors in normal human lymphocytes. Induction of glucocorticoid receptor activity by phytohemagglutinin stimulation. J Biol Chem 252:2972, 1977
14. Okret S, Carlstedt-Duke J, Wrange Ö, Carlström K, Gustafsson J: Characterization of an antiserum against the glucocorticoid receptor. Biochim Biophys Acta 677:205, 1981
15. Scatchard G: The attractions of proteins for small molecules and ions. Ann N Y Acad Sci 51:660, 1949
16. Schlechte JA, Ginsberg BH, Sherman BM: Regulation of the glucocorticoid receptor in human lymphocytes. J Steroid Biochem 16:69, 1982
17. Schmid F: Paediatrische Radiologie. Springer Verlag, Berlin–Heidelberg–New York 1973
18. Shields JR, Resnik R: Fetal lung maturation and the antenatal use of glucocorticoids to prevent the respiratory distress syndrome. Obstet Gynec 34:343, 1979
19. Simonsson B: Evidence for a glucocorticoid receptor in human leukocytes. Acta Physiol Scand 98:131, 1976
20. Szabó I, Vértes M, Bódis J, Lányi E, Sauerhering E: Steroid receptors in human fetal lung. Lancet 2:751, 1980


*Received 23 February 1983*

T Kerepesi MD
Pf 32
H-4012 Debrecen, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 349—353 (1983)*

# Reticulin antibodies in coeliac disease

J HENKER, M ZUGEHÖR, J MORRENZ

Department of Paediatrics, Carl Gustav Carus Medical School, Dresden, and Institute of Medical Microbiology and Epidemiology, Medical School, Magdeburg, GDR

The diagnostic value of demonstrating reticulin antibodies in children affected by coeliac disease is discussed. The antibodies were shown by immunofluorescence in 201 serum samples of 82 patients during the initial phase, during gluten provocation after several months of gluten-free diet. Demonstration of reticulin antibodies is not useful in screening for coeliac disease in patients suspect of the condition since both false positive and negative results occur in spite of the high sensitivity of the test. Determination of the antibodies is, however, a useful guide in dietary control. The antibodies discriminate coeliac disease from cow's milk protein intolerance.

The jejunal mucosa fulfils two principal tasks, viz. absorption of nutrients and defence against macromolecules and microorganisms. Normally, products of intraluminal digestion are either absorbed, sometimes after further cleavage occurring in the microvilli, or repelled by the jejunal mucosal barrier. Therefore, any mucosal damage may be accompanied by absorption of nutritional antigens and production of antibodies against them. In children, cow's milk protein, gliadin and reticulin are the most frequent nutritional antigens. Governa et al. [5] have shown that reticulin antibodies are directed more against nutritional reticulin rather than the reticulin of the own body. The most frequent cause of severe jejunal mucosal damage of children is coeliac disease.

Since the appearance, course and disappearance of antibodies against nutritional antigens depend much on the condition of the jejunal mucosa, it may be anticipated that determination of these antibodies might be helpful in controlling the disorder by diet. In previous studies [6, 17] we could show that this was particularly true for reticulin antibodies. Production of antibodies against nutritional antigens in coeliac disease is an epiphenomenon, it has thus nothing to do with the ultimate pathogenesis of the disorder.

In this paper we report on the results obtained in a large number of patients.

## MATERIALS AND METHODS

Reticulin antibodies were determined in 201 serum samples taken from 82 children aged 7 months to 17 years, in various phases of coeliac disease (Tables I, II).

The diagnosis of coeliac disease was based upon the clinical and jejunal biopsy criteria of the European Society for Paediatric Gastroenterology and Nutrition [8], i.e. a typical history, laboratory findings and a subtotal villous atrophy in the jejunal biopsy specimen. Serial jejunal biopsies

TABLE I

Number of patients and sera examined for reticulin antibodies

| | No. of patients | No. of sera |
|---|---|---|
| Children with coeliac disease | 82 | 201 |
| Children with acute or chronic intestinal disease | 96 | 96 |
| Children without intestinal disease | 32 | 32 |

TABLE II

Reticulin antibody titres in children with coeliac disease under various nutritional conditions

| Titre | Group | | | | |
|---|---|---|---|---|---|
| | I n=31 | II n=143 | III n=27 | IV n=96 | V n=32 |
| 1280 | 2 | — | — | — | — |
| 640 | 1 | — | 1 | — | — |
| 320 | 10 | — | — | — | — |
| 160 | 2 | — | 1 | — | — |
| 80 | 4 | — | 4 | — | — |
| 40 | 2 | 4 | 12 | 3 | — |
| 20 | 7 | 6 | 3 | 4 | — |
| 10 | — | 6 | 2 | 4 | — |
| less than 10 | 3 | 127 | 4 | 85 | 32 |
| Percentage of positive sera | 90.3 | 11.2 | 85.2 | 11.5 | 0 |
| Percentage of negative sera | 9.7 | 88.8 | 14.8 | 88.5 | 100 |

Group I: no diet (initial phase)
Group II: at least three months gluten-free diet
Group III: at least three months gluten provocation
Group IV: controls with aspecific intestinal symptoms
Group V: controls without intestinal disease

were not considered necessary for the initial diagnosis. For histological stereomicroscopic classification Shmerling's typing [13] was used: Type I (normal), Type II (partial villous atrophy), Type III (subtotal or total villous atrophy).

The control group consisted of 96 children aged 5 months to 14 years, admitted for acute or chronic intestinal disease, in whom coeliac disease was excluded by the subsequent course of the disease. In some of these patients jejunal biopsy was also done; normal or slightly altered jejunal mucosa was the finding in each case. Only 5 children with confirmed cow's milk protein intolerance exhibited moder-

ate or severe mucosal changes of Type II or III. Another control group comprised 32 children aged 6 months to 12 years: with no intestinal symptoms or complaints.

Sera were deep-frozen immediately after taking the blood sample and kept at −20 °C until determination. The person performing the serological work was not aware of the diagnosis.

For reticulin antibody determination frozen sections of guinea-pig kidneys were incubated with the sera diluted 1:10 and stained with FITC labelled goat antihuman globulin produced by the State Institute for Immune Preparations and Culture Media, Berlin. The preparations were then examined in a microscope Fluoval I, of Carl Zeiss, Jena, GDR. Sera exhibiting positive fluorescence in the tubular basal membrane and Bowman's capsule were subsequently titrated.

## Results

Results are shown in Table II. Reticulin antibodies could be demonstrated in 90.3% of children with recent, untreated coeliac disease while a positive test was obtained in 11.2% of children affected by coeliac disease and treated for at least three months. In children in whom after at least three months gluten provocation was performed, positivity was again as high as 85.2%. Reticulin antibodies were present in 11.2% of children affected by aspecific intestinal diseases, the highest titre was 1:40. In 6 out of the children with a positive test for reticulin antibody a jejunal biopsy was carried out; in two children the histology was normal, two had moderate cellular infiltration accompanying normal villous findings and again two exhibited partial villous atrophy.

In none of the 5 children with proven cow's milk protein intolerance was a reticulin antibody demonstrable although the blood samples were obtained in the acute phase of the disease and jejunal changes of Type II or III were seen in all the 5 patients.

In the healthy children without any intestinal symptom or complaint no reticulin antibodies were found.

In a number of sera gluten antibodies were determined for comparison of the sensitivity and specificity of the two tests; the results will be published elsewhere.

## Discussion

Prevalence of reticulin antibodies in coeliac disease is between 33 to 93% [2, 4, 6, 10, 12]. The frequency is higher in children than in adults. In two earlier studies we observed a frequency of 70 and 79%, respectively, in children affected by coeliac disease and exhibiting total villous atrophy [6, 17]. The higher percentage (90.3%) of positive findings in the present material was due to the fact that in the previous studies the titres were correlated to the actual type of mucosal alteration and e.g. in patients with Type III no difference was made whether they had florid coeliac disease or were provoked with gluten after a gluten-free diet. The technique was also more adequate in the present study.

In the course of gluten-free dietary treatment the antibodies disappear or at least show a marked reduction in titre; after at least three months

of treatment only 11.2% of the sera were still positive. The persisting positivity can be explained by the observation that in some cases disappearance ensues only after four months or more. Of course, imperfect adherence to the diet could not be excluded, either.

On the basis of our findings it can be stated that determination of reticulin antibodies is a useful indicator of the quality of treatment. In spite of the fairly high grade of specificity, i.e. only 11.5% of the sera obtained from children affected by non-coeliac intestinal diseases and none of the sera of children having no intestinal symptoms at all were positive for reticulin antibodies, the reticulin antibodies cannot be used for screening cases suspect of coeliac disease in order to find out in which patient should a jejunal biopsy be carried out: there are both false positive and false negative results. In addition, in suspect cases jejunal biopsy cannot be avoided since it may reveal other causes of malabsorption in addition to coeliac disease; thus, the test cannot be replaced by anything in the diagnostics of malabsorption.

In family studies, a search for reticulin antibody positive members may be useful: by this method symptom-free candidates for jejunal biopsy can be selected [7, 14, 15, 16]. It is also noteworthy that reticulin antibodies are present in a fairly high percentage of sera taken from patients affected by other disorders like dermatitis herpetiformis [4, 9, 11], rheumatoid arthritis [9], Crohn's disease [1, 4], Sjögren's syndrome [9] or heroin addiction [9]. However, up to now no case afflicted by cow's milk protein intolerance with demonstrable reticulin antibodies has been described [3, 12, 17]; also in our own 5 patients with this condition no antibodies could be demonstrated although the blood samples were taken during the acute phase of the condition.

## References

1. Alp MH, Wright R: Autoantibodies to reticulin in patients with idiopathic steatorrhoea, coeliac disease, and Crohn's disease, and their relation to immunoglobulins and dietary antibodies. Lancet 2:682, 1971
2. Bardare M, Villani R, Giunta A: Anti-reticulin antibodies in malabsorption syndromes. Helv Paediatr Acta 29:203, 1974
3. Essen R von, Savilahti E, Peltonen P: Reticulin antibody in children with malabsorption. Lancet 1:1157, 1972
4. Etermann KP, Feltkamp TEW: Antibodies to gluten and reticulin in gastrointestinal diseases. Clin Exp Immunol 31:92, 1978
5. Governa M, Franchini I, Cella GD, Durand P: Serum anti-reticulin antibody as further evidence of the increased immune response to dietary antigens in coeliac children. Helv Paediatr Acta 28:267, 1973
6. Henker J, Zugehör M, Morenz J: Retikulin-Antikörper bei kindlicher Zöliakie. Dtsch Gesundh Wes 34:83, 1979
7. Mallas EG, Williamson GN, Cooper BT, Cooker WT: IgA class reticulin antibodies in relatives of patients with coeliac disease. Gut 18:647, 1977
8. McNeish AS, Harms HK, Rey J. Shmerling DH, Visakorpi JK, Walker-Smith JA: The diagnosis of coeliac disease. A commentary of the current practices of members of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN). Arch Dis Child 54:783, 1979
9. Rizzetto M, Doniach D: Types of "reticulin" antibodies detected in human sera by immunofluorescence. J Clin Path 26:841, 1973

10. Rotthauwe HW, Sennekamp J, Emons D, Becker M: Antiretikulin-Antikörper und präzipitierende Antikörper gegen Nahrungsmittelprotein im Serum von Kindern mit Cöliakie. Eur J Pediatr 121:215, 1976
11. Seah PP, Fry L, Hoffbrand AV, Holborow EJ: Tissue antibodies in dermatitis herpetiformis and adult coeliac disease. Lancet 1:834, 1971
12. Seah PP, Fry L, Holborow EJ, Rossiter MA, Doe WF, Magelhaes AF, Hoffbrand AV: Antireticulin antibody: Incidence and diagnostic significance. Gut 14:311, 1973
13. Shmerling DH: Peroral intestinal mucosal biopsies in infants and children. Helv Paediatr Acta Suppl 22:1, 1970
14. Stern MS, Bender SW, Grüttner R, Posselt HG, Strobel S: Serum antibodies against gliadin and reticulin in a family study of coeliac disease. Eur J Pediatr 135:31, 1980
15. Stevens FM, Lloyd R, Egan-Mitchell B, Mylotte MJ, Fotrell PF, Wright R, McNicholl B, MacCarthy CF: Reticulin antibodies in patients with coeliac disease and their relatives. Gut 16:598, 1975
16. Stokes PL, Ferguson R, Holmes GKT, Cooke WT: Familial aspects of coeliac disease. Quart J Med 45:567, 1976
17. Zugehör M, Bannert N, Morrenz J: Immunpathogenese und Immundiagnostik der Zöliakie im Kindesalter. Kinderärztl Prax 46:1, 1978

*Received 1 March 1983*

J Henker MD
Fetscherstr 74
8019 Dresden, GDR

*Acta Paediatrica Hungarica, 24 (4), pp. 355—360 (1983)*

# Relationship between placental perfusion and endocrine parameters of pregnants in cases of intrauterine growth retardation

J Doszpod, MG Csákány, M Török, I Gáti

Department of Obstetrics and Gynaecology, Postgraduate Medical School, Budapest, Hungary

The placental perfusion index (PPI) measured 1–27 days before delivery was compared with maternal urinary and serum oestriol (OT) and serum human chorial somatomammotropine (HCS) levels in the mothers of 24 newborns born with intrauterine growth retardation. No significant correlation between placental perfusion and the above endocrine parameters was found. Placental perfusion was not reduced in every case of intrauterine growth retardation. Mathematical analysis has shown that hit accuracy can be increased by the use of more endocrine parameters in pathological pregnancy.

Measurement of certain endocrine parameters is useful in the prenatal diagnosis of placental insufficiency and in monitoring pathological pregnancies. Determination of urinary steroid excretion offers information about the fetoplacental unit and the maternal serum level of some proteohormones may supply information concerning the condition of the placenta. In our department the daily excretion of oestriol and of maternal serum oestriol levels (OT) and of maternal serum human chorial somatomammotropin (HCS) is a routine measurement. Earlier we have shown that serum HCS and OT levels were lower in pregnant mothers who subsequently gave birth to babies with intrauterine growth retardation.

Measurement of placental perfusion is another method which has proved useful in prenatal diagnosis of intrauterine malnutrition. Decreased placental perfusion has been incriminated for placental insufficiency and regarded as the first sign of incipient placental failure [1, 2].

In the present study we have attempted to clarify whether there was a relationship between changes in endocrine parameters and in placental perfusion in pregnant mothers giving birth to malnourished babies.

## Materials and Methods

A retrospective comparison of maternal serum and urinary oestriol excretion, and serum HCS with placental perfusion values was performed in mothers of babies born with intrauterine growth retardation between 1 June, 1981, and 31 May, 1982, in whom placental perfusion had been determined 1–27 days prior to delivery. Only cases with an exactly known gestational age were included in the study.

Among the 24 cases, in 8 mothers gestosis of variable severity was the cause of the intrauterine malnutrition, one mother had diabetes mellitus. Fifteen mothers were free of symptoms and complaints. Grading of the severity of gestosis was carried out by the gestosis index recommended by the World Health Organization.

All retarded babies had a birth weight lower than the 10 percentile value for the corresponding gestational age and neonatological examination revealed physical signs of intrauterine malnutrition in every case.

In additional 12 cases similar measurements were carried out because of suspected intrauterine malnutrition but subsequent intrauterine development was normal and all babies proved to be eutrophic at birth: these babies served as control.

Placental perfusion was measured by a method using $^{113}InCl_3$ [3]. A relative number, the placental perfusion index (PPI), can be calculated from the difference between the activity of radiation deriving from the placenta and from the placenta-free myometrium. In our experience values of PPI lower than 2 indicate a restricted placental perfusion and values below 1 point to a situation threatening fetal life.

Oestriol was determined in 24 hour urine samples by our own method uniting the method of Ittrich modified by Kecskés et al and the method of Brown [4]. Serum oestriol was measured by the oestriol (total) RIA kit of Amersham Laboratories, serum HCS by hCS/hPL test RIA kits of Pharmacia Phadebas$^R$. The results were expressed in SI units.

Evaluation of the serum values was carried out by standard values indicated by the producing firm, for urinary OT we used our own standard value system. Values falling below the 2 SD limit below the mean were regarded as abnormal.

Additional tests (CTG, amnioscopy, repeated echography, amniocentesis for L/S determination, etc.) were done whenever indicated.

## Results

Results are summarized in six tables. Tables I to III demonstrate the three groups of the material. Group 1 comprises dysmature cases without maternal toxaemia, Group 2 dysmature cases with maternal toxaemia and Group 3 is the eutrophic control group. In each table birth weight, gestational age at the time of measurement, the value of PPI and of the endocrine parameters obtained at the time of perfusion measurements (serum HCS and OT, daily excretion of OT) are indicated.

In the group comprising 16 dysmature babies whose mothers had no toxaemia, less than 28 days elapsed between determination of endocrine parameters and placental perfusion on the one hand and birth on the other hand. PPI values below 1 were found in one case, values below 2 in four cases. Urinary oestriol excretion was low in 10, serum oestriol in 3 and serum HCS in 8 cases.

In the group of 8 dysmature babies whose mother had toxaemia determinations were carried out also within 28 days prior to birth. Again, a PPI value lower than 1 was encountered in one case, values lower than 2 in four additional cases. Abnormally low oestriol excretion was found in five cases, low serum oestriol in one case while a low HCS value in four cases.

In the control group (12 cases) 1–63 days elapsed between the measurements and delivery. PPI was higher than 2 in all cases, only one case each

TABLE I

Endocrine parameters in dysmatures without maternal toxaemia (Group 1)

| Serial number of case | Weight at birth g | Gestational age at time of measurement week | Interval between measurement and delivery day | PPI | HCS µg/ml | SeOT ng/ml | Urinary OT µmol/l |
|---|---|---|---|---|---|---|---|
| 1 | 1200 | 33 | + 6 | 0.98 | 0.5* | 88 | 24* |
| 2 | 2500 | 35 | +27 | 3.02 | 2.4* | 102 | 52 |
| 3 | 1990 | 39 | + 6 | 3.99 | 2.5* | 150 | 55 |
| 4 | 2500 | 39 | + 6 | 3.91 | 2.0* | 28* | 35* |
| 5 | 1970 | 36 | +10 | 2.25 | 5.0 | 136 | 30* |
| 6 | 2600 | 38 | + 1 | 3.65 | 2.7* | 76 | 18* |
| 7 | 1100 | 37 | + 7 | 1.41 | 3.3* | 136 | 25* |
| 8 | 2550 | 38 | +11 | 1.71 | 5.1 | 147 | 32* |
| 9 | 2400 | 36 | +25 | 3.17 | 5.0 | 153 | 42* |
| 10 | 2600 | 38 | + 7 | 2.07 | 5.5 | 55* | 62 |
| 11 | 1810 | 35 | +10 | 1.42 | 4.4 | 94 | 40 |
| 12 | 1850 | 37 | + 5 | 2.13 | 4.0* | 176 | 88 |
| 13 | 2470 | 37 | +17 | 2.48 | 3.8* | 166 | 37* |
| 14 | 2500 | 38 | +10 | 3.01 | 4.7 | 66* | 44* |
| 15 | 2650 | 34 | +24 | 1.88 | 4.2 | 75 | 23* |
| 16 | 2600 | 39 | + 4 | 3.71 | 6.2 | 104 | 96 |

* abnormally low value

TABLE II

Endocrine parameters in dysmatures with maternal toxaemia

| Serial number of case | Weight at birth g | Gestational age at time of measurement week | Interval between measurement and delivery day | PPI | HCS µg/ml | SeOT ng/ml | Urinary OT µmol/l |
|---|---|---|---|---|---|---|---|
| 17 | 2550 | 40 | + 1 | 2.89 | 3.8* | 84 | 25* |
| 18 | 1530 | 32 | +15 | 0.97 | 4.2 | 168 | 28* |
| 19 | 2300 | 34 | +18 | 1.77 | 5.2 | 220 | 47 |
| 20 | 1910 | 32 | +17 | 1.83 | 5.0 | 40 | 26* |
| 21 | 2000 | 34 | +27 | 2.04 | 2.1* | 36* | 45 |
| 22 | 1750 | 33 | + 3 | 2.23 | 3.8 | 62 | 40 |
| 23 | 2250 | 36 | + 7 | 1.19 | 3.7* | 62 | 40* |
| 24 | 1280 | 35 | + 5 | 1.47 | 1.2* | 85 | 20* |

* abnormally low value

had a low oestriol excretion or a low serum HCS.

In order to establish whether changes in placental perfusion and the hormonal parameters were of the same direction and order, correlation coefficients were calculated. Table IV demonstrates that PPI was not cor-

TABLE III

Endocrine parameters in eutrophic newborns

| Serial number of case | Weight at birth g | Gestational age at time of measurement week | Interval between measurement and delivery day | PPI | HCS µg/ml | SeOT ng/ml | Urinary OT µmol/l |
|---|---|---|---|---|---|---|---|
| 1 | 3600 | 34 | +27 | 2.72 | 7.6 | — | 40 |
| 2 | 3300 | 35 | + 5 | 2.57 | 5.4 | — | 62 |
| 3 | 3500 | 38 | +12 | 3.15 | 8.0 | 196 | 94 |
| 4 | 3000 | 36 | +17 | 2.54 | 4.0 | 200 | 67 |
| 5 | 3950 | 38 | + 6 | 3.04 | 5.2 | 175 | 35* |
| 6 | 3250 | 35 | +34 | 3.80 | 5.0 | 90 | 63 |
| 7 | 3000 | 31 | +63 | 2.80 | 6.6 | 247 | 42 |
| 8 | 3100 | 33 | +36 | 2.95 | 6.5 | 67 | 45 |
| 9 | 2300 | 34 | +11 | 4.45 | 4.9 | 260 | 49 |
| 10 | 2700 | 36 | + 7 | 3.07 | 7.4 | 210 | 84 |
| 11 | 3350 | 33 | +15 | 3.45 | 5.1 | 158 | 51 |
| 12 | 4100 | 40 | + 1 | 3.07 | 5.6* | 143 | 66 |

* abnormally low value

TABLE IV

Correlation coefficients between PPI and hormonal values in the three groups

| | PPI/HCS | PPI/SeOT | PPI/Urinary OT |
|---|---|---|---|
| Group 1 (n=16) | 0.302 | 0.179 | 0.342 |
| Group 2 (n=8) | 0.459 | 0.469 | 0.263 |
| Group 3 (n=12) | 0.176 | 0.019 | 0.013 |

The $r$-values did not significantly differ from zero in any of the cases

TABLE V

Percentage of pathologically low hormone values within each group

| | HCS | SeOT | Urinary OT |
|---|---|---|---|
| Group 1 (n=16) | 50 | 18.8 | 62.5 |
| Group 2 (n=8) | 50 | 12.5 | 62.5 |
| Group 3 (n=12) | 8 | 0 | 8 |

TABLE VI

Distribution according to number of abnormal hormonal findings in the individual patients

| | Number of patients with | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| | abnormal hormonal findings | | | |
| Group 1 (n=16) | 2 | 8 | 5 | 1 |
| Group 2 (n=8) | 2 | 1 | 5 | 0 |
| Group 3 (n=12) | 10 | 2 | 0 | 0 |

Group 1/Group 2: $\chi^2 = 4.248$ $p < 0.05$
Group 2/Group 3: $\chi^2 = 10.280$ $p < 0.001$
Group 1/Group 3: $\chi^2 = 14.680$ $p < 0.001$
0: all the three values are normal
1: one pathologic value
2: two pathologic values
3: all the three values are pathologic

related with any of the hormone values, i.e., placental perfusion showed no relationship to fetoplacental hormone production or to placental proteohormone levels. Table V shows the percentage of abnormal hormone values within each group. It can be seen that the highest percentage of an abnormal finding was 62.5% low oestriol excretion in the groups with intrauterine growth retardation.

Comparison of the number of cases with simultaneous occurrence of more than one abnormal hormonal finding is represented in Table VI. The $\chi^2$-test revealed a significant difference within each pair of groups in this respect. A much higher percentage of abnormal findings was encountered in dysmaturity as compared to the normal group. Similarly, dysmaturity caused by toxaemia was accompanied by more abnormal hormonal findings than dysmaturity without maternal toxaemia.

All three hormone values were simultaneously low in a single case, in Case 4 of Group 1. In this patient the PPI value was completely normal (3.91). Subsequently a newborn of 2500 g was born during the 39th gestational week, the baby was healthy.

Among the 24 dysmature fetuses 2 intrauterine deaths occurred. In both cases there was a pathologically low PPI value (0.98 and 1.19, respectively) and urinary oestriol excretion and serum HCS were low. In these cases, serum oestriol was normal.

## DISCUSSION

We found no significant correlation between placental perfusion and placental endocrine parameters. In certain cases changes in PPI are thus independent of maternal oestriol and HCS changes. The two methods

furnish information on two different aspects of prenatal growth.

It has been anticipated that all kinds of placental insufficiency are introduced by a decrease in placental perfusion, thus in every case a placental hypoperfusion would be the cause of dysmaturity [1, 2, 5]. Our data showed that placental perfusion is not invariably low in cases of intrauterine growth retardation. This may mean that intrauterine malnutrition cannot fully be ascribed to restricted placental perfusion, and other factors must also be taken into consideration.

The level of hormones produced by the placenta is rather independent of placental perfusion, in other words, the quantity of compounds produced by the syncytiotrophoblasts and released into the maternal circulation is not a simple function of placental perfusion. Hormone values may be normal in cases of markedly depressed placental perfusion, or, conversely, normal placental perfusion may be accompanied by low hormone values; of course, both may be simultaneously low. The result is an intrauterine growth retardation in both cases. In some instances the malnutrition may be ascribed to low placental perfusion but normal hormone production in the placenta shows that damage to placental tissue is not irreversible for a long time. In other cases placental insufficiency reflected in abnormal production of surface enzymes may remain unaccompanied by abnormal placental perfusion [6].

Mathematical analysis shows that the more the hormonal parameters examined, the higher the probability of detecting pathological conditions is. In practice, at least urinary excretion of oestriol and maternal serum HCS have to be measured in pregnancies which seem to be pathological.

## References

1. Clavero-Nunez JA, Ortiz-Quintana L, Aparicio-Bustos JL: Utero-placental blood flow and fetal weight. Its relationship in pregnancies at term. Proc 6th European Congress of Perinatal Medicine, Vienna 1978
2. Grünberger W: Maternal hypotension: does medication influence fetal outcome? Gynecol Obstet Invest 10:32, 1979
3. Hünermann B, Hansmann M, Stolp W: Die pränatale Messung der Plazentaduchblutung und des Plazentavolumens. Arch Gynecol 214:311, 1973
4. Kecskés L, Mutschler F, Glós I, Farkas I, Thán E, Czeglédi J, Kóbor J: Indirekte papierchromatographische Methode zur Bestimmung der Harnoestrogene. Acta Endocrinol (Copenhagen) 38:559, 1969
5. Lunell NO, Sarby B, Lewander R, Nylund L: Comparison of uteroplacental blood flow in normal and intrauterine growth retarded pregnancy. Gynecol Obstet Invest 10:106, 1979
6. Wulf KH: Das Plazentainsuffizienz Syndrom. Z Geburtshilfe Perinatol 185:2, 1981

*Received 20 March 1983*

J Doszpod MD
P.O. Box 112
1389 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 361—366 (1983)*

# Cerebrovascular occlusion in childhood

ILONA DOBRONYI, A PÁSZTOR, I NAGY, E PARAICZ

National Institute of Neurosurgery, Budapest, Hungary

Among 2493 patients undergoing cerebral angiography 43 children were found to have cerebrovascular occlusion. The diagnosis, aetiology, management and care of the condition is outlined. It is stressed that angiography is indispensable in diagnosis.

Since the advent of cerebral angiography, occlusion of the blood vessels of the brain has been recognized with increasing frequency as a cause of acute hemiplegia in children. In several reviews special attention has been paid to the aetiology of hemiplegia in addition to the importance of clinical symptoms, localisation of the obstruction and its outcome [2, 5, 6, 11]. Solomon et al. [14] found 16 patients affected by cerebrovascular obstructive disorders among 86 children with acute hemiplegia. Chiofalo et al. [3] described detailed clinical and electroencephalographic findings of 26 children and young adults afflicted by occlusion of a cerebral artery. Livet et al. [8] reported 16 patients with cerebrovascular occlusion and reviewed the clinical and computer-tomographic diagnosis of the disorder in childhood. Hungarian authors [11] reported on 1200 angiographies carried out in children; among these 16 patients had cerebrovascular occlusion. Single cases with rare aetiology have also been described [4, 12, 13].

In the period 1955 to 1981, 2493 angiographies were performed in children admitted to our institute. In 43 cases occlusion and in 14 stenosis was encountered in the supply area of the internal carotid arteries.

The localization of the occlusion was as follows. In 24 patients the main trunk of the carotid artery was occluded, in 9 the cervical and in 15 the intracranial section. In 15 patients the occlusion was on the right and in 8 on the left side and in one case on both sides. Complete occlusion of the cerebri media artery occurred in 10 patients, of the distal branches in 9 cases; of these, 11 were on the right and 4 on the left side.

Of the patients 20 were boys and 23 were girls. The mean age at onset is not known since several years may have elapsed between the appearance of the first, mild symptoms and the time of angiography.

The aetiological factors were as follows. In 11 cases the occlusion could be ascribed to infection, in 5 to congenital heart defect leading to embolization, in 7 to progressive proliferation of the intima, in 13 to cervical or skull injury and in 7 children no aetiological factor could be identified.

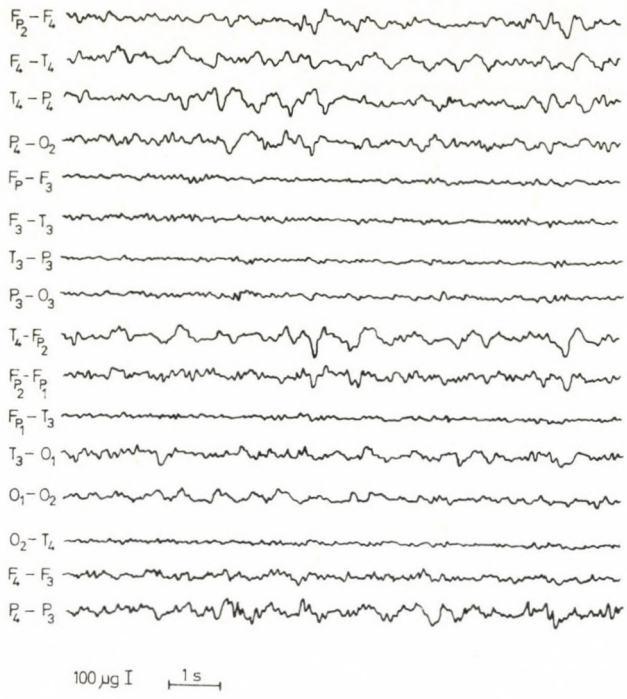



FIG. 1. H.B. 12 years old girl. EEG. The first four channels show the right side activity damaged by vascular occlusion and consisting mostly of theta and delta waves. On the left side slow alpha and fast theta activity indicating an affected circulation

Headaches and convulsions were the most frequent presenting symptoms, not infrequently acute hemiparesis or hemiplegia were the reason for admission. Hemiparesis or hemiplegia was often complicated by cerebral nerve palsy, in some instances by aphasia or partial reduction of the visual field. Sometimes symptoms of meningeal irritation or loss of consciousness were present. The eye-ground findings were usually negative except in cases with pronounced cerebral oedema. Electroencephalography frequently revealed diffuse or focal deceleration accompanied in some instances by paroxysmal activity. The diagnosis was based on the angiographic finding (Figs 1, 2, 4).

The diagnosis can only be verified by angiography. Computer tomography may be helpful in determining the extension of the damaged area or in judging the subsequent evolution of collateral circulation within the supply area of the affected blood vessel (Fig. 3).

Earlier, anticoagulant (heparin) treatment was the rule. At present, improvement of the cerebral microcirculation and the prevention and relief of vasospasms by plasma expanders and papaverine or vinpocetin

over several days are the main aims of therapy. Adequate fluid intake, control of systolic blood pressure, treatment of eventual cerebral oedema, adequate oxygenation of the brain eventually by intubation, tracheostomy and mechanical ventilation, treatment or prevention of eventual convulsions are of importance. After the acute phase of the disease, oral vinpocetin therapy is indicated for months or years. In one case a bypass was performed after the acute phase in order to improve

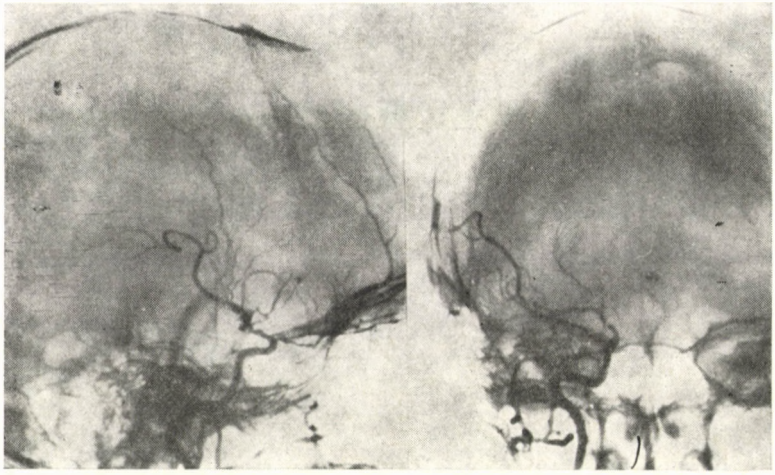


FIG. 2. Same patient as in Fig. 1. Anteroposterior and lateral carotid angiogram. Marked obstruction of the intracranial portion of the common carotid. The cerebri anterior artery does not fill from the right side, incomplete filling of the cerebri media artery

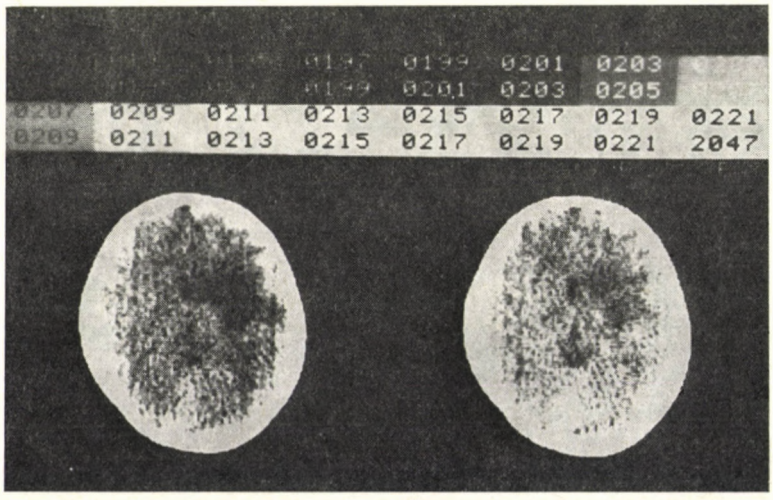



FIG. 3. Same patient as in Fig. 1. Computer tomogram of brain. Hypodensity of irregular shape in right precentral region corresponding to the vascular occlusion

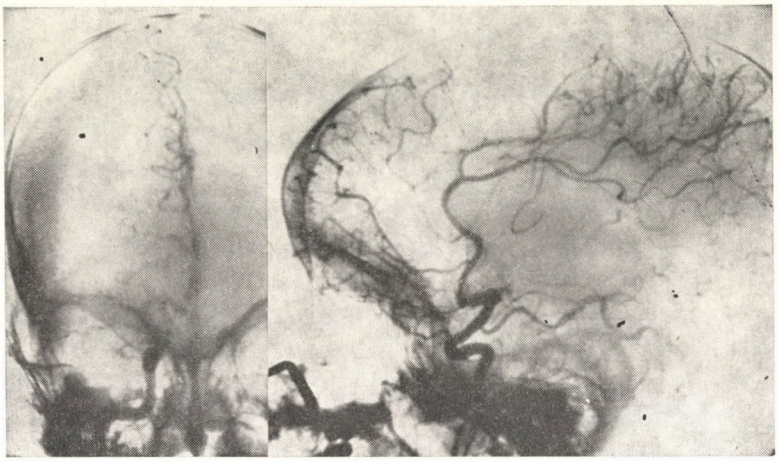


FIG. 4. A. P. 11 years old boy. Anteroposterior and lateral cerebral angiograms show complete occlusion of cerebri media artery

collateral circulation, without any convincing effect.

In the symptoms are severe during the acute phase, lethal outcome may occur. No special measures are indicated in cases with mild symptoms. In the majority, motor handicap due to hemiparesis, aphasia, mental damage or convulsive disorders affect the quality of the patients' life.

## DISCUSSION

Occlusion of the trunk or some branch of the internal carotid artery is a comparatively frequent cause of hemiplegia in infants or children. The sites of predilection are the section adjacent to the branching of the common carotid, the intracranial section of the trunk, the initial part of the cerebri media artery and its distal branches. Occlusion of the anterior cerebral artery is an infrequent finding.

The onset may be acute or the symptoms may develop in several steps. The occlusion may be due to vascular malformation, toxic damage (drugs, narcotics, X-rays), inflammatory changes due to infection, tumours, injury, intimal proliferation of unknown aetiology or embolisation, especially in children affected by congenital heart malformations. Thrombosis of the internal carotid artery is a well-known complication of cervical injury or surgery. In blunt skull injury, damage to the temporal lobe may deteriorate microcirculation and provoke focal cerebral oedema leading to vasospasms or occlusion of the cerebri media artery [15].

In cases due to infection or toxic damage, symptoms pointing to cerebral vasospasm, such as headache, numbness in the extremities, eventually convulsions usually precede the full-blown clinical picture of complete

occlusion. Fibromuscular dysplasia is a condition characterized by generalised malformations of the connective tissue of the blood vessels; the appearance of the carotid artery resembling a string of pearls is only one of the manifestations. The condition sooner or later leads to complete occlusion and is frequently complicated by arterial hypertension due to similar renovascular involvement.

The severity of clinical symptoms may vary from mild transitory hemisymptoms to severe hemiplegia or coma.

The patient's fate is largely determined by the nature of the underlying disease and the development of collateral circulation. In our experience, the occlusion is definite and leads to permanent neurological sequelae in most cases caused by a tumour or progressive intimal proliferation or when it occurs postoperatively.

Traumatic occlusion may cause severe neurological symptoms but often there is hope for remission. Occlusion due to inflammatory changes is frequently transitory and complete recovery may ensue. Collateral circulation usually develops in children with an occlusion of the trunk of the internal carotid provided that no other lesions are present. The prognosis is worse if the occlusion develops in the cerebri media artery near to its origin.

In therapy, acute thrombectomy is a possibility, but the time elapsing until angiography is usually too long, and after some hours no recirculation can be expected from surgery. After the acute phase it may be attempted to create a bypass. In patients needing non-surgical intensive care the main aim is to improve cerebral microcirculation and oxygenation. Surgical treatment for space reducing conditions like tumours or haematomas and medical treatment of diffuse or local cerebral oedema accompanying the occlusion may be indicated. Later on, these children need regular care and follow-up. Drugs such as vinpocetin preventing subsequent vasospasms caused by toxic agents or hypertension must be administered for months or even years.

The majority of survivors are affected by motor disorders, mental damage, and aphasia.

## References

1. Barmada MA, Moossy J, Shuman RM: Cerebral infarction with arterial occlusion in neonates. Ann Neurol 6:495, 1979
2. Carter S, Gold AP: Acute infantile hemiplegia. Paediatr Clin N Am 14: 851, 1967
3. Chiofalo M, Madsen J, Fuentes A, Basauri L, Castro M: Occlusive arterial disease of the child and young adult. Child's Brain 4:1, 1978
4. Cohen N, Berant M, Simon J: Moyamoya and Fanconi anemia. Pediatrics 65, 804, 1980
5. Ferris EJ, Levine HL: Cerebral arteritis: classificaton. Radiology 109:327, 1973
6. Jójárt G, Fekete FP, Szénásy J: Verschluß der Arteria carotis interna bei einem Kind mit chronischer Myokarditis. Acta Paediatr Acad Sci Hung 16: 23, 1975
7. Ladurner G, Sager WD, Hoffer H: Computer tomography in cerebrovascular diseases. Fortschr Med 97:1652, 1979
8. Livet MO, Rayband Ch, Pinsard N, Bernard R: Aspects diagnostiques des

occlusions artérielles cerebrales Ann Pédiatr (Paris) 27: 227, 1980
9. Merrick J: Acute hemiplegia in infancy and childhood. NDK-Ugeskr Laeg 141: 1567, 1979
10. Miwa S, Murata T, Okumura A: Basilar artery occlusion in childhood. Brain Develop (Tokyo) 10:350, 1978
11. Paraicz E, Szénássy J, Király M, Vajda J: Angiography of cerebral arterial diseases in childhood. In: Reconstructive Surgery of Brain-Arteries, ed Mérei FT Akadémiai Kiadó, Budapest 1974
12. Rajakulasingam K, Cerullo LJ, Raimond AJ: Childhood Moya-moya syndrome of postradiation pathogenesis. Child's Brain 5:467, 1979
13. Selby G, Walker GL: Cerebral arteritis in cat scratch disease. Aust Neurol 29: 1413, 1979
14. Solomon G, Hilary S, Gold P, Carser S: Natural history of acute hemiplegia of childhood. Brain 93: 107, 1980.
15. Weigel K, Ostertag CB: Traumatic occlusion of the middle cerebral artery. Neurochirurgia 24:30, 1981

*Received 25 March 1983*

I Dobronyi MD
Amerikai út 57
1145 Budapest, Hungary

*Acta Paediatrica Hungarica, 24 (4), pp. 367—370 (1983)*

PRELIMINARY COMMUNICATION

# Non-invasive examination of pulmonary stenosis by transcutaneous Doppler technique

M BARBACKI, K SANDHAGE

Children's Clinic No. 1, Cracow, Poland, and University Children's Hospital, University of Würzburg, FRG

Analysis of the transcutaneous Doppler velocity blood flow curve was performed in a 12 year old girl with pulmonary stenosis. The blood flow indices of the pulmonary artery were compared with those obtained in a control group.

To our knowledge, transcutaneous Doppler analysis of the blood flow curve of the pulmonary artery in children with pulmonary stenosis has not been performed. In the present paper such an attempt is reported.

## MATERIALS AND METHODS

The 12 years old girl W.G. had slight pulmonary stenosis confirmed by angiocardiography. The only abnormal value was the right ventricular pressure of 36–40/0 mm Hg. As a control group, 26 healthy children were examined. A Siemens Doppler ultrasound blood flow detector transmitting a continuous beam of 5 MHz was used. A Doppler probe, containing piezoelectric transducers of 16 $mm^2$ area was applied to the second left intercostal space near the sternum, using an ultrasonic contactant. The purest and loudest sound audible in the loudspeaker was obtained by gently maneuvring the probe. The sound was registered by a three-channel recorder together with the ECG and phono curves from standard limb leads (Fig. 1).

In each child four ultrasound systolic flow complexes of the clearest outline and greatest amplitude were analysed. The measurements performed were (Fig. 2):

(a) indices of blood flow with respect to time (in ms)

1. $t_{max}$ = initial maximal acceleration time: interval between the beginning upslope of the ultrasound systolic wave (s.w.) and the point of projection of the peak of the initial steeper upslope of s.w. (s.u.s.w.) on the baseline
2. $t$ = entire acceleration time: interval between the beginning upslope of s.w. and the point of projection of the peak of s.w. on the baseline
3. PEP = interval between the beginning of the ECG Q wave and the upslope of s.w.
4. $t_{max}/t$,
5. $PEP/t_{max}$,
6. $PEP/t$

(b) indices of blood flow with respect to velocity or velocity and time (in irrational units)

1. $w/c^*$ $(=V_1')$
2. $w_1/c$ $(=V_1'')$

* w, $w_1$, c = amplitude (in mm) of the peak of s.u.s.w., the top of s.w. and one step of the device's scale, respectively (Fig. 2)

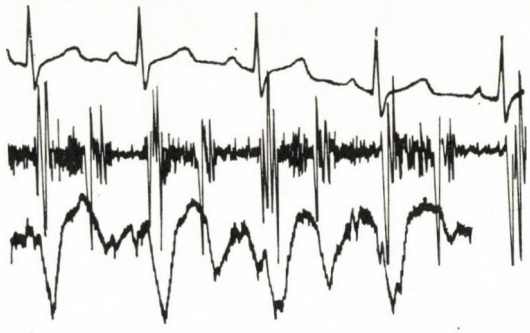


FIG. 1. Doppler velocity blood flow curve of pulmonary artery (below) in patient registered synchronously with ECG and PCG curves

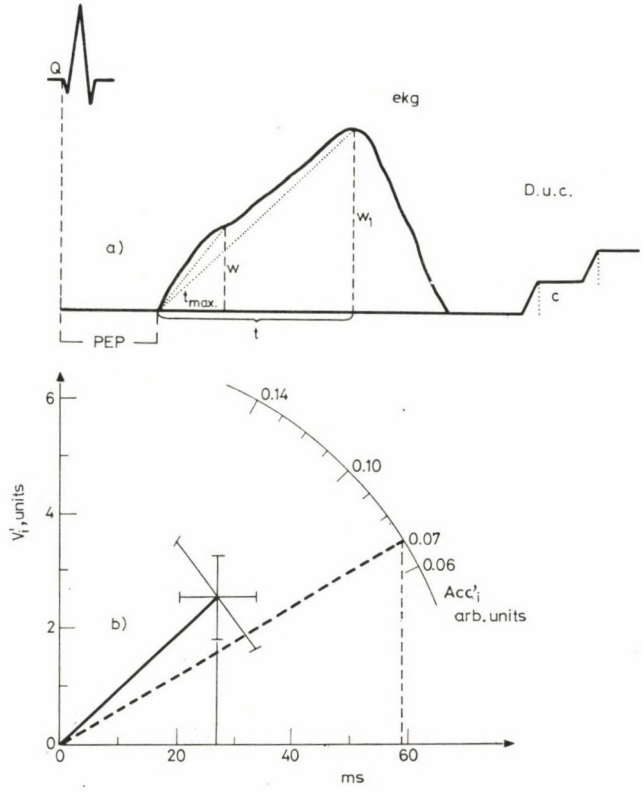



FIG. 2. Panel a: method of derivation of choiced blood flow indices from Doppler curve. Dotted lines represent the approximate values of blood acceleration during $t_{max}$ or $t$. Panel b: scheme representing the blood flow indices concerning the initial upslope of the Doppler curve. Continuous line (with SD values) and broken line represent the control group and the patient, respectively. Other designations are explained in the text

3. $V'_i/V''_i$ = instantaneous initial and entire linear blood velocity and their quotient, respectively
4. $dV'_i/dt_{max}$ ** ($=Acc'_i$)
5. $dV''_i/dt$ ($=Acc''_i$)
6. $Acc'_i/Acc''_i$ = instantaneous initial maximal and entire linear blood acceleration and their quotient, respectively
7. $V'_i \times t_{max}/2$ ($=A'_i$)
8. $V''_i \times t/2$ ($=A''_i$)
9. $A'_i/A''_i$ = area under the s.u.s.w., under the entire ultrasound flow systolic curve and their quotient, respectively.

## Results

The greatest differences (the values above 2 SD of the mean of the control group) between the patient and the healthy children with respect to the value of $t_{max}$ (which was higher in the patient) and some of its derivatives ($t_{max}/t$, $PEP/t_{max}$, $A'_i$, $A'_i/A''_i$), were measured (Fig. 2).

## Discussion

Non-invasive techniques such as the ultrasonic Doppler method now gradually replace heart catheterization and angiocardiography [1, 6, 7]. A continuous wave device with broad beam and lack of range-gating as compared to pulsed ultrasonic Doppler techniques, was used in this study. A close similarity between the pulsed and the continuous wave data was regularly found by some authors and the differences appeared to be within the range of normally occurring short-term variations and experimental error [3].

Pulmonary artery blood flow was determined by other authors from the second left intercostal space by means of Doppler devices in newborns, children and adults [1, 2, 7].

Indices with respect to time (expressed in ms) can be obtained from the Doppler curve. The technique, however, offers no possibility to obtain real values for blood velocity in the pulmonary artery, thus in the present paper the indices of that velocity are expressed in irrational units.

In the present study the greatest differences between the indices concerning the initial upslope of the Doppler curve of the patient and the control group were caused by an elongation of the $t_{max}$ which in spite of the greater $V'_i$ caused the comparatively low value of $Acc'_i$ in the patient (Fig. 2).

The other non-invasive method of circulatory system examination, regarded till now as the most precise of all non-invasive techniques, is tetrapolar impedance rheography [4, 5]. Recently, Szafjanski and Palko have performed a quantitative estimation of the blood flow in the right pulmonary artery in children by means of their own method based on the current tetrapolar technique of transthoracic impedance measure-

** measurement of the linear blood acceleration or calculation of indices with respect to the area, was performed by triangular approximation (Fig. 2)

ment along the course of that artery [9].

The results presented in this paper concerning $t_{max}$ agree well with those of Szafjanski et al. [8] who examined a few children with pulmonary stenosis by means of their own impedance method.

Further studies will have to decide whether the Doppler method would prove of use in the diagnosis as well as in the quantitative evaluation of pulmonary stenosis.

## References

1. Brubakk AO, Angelsen BAJ, Hatle L: Diagnosis of valvular heart disease using transcutaneous Doppler ultrasound. Cardiovasc Res 11:461, 1977
2. Cross G, Light LH, Sequeira RF: Transcutaneous comparison of blood flow velocity in the aorta and pulmonary artery in children. J Physiol (Lond) 240:16P, 1974
3. Huntsman LL, Gams E, Johnson CC, Fairbanks E: Transcutaneous determination of aortic blood flow velocities in man. Am Heart J 89:605, 1975
4. Lababidi Z, Ehmke DA, Durnin RE, Leaverton PE, Lauer RM: Evaluation of impedance cardiac output in children. Pediatrics 47:870, 1971
5. Lang E, Durst OE, Weikl A: Die Impedanzkardiographie. Bedeutung der Methode und ihre Grenzen. MMW 116: 1661, 1974
6. Sequeira RF, Light LH, Cross G, Raftery EB: Transcutaneous aortovelography. A quantitative evaluation. Br Heart J 38:443, 1976
7. Stevenson JG, Kawabori I, Guntheroth WG: Pulsed Doppler echocardiographic evaluation of the cyanotic newborn: identification of the pulmonary artery in transposition of the great arteries. Am J Cardiol 46:849, 1980
8. Szafjanski B, Czarnowska-Kozub M, Gizycka I, Sielska M, Potocka K, Palko T: Examination of pulmonary blood flow by means of own impedance method in patients with congenital heart diseases and stenosis of pulmonary artery. In: Proc. Conference on Diagnosis and Surgical Treatment of Congenital Heart Diseases and Rhythm Disorders in Children (in Polish). Polish Academy of Sciences, Warszawa 1982. No. 15
9. Szafjanski B, Palko T: Impedance rheography for determination of systemic and pulmonary blood flow (in Polish). Pediatr Pol 56:1121, 1981

*Received 20 April 1982*

M Barbacki MD
Boh. Stalingradu 77/11
31-052 Kraków, Poland

*Acta Paediatrica Hungarica, 24 (4), pp. 371—379 (1983)*

# Book reviews

H. WENDT, R.-M. KUMMER, G. TUCHSCHEERER: *Spieltherapiekatalog.* 144 Seiten mit 122 farbigen Abbildungen. Georg Thieme, Leipzig 1981. Preis M 25,—

Die Zielsetzung der Verfasser war, den im Gesundheits- und Schulungswesen tätigen Fachkräften, sowie den Eltern verhaltensgestörter Kinder ein Hilfsmittel zur effektiven Spieltherapie vorzulegen.

Der Katalog dürfte jedoch in dieser Hinsicht ziemlich wenig bieten. In dem einleitenden Kapitel über die Bedeutung des Spielens für die Persönlichkeitsentwicklung wird die Frage in erster Linie von Seiten der kognitiven Funktionen und Bewegungsübungen angenähert. Das, was man über die Wichtigkeit des Spielens für die affektive Entwicklung und die grundlegend wichtige Rolle bei der Entfaltung der symbolischen Funktionen, Phantasie und Kreativität findet, scheint viel zu wenig und blaß zu sein. Die elaborative Rolle des Spielens wird nicht erwähnt, wo doch ohne die Erkennung der elaborativen Funktion und deren therapeutische Anwendung in der Spieltherapie von ihrem wesentlichsten therapeutischen Effekt beraubt wird. Es wird angedeutet, daß die Beobachtung des Spielens die Erschließung der psychischen Probleme ermöglicht, doch werden dazu keine Anhaltspunkte angegeben, und der größte Teil der angeführten Gruppenspiele eignet sich zur Realisierung der Konfliktenthüllung nicht.

Der Therapieablauf ist in vier Phasen eingeteilt: in der ersten wird die Lockerung des Verhaltens, in der zweiten die Anregung zur Aktivität, in der dritten die Ausgestaltung von Bindung und Identifikation — hauptsächlich in Rollenspielen —, und in der Endphase die Förderung von Selbständigkeit und Entscheidungsfähigkeit — durch Konstruktions- und Regelspiele — erstrebt.

Die im Buch demonstrierten praktischen Hinweise sind für Erzieher in Kindereinrichtungen sehr nützlich, sie eignen sich aber weniger zur Planung eines Therapieverlaufes.

Die Literaturangaben sind ziemlich alt und unvollständig, es fehlen viele eminente Namen des Gebietes der Spieltherapie, so z.B. M. Lowenfeld, Autor des "Weltspiel" Spieltests und Therapiemittels.

Agnes L. ENGELMAYER

*Antibiotika-Prophylaxe in der Pädiatrie.* Herausgegeben von M. KIENITZ und D. ADAM. XII + 212 Seiten mit 10 Abbildungen und 58 Tabellen. Gustav Fischer Verlag, Stuttgart–New York 1982. Preis DM 34,—

Das Buch beinhaltet die Referate und Diskussionen einer in Frankfurt am Main im Jahre 1980 abgehaltenen Arbeitstagung, an der mehrere kompetente deutsche Wissenschaftler die vielschichtigen und oft kontroversen Probleme der Antibiotika-Prophylaxe zur Debatte stellten.

Das Thema wurde um fünf Fragen gruppiert: 1. Grundlagen; 2. Prophylaxe bei primär gesunden Kindern; 3. Infektionsprophylaxe in pädiatrischen Institutionen;

4. Infektionsprophylaxe bei vorgeschädigten und chronisch kranken Kindern; 5. Kinderchirurgische Indikationen. Im Rahmen dieser Teile wurden etwa 23 Probleme eingehend besprochen. Der erste Teil faßt die bakteriologischen und immunologischen Grundlagen zusammen, der zweite Teil ist der Prophylaxe bei Meningokokkeninfektionen, Pertussis, Haemophilus influenzae, A Streptokokkeinfektion und Tuberkulose gewidmet. Im dritten Teil finden wir die in den Kliniken und Institutionen auftretenden Infektionen und deren mögliche Prophylaxe, z. B. enterale Staphylokokken oder Streptokokkeninfektionen, ferner allgemeine und spezielle Maßnahmen bei Früh- und Neugeborenen oder bei lokalen therapeutischen Eingriffen. Im vierten Teil werden die Reinfektionsprophylaxe bei Harnweginfekten, beim nephrotischen Syndrom, Vorbeugungsmöglichkeiten beim rheumatischen Fieber, bei Herzfehlern, Infekten nach Splenektomie, bei chronischen Atemweginfektionen, Mukoviscidose, Leukämie, Immundefekten und Meningitis purulenta behandelt. Das letzte Kapitel befaßt sich mit den Indikationen bei abdominalen Eingriffen, offenen Frakturen oder Weichteilverletzungen und Verbrennungen.

Jeder Beitrag wurde aufgrund bedachtsam gesammelter Literaturangaben und eigener Erfahrungen zusammengestellt. Abweichende oder gegensätzliche Meinungen wurden in den Diskussionen womöglich auf einen gemeinsamen Nenner gebracht. Das Symposium hat wieder bewiesen, daß es außer die klassischen Indikationen, wie Prophylaxe des rheumatischen Fiebers, noch eine Reihe von Erkrankungen und Eingriffen gibt, bei denen eine länger andauernde Antibiotikagabe in Frage kommen kann.

Für den Allgemeinarzt und in der Klinik tätigen Kinderarzt wird mit diesem Band eine nützliche Orientierungshilfe über den derzeitigen Stand der Antibiotika-Prophylaxe in der Pädiatrie in die Hand gelegt.

K. SCHMIDT

Ch. THIELE: *Grundriß der Kinderanästhesie.* 130 Seiten mit 40 Abbildungen und 34 Tabellen. Verlag Volk und Gesundheit, Berlin 1982. Preis M 45,—

Das Taschenbuch ist der 6. Supplementband zur Zeitschrift Anaesthesiologie und Reanimation. Für den praktisch tätigen Anästhesisten bietet es eine gute Zusammenfassung der Besonderheiten der kindlichen Anästhesie in einer korrekten und didaktischen Gliederung vom Säuglingsalter bis zum Schulalter.

Einleitend werden Körpermaße, Atmung, Kreislauf, Wasser-Elektrolyt-Haushalt, Nierenfunktion, Säure-Basen-Haushalt und Temperaturregulation erörtert. Das nächste Kapitel ist der Pharmakologie der Narkose gewidmet, wobei auch auf die Nebenwirkungen hingewiesen wird. (Die in der DDR gebräuchliche Benennung einzelner Medikamente wirkt im Ausland etwas störend.) Besonders eingehend werden die Eigenschaften von Halothan und die leberschädigenden Faktoren des Mittels besprochen. Bei der Aufzählung der intravenösen Narkotika vermißt man einige Steroide und Muskelrelaxanzien. Außer den technischen Voraussetzungen wird die Bedeutung der entsprechenden Überwachung ausführlich behandelt. Im Abschnitt über die Indikation und Technik der Intubation wird die nasotracheale Intubation kurz berührt, im Hinblick auf ihre Rolle im Kindesalter vielleicht zu kurz. Für die Anwendung von Tuben mit Manschetten gibt die Autorin das 7 Lebensjahr an; im allgemeinen wird unte. 10 Jahren darauf verzichtet. Man vermißt die Erwähnung der im Kindesalter sich gut bewährten Lokalanästhesie. Die Tabellen, die hinsichtlich der Infusionstherapie den prä-, intra- und postoperativen Flüssigkeitsbedarf demonstrieren, sind äußerst nützlich. In dem Kapitel über die Komplikationen der Anästhesie und deren Verhütung und Therapie finden wir außer den wohlbekannten die sehr seltenen, doch gefährlichen Störungen, wie z.B. die maligne Hyperthermie. Auf einer mehr-

seitigen Tabelle werden abschließend die anästhesiologischen Besonderheiten bei einigen pädiatrischen Syndromen angeführt.

Das Thema und der wertvolle Text der Monographie hätten besseres Papier und vor allem bessere Zeichnungen verdient. Außer Anästhesisten wendet sich die Arbeit auch an Kinderchirurgen und Anästhesieschwestern.

Kinga JELLINEK

J. EICHHORN, R. GOETZE, M. KLEIN: *Zu Problemen der Diagnostik, Erziehung und Bildung bei Kindern mit autistischem Syndrom*. 118 Seiten mit 2 Abbildungen und 11 Tabellen. Verlag Volk und Gesundheit, Berlin 1982. Preis M 29,—

Das Buch besteht aus vier Abhandlungen der drei Autoren. Das Gepräge, die Schreibweise der einzelnen Beiträge ist wohl unterschiedlich, sie bieten aber ein umfassendes Bild über das Thema.

Die Arbeit von M. Klein beruht auf Untersuchungen und Nachuntersuchungen an 33 autistischen Kindern, die von 3000 Patienten der kinderpsychiatrischen Klinik in Brandenburg wegen spezifischen Kontaktstörungen ausgewählt wurden. Die gründliche und gut dokumentierte Untersuchung sucht eine Antwort auf die Fragen der ätiologischen Faktoren, die Aussichten von Entwicklung und Förderung zu finden. Der Verfasser betrachtet den kindlichen Autismus als Folge einer im Frühkindesalter erlittenen Hirnschädigung mit sekundärem Mentaldefekt, bei dem die Kontaktstörung nur ein Teilsymptom darstellt. Das Erreichen einer "relativen Selbständigkeit" hängt eher von der Zeitdauer der Förderung als vom Intellekt ab. Der initiale Schweregrad der Kontaktstörung hat keine prognostische Bedeutung für die spätere Förderungsmöglichkeiten.

Zwei Kapitel von R. Goetze befassen sich mit der rehabilitativen Spracherziehung. Es wird betont, daß die Sprache als Mittel der Verständigung, des Erkennens, Denkens und der Verhaltensregulation in einem einheitlichen Prozeß aufgebaut werden, daß die Erziehung in der präverbalen Phase begonnen werden soll. Vier demonstrative Tabellen fassen beiliegend die Modelle zur Führung des Sprachaufbaus zusammen.

Der letzte Teil des Bandes ist die deutsche Publikation der in London 1979 erschienenen Studie von J. Eichhorn. Der seither verstorbene Autor schildert in dieser Arbeit in allen Einzelheiten die sich bei autistischen Kinden und Jugendlichen ergebenden Probleme, Fragen der Lebensführung, Förderung und sozialen Anpassung. Aus dem Text dieser Abschnitte zeichnet sich plastisch die eigenartige Persönlichkeit dieser Kinder und auch die grenzlosen Bemühungen der Betrauer ab und dies aufgrund des Wissensgut und der Beobachtungen einer Autorität und des tief humanen Menschen, der Jahre hindurch mehrere autistische Kinder in seine eigene Familie aufgenommen und mit seiner Frau rehabilitationspädagogisch betreut hat.

Das Buch ist als Band 36 der Schriftenreihe Beiträge zum Sonderschulwesen und zur Rehabilitationspädagogik erschienen.

Mária LADÓCSY

LECHNER, K.: *Blutgerinnungsstörungen*. XII + 268 Seiten mit 22 Abbildungen. Springer-Verlag, Berlin–Heidelberg–New York 1982. Preis: DM 78,—

Dieses Buch ist der zweite Band der "Laboratoriumsdiagnose hämatologischer Erkrankungen". Es gliedert sich in 12 Kapitel. Das erste ist eine kurze aber präzise Beschreibung der Physiologie der Hämostase und der wichtigsten biochemischen Eigenschaften der Gerinnungsfaktoren. Im zweiten und dritten Kapitel wird ein Überblick über die angeborenen und erworbenen Störungen der Gerinnungsfaktoren bzw. über die Hämostasestörungen bei verschiedenen Organ- und Organsystemerkrankungen gegeben. Im vierten Kapitel

beschreibt der Autor die Pathogenese der Immunkoagulopathien, wobei er besonders die gegen einzelne Gerinnungsfaktoren entstehenden Inhibitoren und Lupus-inhibitoren hervorhebt. Der fünfte Abschnitt beschäftigt sich mit der Pathogenese, den Verlaufsymptomen und der Diagnose der disseminierten intravaskulären Gerinnung. Im folgenden Kapitel werden die Physiologie und die Funktion der Plättchen sowie die quantitativen und qualitativen Störungen insbesondere der biochemische Hintergrund der Funktionsstörungen beschrieben. Im siebten Abschnitt berichtet der Verfasser über die Biochemie der Fibrinolyse und der fibrinolytischen Aktivität und über die Abweichungen bei verschiedenen physiologischen und pathologischen Zuständen. Desweiteren beschäftigt sich das Buch mit den Labor-Untersuchungsmethoden. Ein allgemeines Einführungskapitel erörtert die allgemeinen Prinzipien bei der Laboratoriumsdiagnostik, die technischen Bedingungen, Reagenzien, Antikoagulantien, die normalen Werte und die Interpretation der Ergebnisse. Danach folgt eine Beschreibung des Global- und Suchtests und dessen Ausführung. Die weiteren drei Kapitel enthalten die Methoden zur Bestimmung der Aktivität und Konzentration der einzelnen Gerinnungsfaktoren, der Thrombozytenzahl, der Plättchenfunktionen und schließlich des fibrinolytischen Enzymsystems.

Die Darlegung der einzelnen Laboratoriumsmethoden ist ausführlich und gut verfolgbar. In jedem Fall wird das Prinzip der Methode, die Vorbereitung der Reagenzien, die genaue Durchführung der Untersuchung, die Auswertung und Bedeutung der Ergebnisse geschildert. Schließlich wird auf die Probleme und Fehlerquellen der Methoden hingewiesen.

Der Aufbau und die Gliederung des Buches sind leicht überblickbar. Beim Gebrauch helfen die Tabellen und Abbildungen im Text sowie das ausführliche Fachregister. Der bekannte Autor faßt in seinem. Buch die modernsten Kenntnisse der Physiologie und Pathologie der Hämostase zusammen, worauf auch die 616 Referenzen aus der Literatur hinweisen. Die Hämostasestörungen stellen ein interdisziplinäres Problem dar, deshalb dürfte das Buch nicht nur die Mitarbeiter des Labors sondern auch alle klinischen Fachärzte interessieren.

B. GOLDSCHMIDT

G. KÖTELES: *X-ray Diagnosis in Neonates.* 174 pages with 124 tables. Akadémiai Kiadó, Budapest 1982. Price DM 46,—, USA $ 18.50

To handle newborn babies is a difficult task even for the young mother. To evaluate the X-rays of babies is a delicate work even for the experienced radiologist not accustomed to such patients. There are other difficulties too with small babies. For instance, the diagnosis is mostly urgent and another difficulty is the patient's inability to cooperate. This little book is intended to help the radiologist in these and similar situations. He will find answers and advice concerning some important diseases and pathologic features of the baby in a concise manner for which heavy handbooks and encyclopaedias have to be searched thoroughly.

In the first chapter the equipments and their use are described and explained by illustrations. The instruments required are enumerated without omitting a single necessary one but not demanding superfluous luxurious miracles. Those listed are fully sufficient for an up-to-date investigation provided the advice and instructions are accepted.

The subject itself is discussed in 5 chapters. These usually begin with a general introduction describing the methods to be used in the special case. The main problems are elucidated in a concise style. The examination is always begun with the simplest method, a plain film. More sophisticated procedures are only employed when this was not sufficient. Non-invasive

methods are always given preference over invasive ones. It is stressed that arteriography, pyelography, scintigraphy, etc., and also CT should only be applied when absolutely necessary.

Some syndromes and related diseases are shown in a logically and clearly arranged table for quick and reliable orientation in these conditions. (There is a small mistake on p. 95: instead of mediastinum, diaphragm is here the correct word.)

The roentgenograms are well-chosen and very illustrative, and most are of good quality. The references are well-chosen and informative.

Ch. M. GEFFERTH

R. SMITH, M. J. O. FRANCIS, G. R. HOUGHTON: *The Brittle Bone Syndrome.* Osteogenesis imperfecta. IX + 218 pages, Butterworths, London 1983. Price £ 30

In this book the rare heritable disorder known as osteogenesis imperfecta is dealt with. The authors' experience is based on 333 personally collected cases. The condition has gained general interest when new investigations had thrown light onto the biochemical changes of connective tissue in the condition. The title of the book was chosen to point to the multiple causes and manifestations of which fragility of bones is merely the main and most conspicuous symptom.

The book consists of 9 chapters. The first is an introduction and clinical summary of the symptoms, of the many synonyms and classifications of the disease. In chapter 2, the skeletal changes are delineated, separately, the severe and the light forms and the peculiarities of infant, child and adult patients are discussed. Emphasis is laid on the strikingly different features of the various forms. The authors distinguish four types including two less defined forms. Extraskeletal, earlier insufficiently respected features are dealt with in chapter 3, comprising the eyes, ears, teeth, skin, joints, the heart and great vessels. Other connective tissue disorders associated with the syndrome are listed in two tables. Pathology is interpreted in chapter 4, beginning with the different findings in skin, bones, ears and eyes due to the heterogeneity of the cases. Earlier and recent biochemical results are compiled in chapter 5, many of them achieved by the authors themselves. Anything that has been revealed in this field concerning the biosynthesis and metabolism of collagen and of connective tissue in general is registered critically, including the relations with phosphate, magnesium and leukocytes. Chapter 6 is devoted to genetics and inheritance; of the four possible forms of the condition, two are inherited as autosomal dominant and the two severe forms including the lethal type as recessive. Diagnosis and differential diagnosis are explained in chapter 7, calling attention to the mild forms often lacking characteristic symptoms. All the possible features of medical and surgical treatment are discussed in chapter 8 where it is concluded that a good education is the most important aid to these intelligent and mentally sound individuals. The rapidly advancing research necessitated to compile the most recent results obtained during preparation of the book in chapter 9, in which papers and meetings held even in 1982 (less than one year before publication of the book!) are considered. In spite of this, many questions have been left open, for instance the relation between clinical features and biochemical findings.

The references occupy more than 33 pages and include papers of not only English-speaking but also many other European authors. It is unfortunate that some names are misspelt (for instance that of the internationally revered Robert Debré and his collaborators), and some German titles are entirely distorted, but this in fact is the only error in this excellent and up-to-date monograph embracing all the old and the most modern knowledge, giving an overall review of investigations,

results, related conditions, differential diagnostic problems and therapeutic possibilities in osteogenesis imperfecta.

CH. M. GEFFERTH

V. M. NESTLER, H-L. SPOHR, H-C. STEINHAUSEN: *Die Alkoholembryopathie*. VI + 98 Seiten mit 13 Abbildungen. Ferdinand Enke Verlag, Stuttgart 1981. Preis DM 39.—

Dieses Büchlein, das der Rezensent leider mit zwei Jahre Verspätung in die Hände bekam, beginnt mit einer Übersicht der bis 1979 erschienen zu Mitteilungen zum Thema (aus 1980 und später stammen nur die Arbeiten des dritten Autors). Diese Übersicht ist musterhaft und gibt eine klare Zusammenfassung der Probleme auch für jene, die sich mit der Frage nie befaßt haben. Danach folgt die Beschreibung der eigenen Untersuchungen. Diese erstreckten sich auf 71 Kindern mit Alkoholsyndrom vom Säuglings- bis zum Jugendalter und 28 Kontrollen. Pädiatrisch wurden all diese Kinder untersucht, doch neurologisch konnten nur 26 und "testpsychologisch" 32 untersucht werden. Dagegen wurde ihre körperliche und ganz besonders ihre psychologische Entwicklung sorgfältig verfolgt. Die Auswertung der Befunde ergab natürlich keine wesentlichen Abweichungen von den früheren Angaben, nur wurden gehäufte Krampfanfälle und ein erhöhtes Ausmaß pathologischer EEG-Befunde ermittelt. Die Häufigkeit in der Neugeborenen-Gesamtpopulation ist auf 1 : 2000 geschätzt, und unter den Berliner Kranken kam die schwerste Form weniger häufig (22,5%) vor als im Tübingener Material von Bierich und Majewski (30%). Leider wurde es gar nicht versucht, die nähere Pathogenese zu klären, und auch vom Alkoholkonsum der Mütter wird nur angegeben, daß bei 28 Frauen der Tagesdurchschnitt 140 g war.

Das Buch dürfte auch noch heute die Forscher des Syndroms interessieren.

P. V. VÉGHELYI

J. VERBOV, N. MORLEY: *Colour Atlas of Paediatric Dermatology*. 157 pages with 370 full-colour illustrations. MTP Press, Lancaster 1983. Price £ 32.50

The needs of medical students, general practitioners, specialists of paediatrics or dermatology were kept in mind by the authors when writing this atlas. For the non-dermatologist, description of a skin disorder and its diagnosis is usually difficult, especially if the patient is a child. The most interesting themes were selected by two excellent clinicians with a sharp eye for practice. Very laudably, the rich material has been divided into as few as eleven chapters, this greatly facilitates orientation.

I. Malformations. Pigmented naevi and various haemangiomas, both discrete and extensive, are presented. Regression of vascular naevi is also demonstrated. A number of pictures of epithelial naevi (n. sebaceus, n. verrucosus, etc.) is offered. II. Only the most important and striking genodermatoses are discussed: the various forms of ichthyosis, ectodermal dysplasia, xeroderma pigmentosum and acrodermatitis enteropathica. III. Here the most frequent neonatal and infantile skin diseases are illustrated. Napkin dermatitis is discussed in a modern interpretation. Many plates illustrate seborrhoid dermatitis and napkin psoriasis, a disorder common in England. The pictures of infectious processes are very convincing. IV. The rich picture material of atopic dermatitis is discussed widely in the text, according to the high number of manifestations. V. Comparatively small space is devoted to changes induced by pyogenic agents, while viral skin diseases receive more attention. Characteristic pictures demonstrate the fungal diseases and the conditions caused by parasites, disorders nowadays showing an increasing incidence. VI. The chapter on psoriasis is rather detailed. This is only natural since the incidence of this disorder is increasing everywhere in the world. A single and not too characteristic plate

illustrates the Mucha-Habermann disease in spite of its incidence being high. Only a small number of other papulosquamous disorders is discussed. VII. The chapter on vascular disorders deals with various conditions of purpura and malignant and benign vasculitis. Mastocytosis is also discussed in this chapter; this classification is incorrect in the reviewer's opinion. VIII. Both the plates and the text illustrating connective tissue disorders are very instructive. IX. The most genuine chapter describes and depicts the classification, aetiology and therapy of bullous disorders; these pictures are excellent. X. The plates of nail and hair disorders are useful in practice. Especially the pictures demonstrating the nail disorders are remarkable. XI. A very useful chapter on miscellaneous topics (some rare diseases, faults in cosmetics, side-effects of drugs, damage induced by therapy etc.) closes the book.

Colour and quality of the great majority of the plates are excellent, the explanations are concise and clear and contain a short description of therapy of the disorder in question. The atlas should be available for all physicians dealing with children.

Eva TÖRÖK

*London '82 ICACI XI. International Congress of Allergology and Clinical Immunology.* Edited by J. W. KERR and M. A. GANDERTON. The Macmillan Press Ltd, London 1983. 560 pages. Price £ 25.00

The eleventh congress of the International Society of Allergology and Clinical Immunology was held in London in October, 1982. Twenty topics were discussed by invited experts in symposia and a large number of free papers and posters were presented. At the time of the congress abstracts were available, while the full text of the symposia, free communications and posters has been edited in this book. References have also been added to the texts read at the congress.

The topic of the first symposium were the mediators of allergic tissue reactions. Samuelsson presented an excellent review on the role of leukotrienes in allergy, the biochemistry of compounds derived from arachidonic acid by lipoxygenase activity and their role in allergy mediation was here discussed. Krilis and coworkers reviewed the biochemical aspects of the same topic. It appears that development of leukotriene antagonists may later play a role in treatment of atopic disorders.

Another symposium dealt with allergic reactions to drugs. The most exciting review was given by Schlumberger on the differentiation between real, instant type drug reactions with demonstrable IgE antibodies and transferable reactivity and the mostly genetically determined pseudoallergic reactions; here the drug itself or some of its metabolites act directly on the immunological effector system.

Prevention of atopic allergic diseases was the main problem discussed at the symposium on paediatric allergy. Special stress was placed on early elimination of known allergens, nutritional ones included, from the environment. Michel et al. offered a list of characteristics of high allergic risk infants and newborns; they declared that parental allergy brings about a risk for allergy in the infant as high as 20 to 80%. IgE levels and IgE immunoglobulins, and cells in the cord-blood, season of birth, gender of the neonate are valuable factors in predicting allergy of the infant.

Only a list of titles of some other symposia can be given here: fibrosing alveolitis, dermatological allergy, food allergy, cell membrane, drug receptors, antibody receptors, diagnostic procedures, modern drug treatment, immunological aspects of allergy, present state of asthma research, role of IgE and IgG, regulation of IgE response airway hyperreactivity, occupational respiratory allergy, allergy to animals and insect stings, the role of lymphocytes in allergic reactions, pharmacokinetics of antiallergic drugs, purification and characterisation of allergens.

The reader obtains an excellent panorama of the present state of allergology and of its most important aspects. It appears that somewhat in contradiction to the title of the congress, clinical immunology played no souverain role, its problems were only mentioned in fields closely connected to allergology.

E. CSERHÁTI

*The asthmatic child in play and sport.* Edited by S. OSEID and A. M. EDWARDS. Pitman Books Ltd, London 1983. Price £ 20.00

Recently, there has been an increasing interest in the consequences of sports and physical load in asthmatic children. This book which is based on the material of a symposium held in Oslo will be useful for experts in the field and general paediatricians alike. The editors have succeeded in rounding up the style of spoken information and in offering a review of the whole field. The participants were all excellent experts, the information supplied by them is up-to-date.

Part one deals with the role of physical activity in the life of children and adolescents. Physical activity is regarded as a part of harmonious development. In the second part exercise induced asthma (EIA) is split off from the heterogeneous group of childhood asthma and its physiological and biochemical aspects are discussed and the pathomechanism of asthma is also briefly reviewed. Problematic aspects of EIA (diagnostic procedures, influence of the environment, loading tests, refractory period) are duly dealt with. A separate chapter describes the standardized techniques of the diagnostic work-up with many useful and practical hints. The fourth part informs about the mode of action of drugs and is helpful in planning pharmacodynamic studies. In addition to the effect of dinatrium cromoglycate, other drug effects are also discussed. The part on the role of physical activity in habilitation and rehabilitation offers an objective and sober picture on this complementary tool. The last chapter describes the practical and organisatory aspects of physical activity treatment. All papers are supplied by copious references.

The great advantage of the book is that it contains the full text of the discussions, opening thus insight into the problematic questions.

J. KELEMEN

Marjorie A. ENGLAND: *A Colour Atlas of Life Before Birth. Normal Fetal Development.* Wolfe Medical Publications Ltd. London 1983. Price: £ 25.—

This atlas offers a complete review of the whole intrauterine development of the human being. From the stage of a zygote resulting of an in vitro fecundation all stages are followed in 1—2 days intervals up to the embryo of 46—48 days. From the 7th week there are illustrations for every week up to full-term birth. The author distinguishes preembryonal, embryonal and fetal stages, within embryogenesis she discriminates an early embryonal stage (up to the 7th week), organogenesis is counted from the stage of coeloma. For the period from fertilisation to 48 days the XXIII horizons of Streeter are used and, in addition, all embryos are demonstrated with exact size and magnification data. Thereby the material, part of which originates from world-known collections, is internationally comparable.

The excellent technique of preparation and photography helps the reader to understand sophisticated processes of organ development e.g. the very complicated evolution of the heart or the gastrointestinal tract. The embryo photograms are usually supplemented by microphotograms of histological sections made of the same embryo. Ultrasonograms of fetuses aged 12 to 23 weeks are a new aspect of the topic, and arteriograms and radiographic records can also be found. The vascular system is illustrated by corrosion prepara-

tions. Development of the osseous system is visualized by the alizarine-red method.

In accordance with the style of an atlas, there is hardly any text, but this little is very comprehensive. All clinical and practical aspects and also a number of malformations receive due attention by being signed by a black point. The atlas is completed with an extremely useful glossary.

This atlas of human intrauterine development seems to me the top in all respects: beauty, perfection, technique are all second to none. To read it is an unprecedented experience.

G. KISZELY

2ND INTERNATIONAL CONFERENCE

# Fetal and neonatal physiological measurements

2nd—4th April, 1984

OXFORD, ENGLAND

Subjects:
- Fetal cardiac investigations
- Cerebral measurements
- Fetal breathing
- Fetal blood gas and pH measurements
- Measurements in neonatal cardiology
- Neonatal respiratory measurements
- Neonatal blood gas and pH measurement
- Sudden infant death syndrome
- Nuclear magnetic resonance and positron emission tomography
- Perinatal technology in developing countries

Information: Dr Peter Rolfe
Department of Paediatrics
University of Oxford
John Radcliffe Hospital
Oxford OX3 9DU
United Kingdom

PRINTED IN HUNGARY

Akadémiai Kiadó és Nyomda, Budapest

# Chart I

PATIENT'S NAME
Date of birth
Place of birth
Name of hospital
District
Transferred immediately following birth to other hospital
Name of hospital
District
Mother's age
Father's age
Gestational week
Birth weight

**INTRAPARTUM FACTORS**
- Preterm-dysmature
  - Delivered preterm
    Owing to impending
    Dysmaturity
    With steroid screen
- Difficult, long labour
  Umbilical cord impairment
  Aberrations in placental adherence
  Amniotic fluid (quality and quantity
  Caesarian section
  Forceps
  Vacuum extraction
  Very fast delivery

**NEONATAL INFECTIONS**
Sepsis
Meningitis
Meningoencephalitis

**ANTIBIOTIC THERAPY**
Lumbar tap
Subdural tap
Ventricular tap

**ANTEPARTUM FACTORS**
- Previous deliveries
  Normal
  Stillborn
  Abortions, habitual
  Abortions, artificial
  Treatment for sterility
- Neurologic diseases of living brothers and sisters
  Neurologic anomalies, diseases of dead sisters and brothers
  Neurologic diseases in maternal family
  Neurologic diseases in paternal family
- Fetal movements
  Siblings
  Sequence of birth
  Postural anomaly
- Planned baby
  Neurological or psychiatric disease during pregnancy
- Proven signs of placental dysfunction
  Proven signs of hydramnios
  Treatment owing to proven placental dysfunction
- Serum test for alfa feto protein performed
  Amniocentesis for alfa feto protein test (performed)
- Genetic anomalies
  Bacterial diseases: syphilis, listeriosis
  Viral diseases: rubella, herpes, simplex varicella, measles, epidemic parotitis, cytomegaly,
  Texoplasmosis
- Haemolytic diseases, serological conflicts
- Endocrine diseases: diabetes, hyperthyroidism, hypothyroidism
- Malnutrition: protein deficiency, vitamin deficiency, trace element deficiency
  Impaired circulation (chronic)
  Toxicosis
  Haemorrhage (excessive)
- Stress conditions
  Other factors

Possible intrinsic
Risk factors
Mother's disease
Family diseases

Extrinsic factors
- Chemical agents: nitro stains, alcohol, nicotine
  Drugs acting on the CNS and others
  Analgesics and anaesthetics during labour

- Traumatisation
  Caput succedaneum
  Cranial fracture laceration
  Cranial fracture with impression
  IC haemorrhage due to traumatisation
  Subdural haemorrhage
- Periventricular matrix haemorrhage
  Ventricular haemorrhage
  Subarachnoideal haemorrhage
  Hypoxia, hyalin membrane disease
  Hypoxia (other reasons)
  Unseparable hypoxia and IC haemorrhage
- Acute fetal distress
  Chronic fetal distress
  Aspiration
- METABOLIC DEFECTS
  Diminished $pCO_2$
  Decreased pH
  Acidosis (severe)
  Impaired cerebral perfusion
  Brain oedema
  Hypoglycaemia
  Hypocalcaemia
  Hypomagnesaemia
  Hyponetraemia
  Hypernatraemia

**NEUROLOGICAL FUNCTIONS AND DEFECTS**
Normal consciousness
Irritable
Hyperirritable
Jittery
Comatose state
Depressed, sleepy
Attentive
Non attentive
Visual fixation present
Visual fixation not present
Cochleopalpebral reflex present
Cochleopalpebral reflex not present
Oral and perioral reflexes present
Oral and perioral reflexes not present
Muscular tone normal
Muscular hypotonia
Floppy tone
Muscular hypertonia
Muscular spasticity
Muscular rigidity
Hemiparesis
Paraparesis
Monoparesis of right arm
Monoparesis of left arm

- Needs neurosurgery
- IC HAEMORRHAGE CONFIRMED BY
  - lumbar tap } positive
  - subdural tap } laboratory
  - ventricular tap } tests
- **TREATMENT**
  Needs full resuscitation (respiration, cardiac, metabolic)
  Needs respiration (intubation)
  Needs assisted respiration
  Needs $O_2$ by mask
  Needs infusion-hydration
  Needs dehydration
  Needs $O_2$ therapy (long term)

**RESULTS OF TREATMENT**
Fast improvement
Slow improvement
In between
Complete recovery
Partial recovery
No sign of neurological defect
Suspicious sign of some neurological defect
Positive signs of neurological defect

**PROGNOSIS**
Needs continuous observation in ward
Needs full developmental neurologic investigation
Needs continuous hospital treatment
Needs continuous careful observation in hospital
Must be transferred to special neonatal care unit
Must be transferred to other special institution (developmental neurology, paediatric surgery, neuro-surgery, cardiac surgery, other)
Can be discharged from hospital but needs careful longitudinal neurological observation
Needs neurohabilitation urgently

- Jaundice
  - Coombs test
    Blue light irradiation
    Enzyme induction
    Exchange transfusion
    Hydration-infusion
    Drugs

**CONVULSIONS**
Mass movements, extension
Local tics (facial, perioral, chewing)
Irregular respiration, apnae
Migrating muscular jerks
Irregular eye movements
Intact consciousness
Impaired consciousness
Convulsive state
Epilepsia partialis continua

**EEG**
- no activity
- depressed activity
- desorganised activity
- focal convulsive activity
- alterating high voltage activity
- normal activity

**ANTICONVULSIVE THERAPY**
STATUS EPILEPTICUS:
- diazepam iv.
- paraldehyde
- thiobarbiturate, oxibarbiturate

MAINTENANCE THERAPY:
- phenobarbital
- diphenylhydantoin
- ACTH

SPECIFIC THERAPY (INTRAVENOUS)
- glucose calcium gluconate
- magnesium sulphate pyridoxine

- Skin — Intact / Defective
- Dura — Intact / Defective
- Skull — Intact / Defective
  - Craniolacunae
  - Fracture
  - Plain X-ray picture
- Head and chest circumference in percentile — Normal / Enlarged / Small
- Brachycephaly
  Plagiocephaly
  Scaphoscephaly
  Turricephaly
  Craniosynostosis
- Parietal / Subbocipital / Frontal / Transpalatal
- Transillumination: Contains Cerebral Tissue
- Encephalocele

The skull and the brain

- Transillumination
  No transparency
  Slight transparency
  Substantial transparency
  Whole skull transparent
- X-ray
  CT
  Sonography
  Scintillography
  Venticulography
  PEG
  Angiography
- Microcephaly I
  Microcephaly II
  Trisomy 4p+, 4p−, 5p−d, 9+, 10q+, 13q, 22+
- SYNDROMES
  Apert
  Crouzon
  Greig
  Pfeiffer
  Russel
  Seckel
  Smith-Lemli-Opitz
  Cleidocranial dysostosis
  Collins
  Other syndromes

- Neurosurgery — Total removal / Subtotal removal
- Histology — Benign / Malignant

**BRAIN STRUCTURE (neuroradiology)**
- Normal
- Neoplasm
- Subdural fluid accumulation
- Hydrocephalus
- Hydranancephaly
  Cortical atrophy
  Porencephaly
  Polycystic periventricular leuco-malacy
  Watershead infarction
  Corpus callosum dysgenesis
  Holoprosencephaly
  Arhynencephaly
- Local haemorrhage
  Diffuse haemorrhage
  Vascular malformation

Confirmation (eventually neurohistological)
- by puncture and aspiration
- by the necessary operation

**LOCALISATION**
- Frontal lobe — Normal / Abnormal — Left / Right
- Parietal lobe — Normal / Abnormal — Left / Right
- Temporal lobe — Normal / Abnormal — Left / Right
- Occipital lobe — Normal / Abnormal — Left / Right
- Cerebellum — Normal / Abnormal — Left / Right / Vernis
- Basal ganglia — Normal / Abnormal — Left / Right
- Hypothalamus — Normal / Abnormal
- Brain stem — Normal / Abnormal

- Laboratory analysis — Normal / Increased protein level
- Fontanellar tap
  - Increased
  - Pressure recording — Normal
- Fontanellar tap / Stain test / Lumbar tap
  - Obstructive — Interventricular Aqueduct Foramen Magendie
  - Communicating
  - Dandy Walker
- Pressure recording — Hypertensive / Normal
- Complications — Haemorrhage, Subcutaneous leaking, Meningitis

- Subdural effusion
  - Aspiration — Successful
  - Drainage — Unsuccessful
  - Ventriculo-atrial valve — Craniotomy — Left / Right — Successful / Unsuccessful / Must be repeated
- Ventriculo-atrial valve / Ventriculo-peritoneal valve — Successful Repeated Removed / Regular control / Reoperation

**BRAIN FUNCTION (electric activity)**
EEG, evoked potentials
- Low voltage, depressed activity
- Dysrhythmic activity
- High voltage bursts
- Low voltage - high frequency
- High voltage - low frequency
- Spike and wave activity

**SEIZURES**
- Grand mal
- Petit mal
- Jackson type
- Irregular
- Consciousness — Lost / Preserved
- Vegetative signs — Present / Not present

**SIGNS OF OCCLUSIVE PROCESS AND DIMINISHED PERFUSION (angiography, scintillography)**
- Scintillography
- Emission tomography
- Computerized angiography
- Frontal cerebral artery — Right / Left
- Medial cerebral artery — Right / Left
- Posterior cerebral artery — Right / Left
- Basilar artery

**ANTICONVULSIVE THERAPY**
- STATUS EPILEPTICUS — Diazepam, Paraldehyde, Thiobarbiturate, Oxibarbiturate
- MAINTENANCE THERAPY — Phenobarbital, Diphenylhydantoin, ACTH
- Effect — None / Less frequent / Very rare / Stopped

**THERAPY**
- Vasodilatators given — Yes / No
- Effect — None / Presumable / Certain / Outstanding

- The face
  - Non cleft median syndrome
  - Cleft median face syndrome
  - Hypertelorism
  - Small orbits
  - Small optic channel — Left / Right
  - Facial hemihypotrophy
  - Large protruding tongue
  - Hypotrophy of tongue — Right half / Left half
  - Partially fixed tongue — Right half / Left half

# Chart II

- The spine
  - Defects (external origin)
    - Aberrant functions in cervical and/or thoracic muscles
      - Cervical
        - Exaggerated Symmetric tonic Neck reaction — Lordosis
        - Exaggerated Asymmetric tonic Neck reaction — Scoliosis
        - Torticollis
        - Hypotonia — Kyphosis
      - Thoracic
        - Exaggerated Symmetric tonic Neck reaction — Lordosis
        - Hypotonia — Kyphosis
  - Defects (internal origin)
    - Birth injuries: Fracture, Luxation — Cervical, Thoracic, Lumbar
    - Malformations
      - Cervical (Klippel-Feil syndrome), Thoracic, Lumbar, Sacral
      - Spina bifida (1 vertebra), Rachischisis (more vertebrae) — LOCALISATION: Cervical, Thoracic, Thoracolumbar, Lumbar, Lumbosacral, Sacral — Confirmed by X-ray: Yes / No — SKIN: Intact / Medullo-vascular layer / Leaking / Not leaking
- The spinal cord
  - Defects
    - Malformations — Meningocele, Meningomyelocele, Myelodysplasia, Diastomatomyelia, Hydromyelia, Dermal sinus — Cervical, Thoracic, Thoracolumbar, Lumbar, Lumbosacral, Sacral
    - Aplasia, Degenerative processes — Spinal athropies / Storage disease
    - Birth injuries — Haematomyelia, Epi and subdural haemorrhage, Spinal arachnitis

**RESULTS OF PRE-OPERATIVE NEUROLOGICAL STUDIES**
- Operative indication — Present / Highly recommended / Parents desire operation / despite thorough information / given by paediatrician / paediatric surgeon / both / Early closure not performed because of the neonate's condition

**URODYNAMICAL STUDY**
BLADDER INNERVATION
- Bladder neck — Normal / Flaccid / Spastic
- Detrusor tonus — Normal / Atonic / Hypotonic / Hypertonic
- Bladder capacity — Normal / No / Small
- Detrusor activity — Normoactive / No activity / Hypoactivity / Hyperactivity
- Contraction type — No contractions / Pathological contractions (small, disorganized) / Pathological contractions (high, disorganized) / Normal contractions
- Spontaneous bladder function — Present / Not present / Activated only by intravesical transurethral / Electric stimulation occasionally regularly
- Vegetative afferentation (confirmed by polygraphy) — Present, pronounced, regular / Present, irregular / Absent

**URINARY INFECTION** — Not present / Present / Received antibiotic treatment

**X-RAY STUDIES**
- Ureters — Normal / Abnormal / Kinked dilated — Present / Not present / Reflux — Present / Not present
- Bladder shape — Enlarged / Shrunken
- Hydronephros — Present / Not present

**RECTAL INNERVATION**
- Anal reflex — Normal / Weak / Absent
- Rectal tonus — Normal / No / Hypotonic
- Rectal activity — Normoactive / No activity / Diminished

- Hydrocephalus developed but no sign of hypertension present
- Hydrocephalus developed, signs of hypertension present
- Indication of ventricular atrial ventile implantation present

- Early closure performed — Wound healing: primear / secundary; No infection occured; Infection occured
- Post operative urodynamic results — Unchanged / Worth / Improved
- Post operative results concearning functions of the lower extremities — Unchanged / Worth / Improved
- Post operative results concearning the rectal functions — Unchanged / Worth / Improved

- Indications for early transurethral intra-vesical electrotherapy — Present / Not present
- Number of stimulations — In 1 series / 2 series / 3 series / 4 series; Under 20 / 30 / 40 / 50 / 60 / 70 / 80 / 90 / 100

- Needs no neurohabilitation, all sensory, mental and motor functions normal
- Needs habilitation of
  - Motor / Visual / Auditive / Vigilance } behaviour

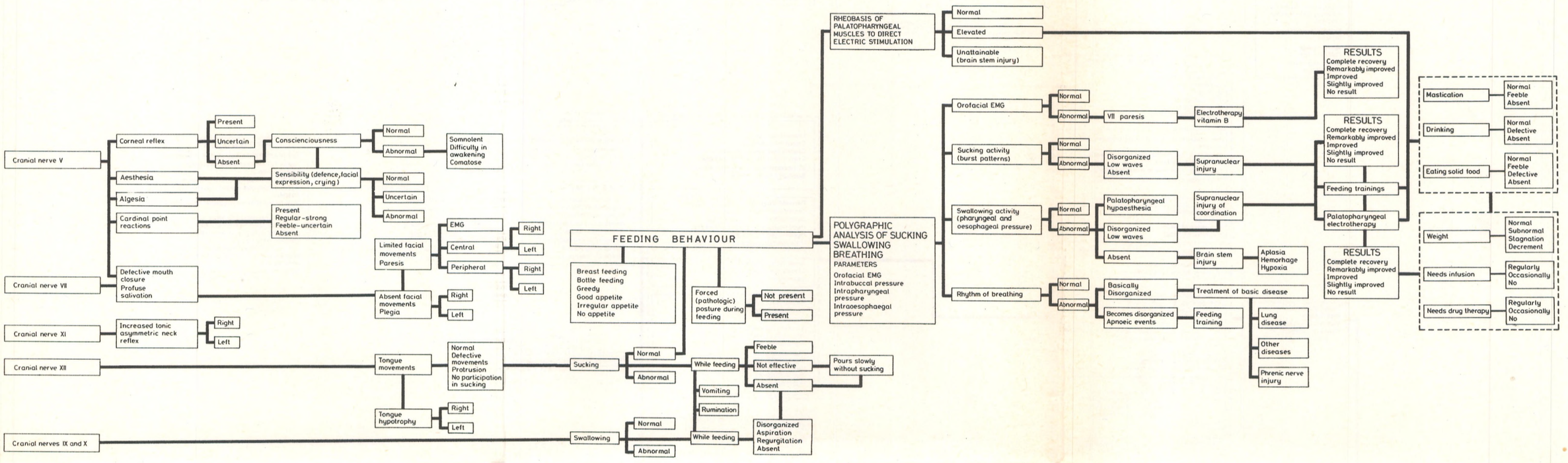
**RESULTS OF MOTOR HABILITATION**
Improoved locomotion unchanged
Needs orthopaedic aids
Needs orthopaedic operation

**RESULTS OF INTRAVESICAL TRANSURETHRAL ELECTROTHERAPY**
- Urine retention — No / Small / Over 20 / 40 / 60 / 80 / 100 ml
- Detrusor activity — Improved tonus / Improved activity / Normal tonus / Normal activity / Partial continence / Total continence (according to age) / Increased capacity / Normal capacity
- In general — Normalisation / Improvement / No improvement

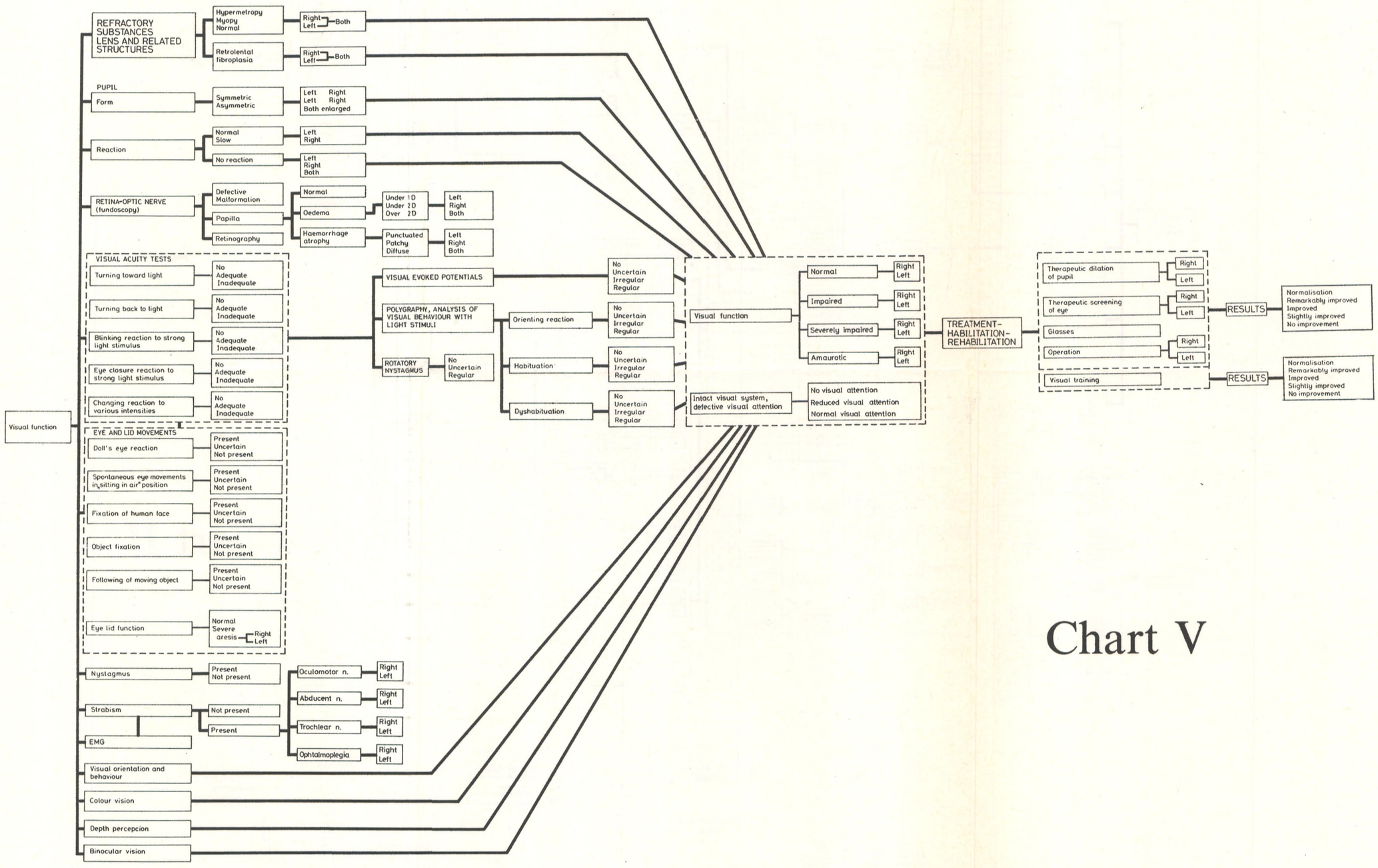
- Indication for early transrectal electrotherapy — Present / Not present

**RESULTS OF RECTAL ELECTROTHERAPY**
- Normal sphincter activity / Improved sphincter activity / Unchanged
- Improved bowel activity / Unchanged

# Chart III




# Chart IV

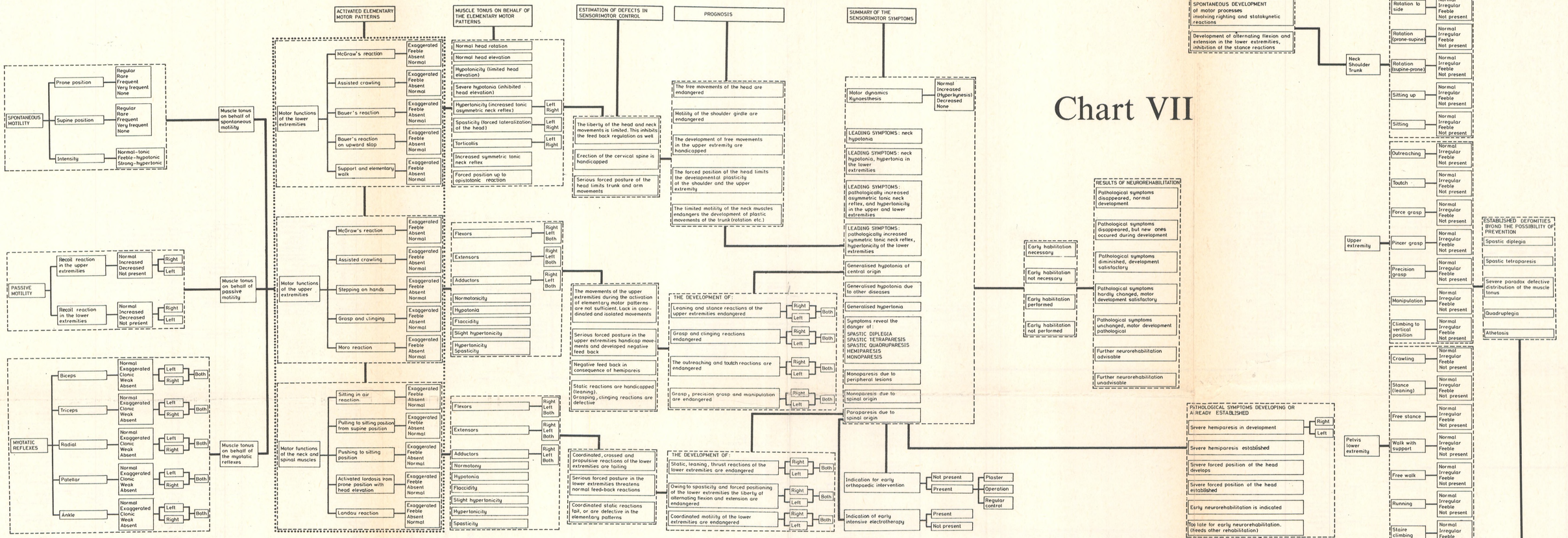


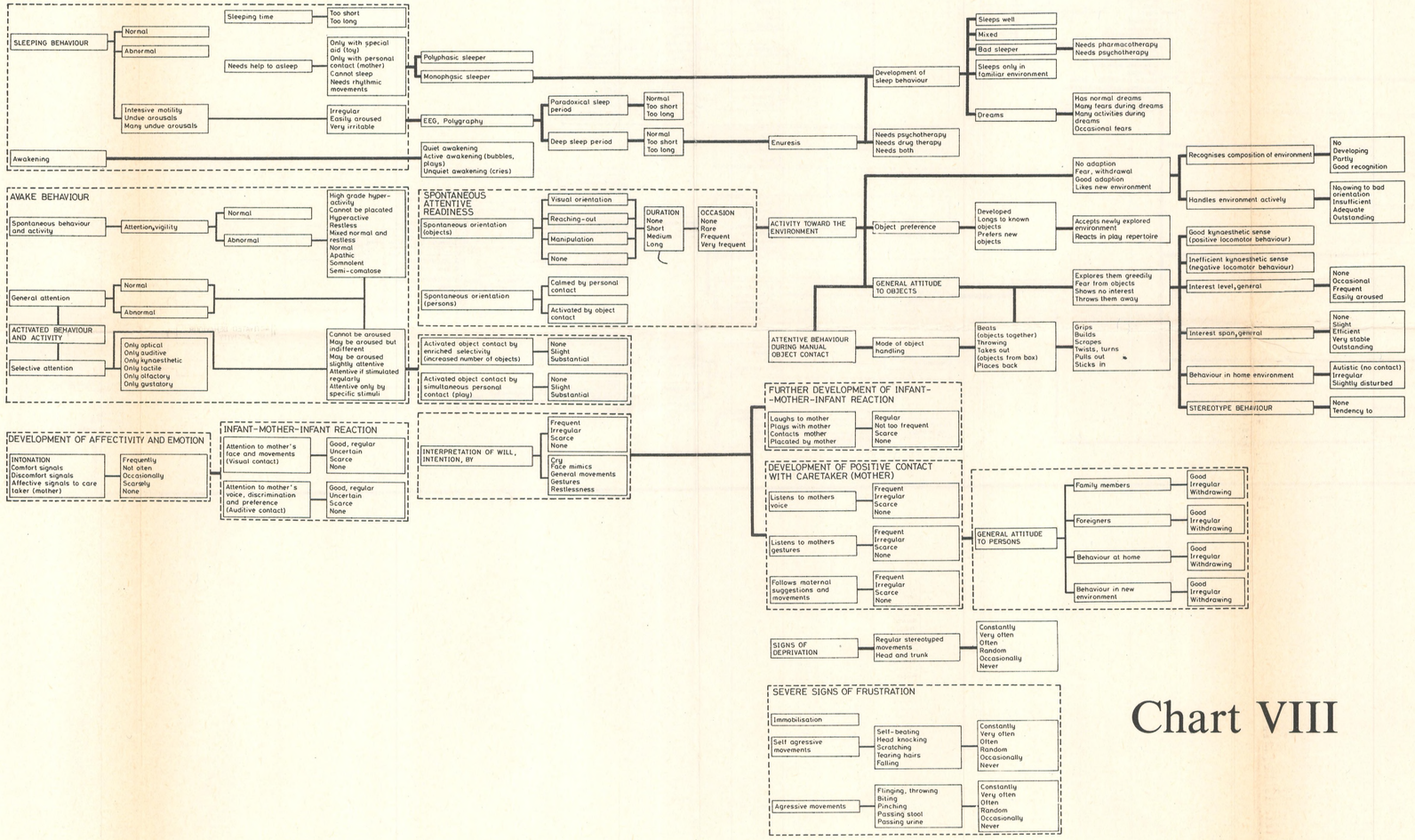

# Chart V




# Chart VI

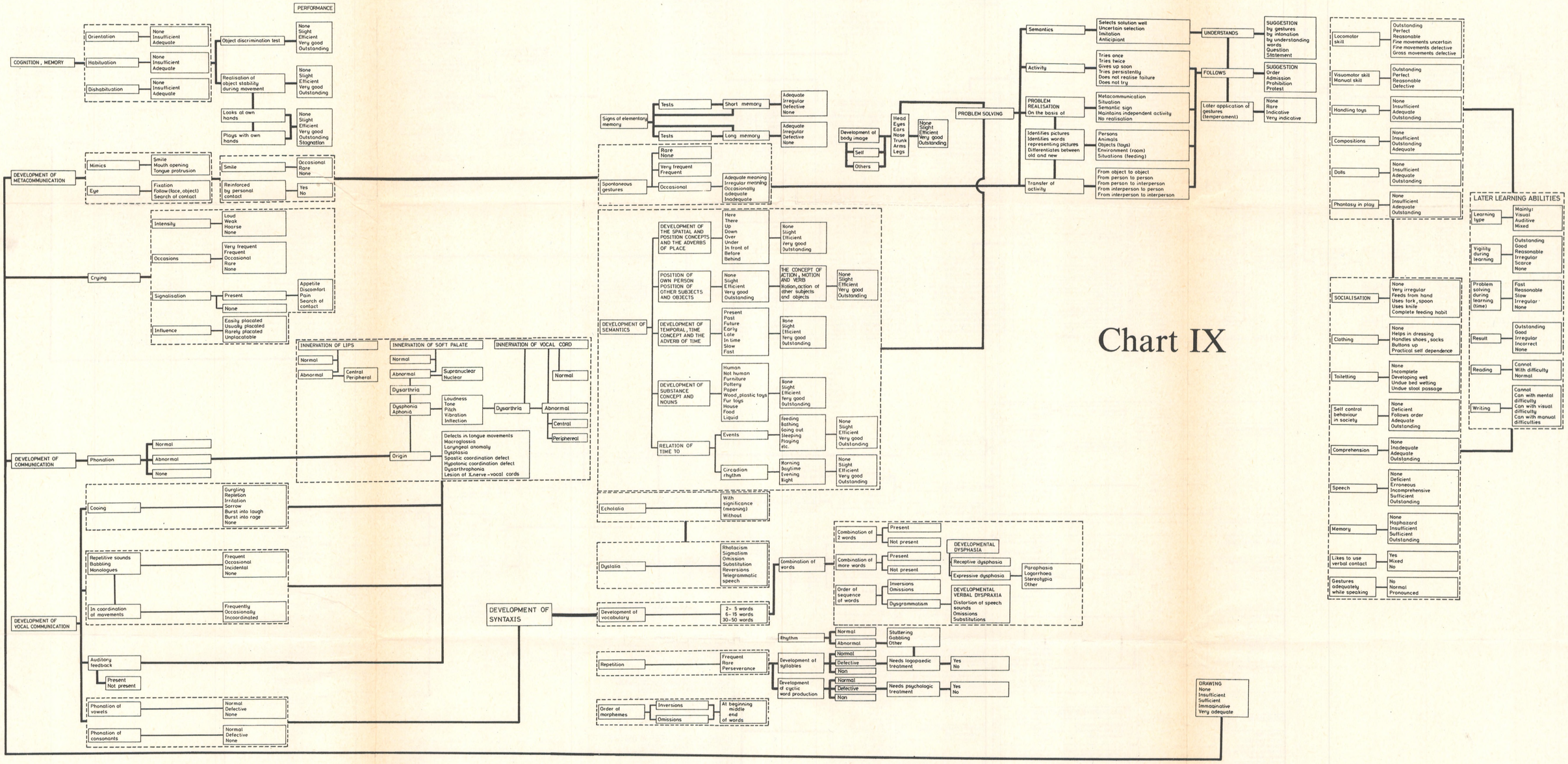
# Chart VII




# Chart VIII

# Chart IX


PERFORMANCE
COGNITION , MEMORY
Orientation
None
Insufficient
Adequate
Habituation
None
Insufficient
Adequate
Dishabituation
None
Insufficient
Adequate
Object discrimination test
None
Slight
Efficient
Very good
Outstanding
Realisation of object stability during movement
None
Slight
Efficient
Very good
Outstanding
Looks at own hands
Plays with own hands
None
Slight
Efficient
Very good
Outstanding
Stagnation
DEVELOPMENT OF METACOMMUNICATION
Mimics
Smile
Mouth opening
Tongue protrusion
Eye
Fixation
Follow (face, object)
Search of contact
Smile
Occasional
Rare
None
Reinforced by personal contact
Yes
No
Crying
Intensity
Loud
Weak
Hoarse
None
Occasions
Very frequent
Frequent
Occasional
Rare
None
Signalisation
Present
None
Appetite
Discomfort
Pain
Search of contact
Influence
Easily placated
Usually placated
Rarely placated
Unplacatable
DEVELOPMENT OF COMMUNICATION
Phonation
Normal
Abnormal
None
INNERVATION OF LIPS
Normal
Abnormal
Central
Peripheral
INNERVATION OF SOFT PALATE
Normal
Abnormal
Supranuclear
Nuclear
Dysarthria
Dysphonia
Aphonia
Loudness
Tone
Pitch
Vibration
Inflection
Origin
Defects in tongue movements
Macroglossia
Laryngeal anomaly
Dysplasia
Spastic coordination defect
Hypotonic coordination defect
Dysarthrophonia
Lesion of X.nerve - vocal cords
INNERVATION OF VOCAL CORD
Normal
Dysarthria
Abnormal
Central
Peripheral
DEVELOPMENT OF VOCAL COMMUNICATION
Cooing
Gurgling
Repletion
Irritation
Sorrow
Burst into laugh
Burst into rage
None
Repetitive sounds
Babbling
Monologues
Frequent
Occasional
Incidental
None
In coordination of movements
Frequently
Occasionally
Incoordinated
Auditory feedback
Present
Not present
Phonation of vowels
Normal
Defective
None
Phonation of consonants
Normal
Defective
None
Signs of elementary memory
Tests
Short memory
Long memory
Adequate
Irregular
Defective
None
Spontaneous gestures
Rare
None
Very frequent
Frequent
Occasional
Adequate meaning
Irregular meaning
Occasionally adequate
Inadequate
DEVELOPMENT OF SEMANTICS
DEVELOPMENT OF THE SPATIAL AND POSITION CONCEPTS AND THE ADVERBS OF PLACE
Here
There
Up
Down
Over
Under
In front of
Before
Behind
None
Slight
Efficient
Very good
Outstanding
POSITION OF OWN PERSON
POSITION OF OTHER SUBJECTS AND OBJECTS
None
Slight
Efficient
Very good
Outstanding
THE CONCEPT OF ACTION , MOTION AND VERB
Notion, action of other subjects and objects
None
Slight
Efficient
Very good
Outstanding
DEVELOPMENT OF TEMPORAL, TIME CONCEPT AND THE ADVERB OF TIME
Present
Past
Future
Early
Late
In time
Slow
Fast
None
Slight
Efficient
Very good
Outstanding
DEVELOPMENT OF SUBSTANCE CONCEPT AND NOUNS
Human
Not human
Furniture
Pottery
Paper
Wood, plastic toys
Fur toys
House
Food
Liquid
None
Slight
Efficient
Very good
Outstanding
RELATION OF TIME TO
Events
Feeding
Bathing
Going out
Sleeping
Playing
etc.
None
Slight
Efficient
Very good
Outstanding
Circadian rhythm
Morning
Daytime
Evening
Night
None
Slight
Efficient
Very good
Outstanding
Development of body image
Self
Others
Head
Eyes
Ears
Nose
Trunk
Arms
Legs
None
Slight
Efficient
Very good
Outstanding
PROBLEM SOLVING
Semantics
Selects solution well
Uncertain selection
Imitation
Anticipiant
Activity
Tries once
Tries twice
Gives up soon
Tries persistently
Does not realise failure
Does not try
PROBLEM REALISATION On the basis of
Metacommunication
Situation
Semantic sign
Maintains independent activity
No realisation
Identifies pictures
Identifies words representing pictures
Differentiates between old and new
Persons
Animals
Objects (toys)
Environment (room)
Situations (feeding)
Transfer of activity
From object to object
From person to person
From person to interperson
From interperson to person
From interperson to interperson
UNDERSTANDS
SUGGESTION
by gestures
by intonation
by understanding words
Question
Statement
FOLLOWS
SUGGESTION
Order
Admission
Prohibition
Protest
Later application of gestures (temperament)
None
Rare
Indicative
Very indicative
Echolalia
With significance (meaning)
Without
Dyslalia
Rhotacism
Sigmatism
Omission
Substitution
Reversions
Telegrammatic speech
DEVELOPMENT OF SYNTAXIS
Development of vocabulary
2 - 5 words
6 - 15 words
30 - 50 words
Combination of words
Combination of 2 words
Present
Not present
Combination of more words
Present
Not present
DEVELOPMENTAL DYSPHASIA
Receptive dysphasia
Expressive dysphasia
Paraphasia
Logorrhoea
Stereotypia
Other
Order of sequence of words
Inversions
Omissions
Dysgrammatism
DEVELOPMENTAL VERBAL DYSPRAXIA
Distortion of speech sounds
Omissions
Substitutions
Repetition
Frequent
Rare
Perseverance
Development of syllables
Development of cyclic word production
Rhythm
Normal
Abnormal
Stuttering
Gabbling
Other
Normal
Defective
Non
Needs logopaedic treatment
Yes
No
Normal
Defective
Non
Needs psychologic treatment
Yes
No
Order of morphemes
Inversions
Omissions
At beginning
middle
end
of words
DRAWING
None
Insufficient
Sufficient
Imaginative
Very adequate
LATER LEARNING ABILITIES
Learning type
Mainly:
Visual
Auditive
Mixed
Vigility during learning
Outstanding
Good
Reasonable
Irregular
Scarce
None
Problem solving during learning (time)
Fast
Reasonable
Slow
Irregular
None
Result
Outstanding
Good
Irregular
Incorrect
None
Reading
Cannot
With difficulty
Normal
Writing
Cannot
Can with mental difficulty
Can with visual difficulty
Can with manual difficulties
Locomotor skill
Outstanding
Perfect
Reasonable
Fine movements uncertain
Fine movements defective
Gross movements defective
Visuomotor skill
Manual skill
Outstanding
Perfect
Reasonable
Defective
Handling toys
None
Insufficient
Adequate
Outstanding
Compositions
None
Insufficient
Outstanding
Adequate
Dolls
None
Insufficient
Adequate
Outstanding
Phantasy in play
None
Insufficient
Adequate
Outstanding
SOCIALISATION
None
Very irregular
Feeds from hand
Uses fork, spoon
Uses knife
Complete feeding habit
Clothing
None
Helps in dressing
Handles shoes, socks
Buttons up
Practical self dependence
Toiletting
None
Incomplete
Developing well
Undue bed wetting
Undue stool passage
Self control behaviour in society
None
Deficient
Follows order
Adequate
Outstanding
Comprehension
None
Inadequate
Adequate
Outstanding
Speech
None
Deficient
Erroneous
Incomprehensive
Sufficient
Outstanding
Memory
None
Haphazard
Insufficient
Sufficient
Outstanding
Likes to use verbal contact
Yes
Mixed
No
Gestures adequately while speaking
No
Normal
Pronounced

# INSTRUCTIONS TO AUTHORS

*Form of manuscript*

Two complete copies of the manuscript including all tables and illustrations should be submitted. Manuscripts should be typed double-spaced with margins at least 4 cm wide. Pages should be numbered consecutively.

Manuscripts should include the title, authors' names and address of the institution where the work was done.

An abstract of not more than 200 words should be supplied typed before the text of the paper.

*Abbreviations* should be spelled out when first used in the text. *Drugs* should be referred to by their WHO code designation (Recommended International Nonproprietary Name); the use of proprietary names is unacceptable.

The *International System of Units* (SI) should be used for all measurements.

*References*

References should be numbered in alphabetical order and only the numbers should appear in the text (in parentheses). The list of references should contain the name and initials of all authors (the use of et al instead of authors' name in the reference list is not accepted); for journal articles the title of the paper, title of the journal abbreviated according to the style used in Index Medicus, volume number, first page number and year of publication; for books the title followed by the publisher and place of publication.

Examples:

Kerpel-Fronius E, Gács GK: Serum insulin values in infants. Acta Paediatr Acad Sci Hung 16:197, 1975

Crosse VM: The Preterm Baby. Churchill Livingstone, Edinburgh and London 1971

Detter JC: Biochemical variation. In: Textbook of Human Genetics, ed. Fraser O, Mayo O, Blackwell Scientific Publications, Oxford 1975, p. 115

*Tables and illustrations*

*Tables* should be comprehensible to the reader without reference to the text. The headings should be typed above the table.

*Figures* should be identified by number and authors' name. The top should be indicated on the back. Their approximate place should be indicated in the text. Captions should be provided on a separate page.

*Proofs and reprints*

Reprints and proofs will be sent to the first author unless otherwise indicated.

A hundred reprints of each paper will be supplied free of charge.

The name and address of the first author should be given after the list of references.

CONTENTS

An orienting diagnostic system in neonatal and infantile neurology
*F Katona* ..... 299

A new acoustic method for discrimination of monozygotic and dizygotic twins
*G Forrai, G Gordos* ..... 315

HLA phenotypes in children with Duchenne muscular dystrophy and their gene carrier mothers
*A László, G Kaiser* ..... 323

Serum alpha-galactosidase activity in children with Duchenne-type muscular dystrophy and in gene carriers
*A László, Z Havass* ..... 327

Antinuclear factor, smooth and striated muscle antibodies in Duchenne-type muscular dystrophy
*A László, J Hudák, E Szabó, L Varga* ..... 331

Changes in cardiovascular risk factors in diabetic children during a camping holiday
*L Barta, A Czinner, M Tichy, M Bedő* ..... 337

Glucocorticoid receptors in circulating lymphocytes of premature infants and newborns
*T Kerepesi, P Arányi* ..... 343

Reticulin antibodies in coeliac disease
*J Henker, M Zugehör, J Morrenz* ..... 349

Relationship between placental perfusion and endocrine parameters of pregnants in cases of intrauterine growth retardation
*J Doszpod, MG Csákány, M Török, I Gáti* ..... 355

Cerebrovascular occlusion in childhood
*I Dobronyi, A Pásztor, I Nagy, E Paraicz* ..... 361

Non-invasive examination of pulmonary stenosis by transcutaneous Doppler technique
*M Barbacki, K Sandhage* ..... 367

Book reviews ..... 371

**Index: 26.021**