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TO THE READERS

OF ACTA PAEDIATRICA HUNGARICA

As editor of the Acta Paediatrica Hungarica it is my job to inform our readers that they keep the last issue of our journal in their hands. With this volume the publication of our periodical has come to its end.

The predecessor of Acta Paediatrica Hungarica, Paediatrica Danubiana, was edited by Professor P. Véghelyi and was published between 1947 and 1949. In 1949, due to the cultural policy of the communist regime, publication of the English-language scientific journal was prohibited. Only a decade later in 1960 when the political climate changed could the periodical be started again with the title Acta Paediatrica Hungarica under the sponsorship of the Hungarian Academy of Sciences. Professor Véghelyi was appointed editor again and worked with enthusiasm until his death in 1986. Thereafter Professor M. Miltényi took over as the editor of the journal.

Until the end of the 1980s Acta Paediatrica Hungarica published papers of high scientific level submitted by paediatricians working in university paediatric departments and in various children's hospitals. In the majority of the cases the authors were, of course, Hungarians, however some 35-40% of the papers came from abroad, e.g. from Poland, Germany, Czechoslovakia, Israel, Turkey, USA. Those years our Acta had a high international reputation and could be found in the major university libraries of various Western European institutions.

In the last 4-5 years, as a consequence of the dramatic changes which have taken place also in the health care and scientific life in Hungary, the number of submitted manuscripts decreased considerably and occasionally their scientific level, as well. Thus, the offer of Springer Verlag to incorporate the Acta Paediatrica Hungarica into the European Journal of Pediatrics similarly to Acta Paediatrica Belgica and Helvetica

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Paediatrica Acta has been considered and readily accepted by the editorial board. The fusion was proposed by Springer Verlag already in 1992 and after 3 years of discussions the time for realization has now arrived. Therefore, the editorial board of Acta Paediatrica Hungarica is calling all the Hungarian paediatricians to submit their papers for publication in the future directly to the European Journal of Pediatrics.

The offer of Springer Verlag includes about 25 copies of the European Journal of Pediatrics which will be provided gratis for the Hungarian Paediatric Association.

Last but not least we would like to express our sincere gratitude to our authors and to the editorial board of the Acta Paediatrica Hungarica for their activity and cooperation. Similarly I owe my thanks to the Division of Medical Sciences and the Publishing House of the Hungarian Academy of Sciences for their support in providing an international scientific forum to represent the activity of the Hungarian physicians.

Budapest, February 1995

Prof. em. Miklós Miltényi
Editor of Acta Paediatrica Hungarica

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TO THE READERS OF ACTA PAEDIATRICA HUNGARICA

In the name of the editors and editorial board I wish to welcome you to the readership of the European Journal of Pediatrics. The fusion of our two journals reflects a growing sense of togetherness in Europe. We are proud that the Hungarian Academy of Sciences has chosen the European Journal of Pediatrics to carry on the task that the Acta Paediatrica Hungarica has fullfilled so well in the past. We will strive to incorporate and continue its tradition as we continue to do with the journals of our Belgian and Swiss colleagues. In spite of the universality of science, contributions from so many different countries with their own needs and styles mirror the cultural diversity of our continent.

By combining forces we will be able to select the best articles from West and East and to inform you about advances in the various subspecialties of pediatrics. Scientists from Eastern Europe will find a platform to publish the best of their work and to make it known to their colleagues in other parts of the world. Review articles will present the state of art in many fields. The section called 'Pioneers in Pediatrics' will remind you of the great pediatricians of the past. 'News for practitioners' summarizes data from other journals that we think may assist pediatricians in their daily routine. We will be delighted to publish letters dealing with previous articles, raising questions or offering criticism. This section is also a forum to present preliminary data and we encourage you to actively participate in its formation and to add to its livelihood. Let us have your criticism and your suggestions to produce an even better journal. A journal not only lives for its readers but also through them.

The European Journal of Pediatrics looks forward to serving you.

J. Spranger
Coordinating Editor
European Journal of Pediatrics

Akadémiai Kiadó, Budapest

Acta Paediatrica Hungarica 34 (1-4), pp. 13-17 (1994)

BONE ANOMALIES IN LEUKAEMIC CHILDREN AND IN THEIR PARENTS AND SIBLINGS

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Received 17 January 1994

Earlier studies suggested an increased prevalence in leukaemic children. Family investigations in this field have not been performed so far. In the present survey the prevalence of bone anomalies and variants of the hand and lower arm was determined in 35 children with acute lymphoblastic leukaemia, in their 30 fathers, 33 mothers and 39 siblings. Roentgenograms of 403 children and 237 adults examined for trauma served as controls. As compared to the controls, a significantly increased prevalence of bone anomalies was found in both leukaemic children and their first degree relatives.

INTRODUCTION

The relationship between childhood malignancy and malformations with special reference to minor morphological aberrations has often been investigated /1, 4, 5, 7, 10/. An association of leukaemia and tumours with mild anomalies of leukaemia and tumours with mild anomalies of the skeleton has also been shown /2, 3, 9, 12/. Since extreme variants and mild malformations of the bones may occur as harmless familial features, only family investigations could determine how far their appearance is related to malignancy in the affected children. To our knowledge no such survey has been published so far. This is why we reviewed hand and lower arm roentgenographs of children with acute lymphoblastic leukaemia (ALL) and of their first degree relatives.

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SUBJECTS AND METHODS

X-ray pictures of the left lower arm, wrist and hand used for bone age determination of 35 ALL-patients (17 boys) were reviewed for morphological anomalies. The mean age of the patients was 17.6 year (range 2-16 years).

With permission of the local ethical committee, on voluntary basis with written content, a roentgenogram of the left lower arm and hand was taken from 102 first degree relatives of the patients. Thus the films of 39 siblings (21 boys; mean age 12.2 years), 30 fathers (mean age 39.5 years) and 33 mothers (mean age 35.4 years) were analysed.

For comparison roentgenograms of 403 children (mean age 11.2 years) and 237 adults examined for trauma were reviewed.

For statistical evaluation the chi-square test was used.

RESULTS

The prevalence of the bone anomalies observed is demonstrated in the Table. As shown by the figures, the frequencies of mild aberrations were 2.7 and 2.9% in the control groups, whereas 22.8% of the patients and 12.8 to 69.6% of their family members had at least one anomaly. The differences between controls and any other groups are statistically significant.

The majority of the subjects had a single anomaly, only one mother had two mild aberrations. Familial anomalies were found only in two cases, these were excluded from the evaluation. No association of ALL with specific anomalies was observed.

DISCUSSION

Gefferth /2/ was the first to call attention to an increased prevalence of mild anomalies of bones in children with ALL. Similar results were obtained in recent surveys /9, 12/ which also failed to demonstrate specific associations between individual skeletal anomalies and ALL. The present findings are in accordance with these observations.

To our knowledge this is the first study in which family investigations are reported. The results suggest significantly higher than normal prevalence of bone anomalies of the lower arm and hand in both the siblings and parents of children with ALL. The anomalies

TABLE I

Anomalies observed on roentgenograms of the left hand and lower arm in children with ALL, in their parents and sibs and in control subjects

	ALL patients N=35	Sibs N=39	Control children N=403	Fathers N=30	Mothers N=33	Control adults N=237
Narrow bone cavity	1	0	1	1	3	1
Short bone	0	0	0	1	1	0
Persisting epiphysis	0	0	0	8	10	4
Bone cysts	1[a] 0	1[a] 0	0	1	2	0
Intraosseal calcification	1	0	0	2	1	2
Pseudo-epiphysis	1	2	1	0	0	0
Twisted radius and/or ulna	2	1[a] 3	9	1[a] 4	3	0
Metacarpal or phalangeal deformities	2	0	0	2	4	0
Total anomalies	7	5	11	19	24	7
Anomaly/ subject	0.20	0.13	0.03	0.63	0.73	0.03
Total number of positive subjects (per cent)	7 (22.8)[b]	5 (12.8)[b]	11 (2.7%)	19 (57.6%)[c]	23 (69.6%)	7 (2.9%)

a familial cases, not included in the evaluation

b $p < 0.01$ against controls

c $p < 0.001$ against controls

proved to be familial in only two cases that were not included in the final evaluation. The majority of extreme variants and mild malformations observed in the patients differed from those of their siblings and parents. This suggests a tendency to non specific mild congenital skeletal anomalies in families with childhood ALL. A similar phenomenon was observed when examining so-called informative morphogenetic variants /8/ in the families of ALL-patients. However, the increased prevalence of these minor morphological aberrations was found in the patients and in their siblings but not in the parents that may suggest a possible recessive association of ALL with minor errors of morphogenesis in general /7, 11/.

Irrespective of inheritance and of limitations of the small series examined, the existence of such an association seems to be probable from different approaches. For lack of more convincing evidence, the increased prevalence of mild morphological anomalies should not be regarded as a sign of predisposition for leukaemia, but the findings so far cannot be ignored.

In addition to morphological anomalies of the body surface and bones, correlations between ALL and other factors such as greater than normal height /6/ and high social class have also been shown. Multivariance analysis of such factors, cytogenetic and immunologic marker characteristics might contribute to the research of predisposition and genetics of ALL. Therefore we think that further family investigations are warranted.

ACKNOWLEDGEMENT

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THE FINAL DATA BASE OF CONGENITAL ABNORMALITIES IN THE HUNGARIAN RANDOMISED CONTROLLED TRIAL OF PERICONCEPTIONAL MULTIVITAMIN SUPPLEMENTATION

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Received 30 May 1994

The final data base of congenital abnormalities in the Hungarian randomised controlled trial of periconceptional multivitamin (including 0.8 mg of folic acid) supplementation is presented here. Of 5453 pregnancies with known outcome, 4862 informative offspring were evaluated. The total rate of all congenital abnormalities was 5.91% (182/2391) in the multivitamin group and 7.61% (182/2391) in the placebo-like trace element group. After the exclusion of 6 cases with neural-tube defect, the difference has remained significant (p=0.04) and the relative risk was 0.80 (0.65, 0.99). This protective effect was explained mainly by the lower rate of cases with congenital cardiovascular malformations, the defects of the urinary system and congenital hypertrophic pyloric stenosis.

INTRODUCTION

Intervention studies indicate that periconceptional supplementation with a multivitamin including the physiological dose of folic acid reduce both the occurrence /8/ and recurrence /18, 19/ of neural-tube defects (NTD) while the pharmacological dose of folic acid alone /14, 15/ reduces the recurrence of NTD. The preliminary results of the Hungarian randomised controlled trial demonstrated a significant reduction of other major congenital abnormalities (CAs) by periconceptional multivitamin (including 0.8 mg of folic acid) supplementation /4/. This primary preventive method has great public health significance as a better alternative to prenatal diagnosis and selective abortion. In addition to the lessening of human suffering, the practical relevance includes the decrease in medical costs.

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The Hungarian randomised controlled trial was appropriate to study the effect of periconceptional multivitamin supplementation on CAs other than NTD. A previous report showed a protective effect of multivitamins on the recurrence of cleft lip /20/. In addition we were interested in the other schisis-type on nonneural midline CAs, i.e., CAs of abdominal wall and diaphragmatic defects because they prefer to associate with NTD, oral clefts and each other /2/. However, our purpose was to evaluate all kinds of CA-types or groups /7/. This paper summarizes the final data base of CAs and some results of its analysis.

METHOD

The Hungarian randomised controlled trial of periconceptional multivitamin supplementation was part of the Hungarian Optimal Family Planning Programme (HOFPP) which was established on February 1, 1984. The HOFPP involves three main steps performed or supervised by qualified nurses: (I) a check of reproductive health /7/, (ii) a three month preparation for conception including multivitamin supplementation and (iii) protection of early pregnancy /3/. Couples who satisfy the following criteria are eligible for participation in the HOFPP: no delayed conception or infertility (i.e., no conception after more than 12 months of sexual activity without contraception); not currently pregnant; voluntary participation. In the first four years of the HOFPP, there were two other criteria: age under 35 in females (older women were referred to the genetic counselling clinic) and no previous wanted pregnancy (induced abortion was not a reason for exclusion).

At the first visit eligible females were informed about the purpose of multivitamin supplementation; and about the `blind` use of one of two kinds of tablets, i.e., asked about whether they agree to their allocation on the basis of a randomisation table. After this, the women were asked to sign a written informed consent and to stop any intake of other vitamins. The participants were advised to take a single tablet of either the "multivitamin": ELEVIT pronatal® (Roche), composed of 12 vitamins (vitamin A 6000 IU until the end of 1989 and 4000 IU in 1990-1992, B1 1.6 mg, B2 1.8 mg, nicotinamide 19.0 mg, B6 2.6 mg, calcium pantothenate 10 mg, biotin 0.2 mg, B12 4.0 µg, C 100.0 mg, D 500.0 IU, E 15.0 mg, folic acid 0.8 mg), four minerals (calcium 125 mg, phosphorous 125 mg, magnesium 100 mg, iron 6.0 mg), and three trace elements (copper 1 mg, manganese 1 mg, and zinc 7.5 mg) or the placebo-like "trace element" (copper 1 mg, manganese 1 mg, zinc 7.5 mg, and vitamin C 7.5 mg) each day for one month before planned conception.

At the second visit women were supplied with supplements for a further three months and were asked to attempt to conceive and to visit us again immediately after the first missed menstrual period. If the participant did not conceive within three months, tablets for the next three months were supplied a month at a time. The purpose of the third visit was the confirmation of pregnancy by a sensitive serum pregnancy test after the first missed menstrual period. Pregnancy was also confirmed

by ultrasonography within two weeks. Further tablets were supplied until the 12th week of gestation. The fourth visit was a `farewell` meeting at the 12th week of pregnancy because after this pregnant women were referred to other clinics for routine prenatal care.

The compliance with the regimen of supplementation was verified (i) verbally in discussion with the women, (ii) by evaluating the check marks of the form for the basal body temperature measurement and (iii) by counting unused tablets when boxes were returned. Women who received a full course of the supplement were defined as those who took the supplement for 28 days before conception and at least until the date of the second missed menstrual period. Women who did not take the supplement on any one day during the pre- and/or postconceptional periods were also classified as having received a full course. Women who received a partial course of the supplement were defined as those who failed for more than one day to take the supplement during the pre- and/or postconceptional periods (in general, these women failed to take the supplement for only a few days). Women who conceived before or during the first month of administration were considered not to have received a supplement.

After the end of the pregnancy we were sent the completed certificate for each of the participants which included, among others, the data and type of pregnancy outcome and any CAs of the offspring, i.e., fetuses or infants. The certificate was filled in by the mothers and confirmed (consigned) by their physician. In Hungary all deliveries and terminations of pregnancies take place in obstetrical inpatient clinics. Considerable effort was undertaken to assure that pregnancy outcomes of all women with a confirmed pregnancy were evaluated. If the completed certificate was not received by one month after the expected date of delivery, a letter was mailed to women asking them to send the completed certificate and/or discharge summary. If there was no response, one of our coworkers visited them home. Only after such efforts were the lack of contact considered as a "dropout" from the study.

Informative offspring with known outcomes (prenatally diagnosed fetuses with CA which were terminated in the second or third trimesters, stillborn fetuses and liveborn infants) were evaluated with particular attention to the occurrence and correct diagnosis or description of CAs. After the report of a case as having CA, as much clinical and pathological information as possible was obtained including any prenatal ultrasonography films, a detailed physician`s description (discharge summary, a written report from the examining physician, etc.) and autopsy records in lethal cases. The data concerning CAs were evaluated by an independent Data Monitoring Group every six month. In addition infants were given a physical examination after the eighth month of life (the average examination was in the 11th month /4/) after a mail or telephone invitation to our Family Planning Centre. After review of medical documents concerning previously diagnosed CAs and diseases, treatments and operations, the examination included, among other things, a paediatric evaluation performed `blind` by two paediatricians. If families did not fulfill our request, they were reinvited. If there was still no response, we contacted the infant`s paediatrician and the medical history, particularly data concerning CAs, diagnosed after birth, were obtained.

Two-tailed chi-square and Fisher exact tests were used for statistical evaluation.

RESULTS

The randomisation of multivitamin/trace element supplementation was stopped on April 30, 1992, while the evaluation of pregnancy outcomes was closed on April 30, 1993. The data on CAs including the postnatal flow-up were evaluated until the end of 1993. Of 5502 participants with confirmed pregnancies, pregnancy outcomes were ascertained in 5453 cases (dropout 0.9%). The numbers of women given full, partial, and no supplements were not significantly different between multivitamin and trace element groups (χ^2_2= 3.96; p=0.14). Demographic factors were similar in the two groups.

The number of informative offspring in the intention-to-treat analysis was 2471 in the multivitamin group and 2391 in the trace element group. In the follow-up study 3692 (81.7%) infants were examined directly by the investigators and the data from 413 (8.5%) were obtained from their paediatricians, thus 4375 infants (90.2%) were evaluated. There was no significant difference in the number of the above subgroups between the multivitamin (n=2222) and trace-element groups (n=2153).

In general CAs are divided into three groups according to severities: lethal, severe (which together constitute major) and mild /9/. However, the differential-diagnosis between severe and mild groups sometimes is not consistent and may be subjective. In addition CAs were separated into two main categories: isolated and multiple (two or more different CAs in the same person) /11/.

The total rate of CAs was 5.91% (146/2471) in the multivitamin group and 7.61 % (182/2391) in the trace element group (Table I). The difference is significant (χ^2_1=5.60; p=0.018). After the exclusion of 6 cases with NTD, the difference is also significant (χ^2_1=4.15; p=0.042) relative risk is 0.80 (0.65, 0.99).

Some CA groups merit a more detailed discussion and it is the purpose of this paper.

There was one CA-group: NTDs related to the main hypothesis that the trial was designed to test. There were six cases of NTD in the group receiving the trace element supplement compared with none in the multivitamin group (Table II). The difference in the occurrence of NTD was highly significant (χ^2_1=6.21; p=0.01) between the study groups. None of the mothers with NTD pregnancy had taken valproic acid or other known teratogens, nor did they have a family history of NTD (Figures 1-6). The expected numbers of different NTD types were calculated on the basis of Hungarian data /10/. Two observed offspring with anencephaly and rachischisis (i.e., spina bifida) seem to be unexpectedly high (expected figure is 0.5),

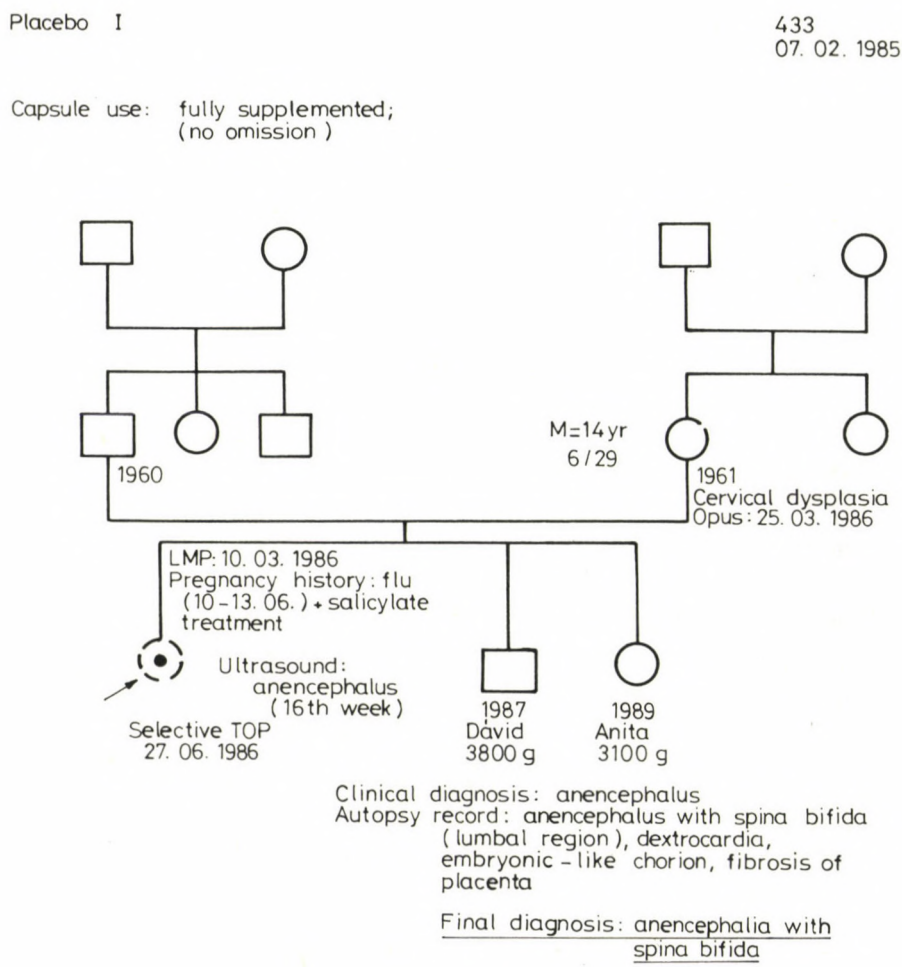


Figure 1: Family and pregnancy history of case 433

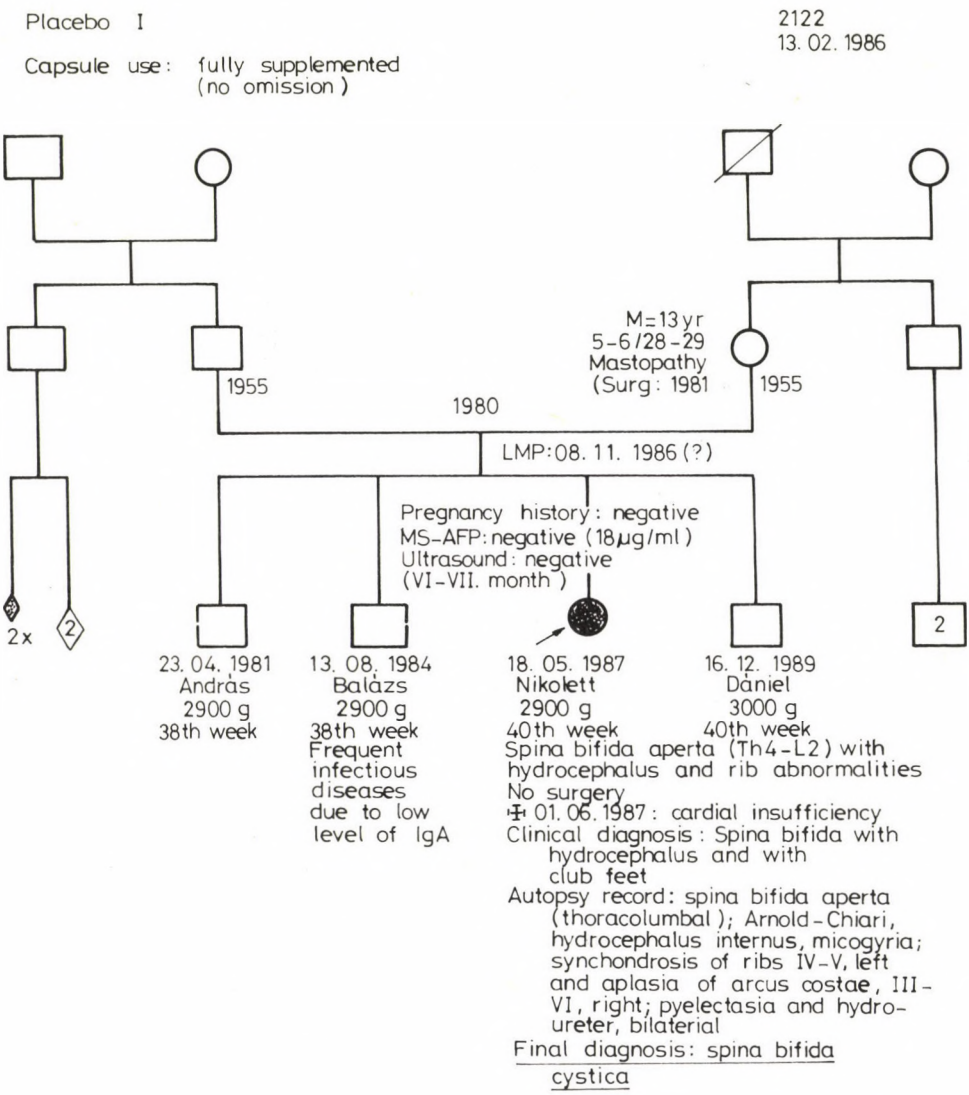
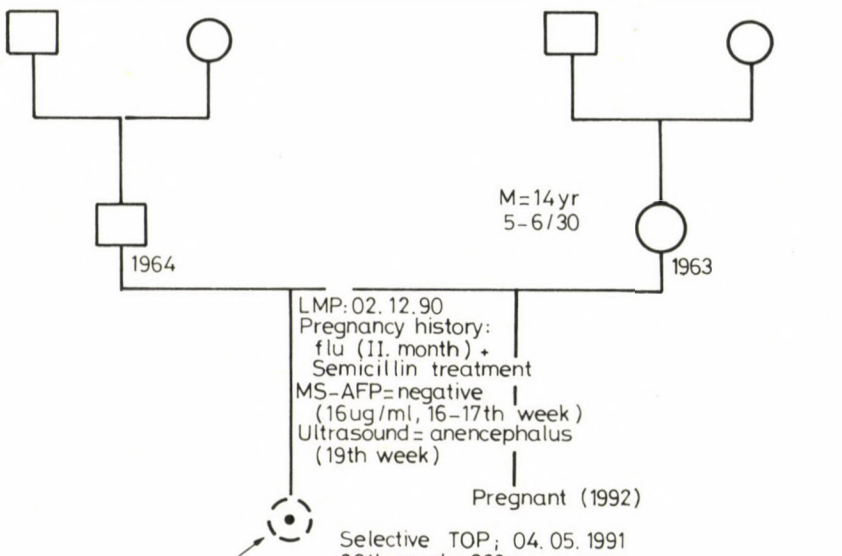


Figure 2: Family and pregnancy history of case 2122

Placebo III

2374
11.12.1990

Capsule use: no supplemented.
She conceived about 14.12.90. She was supplied with capsules on 11.12.90, she had to start the use of capsules on about March. After the recognition, she was not supplied further capsules.



Final diagnosis: anencephalus with spina bifida cystica

Figure 3: Family and pregnancy history of case 2374

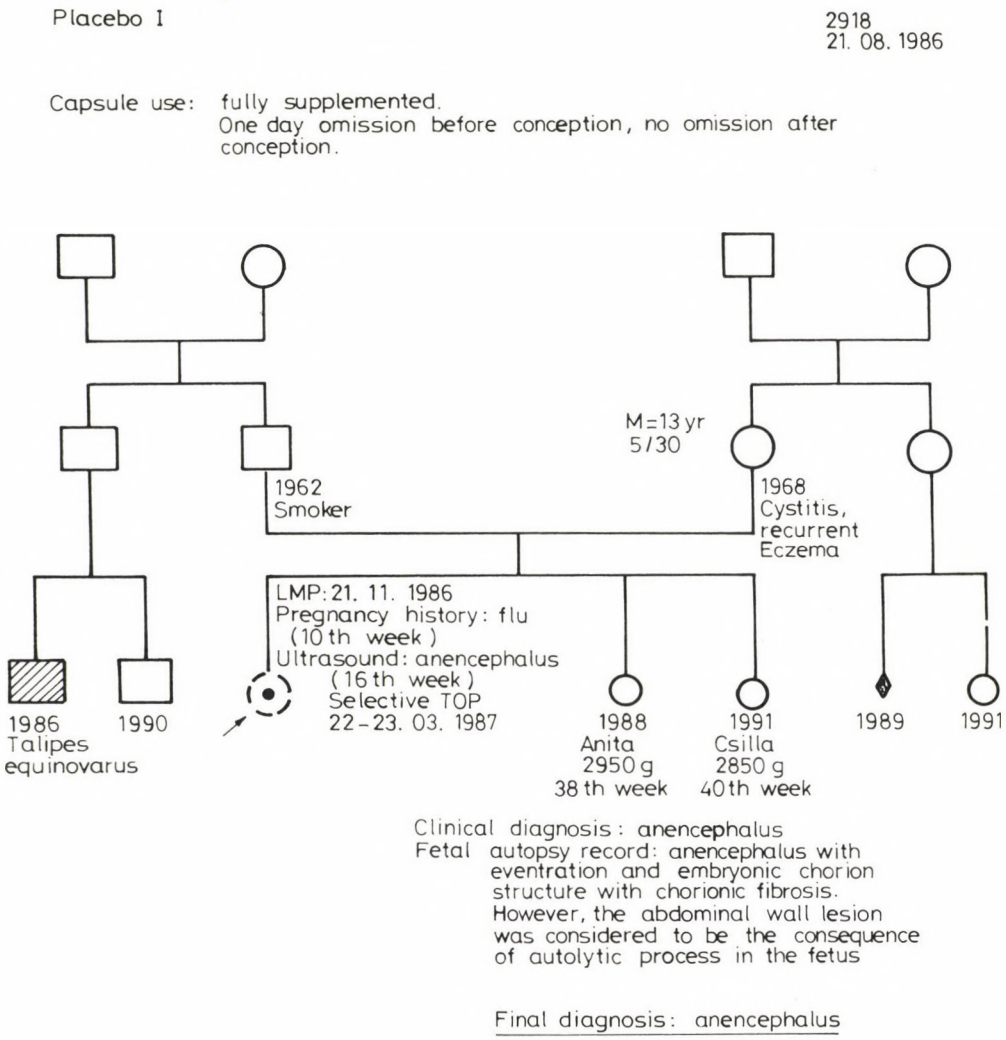


Figure 4: Family and pregnancy history of case 2918

Placebo II

3963
12. 12. 1987

Capsule use: Partially supplemented
No omission within 10 months, after one year of participation she was supplied with capsules and she used them. However, it was not cheked, AIH was launched, the third one was successful.

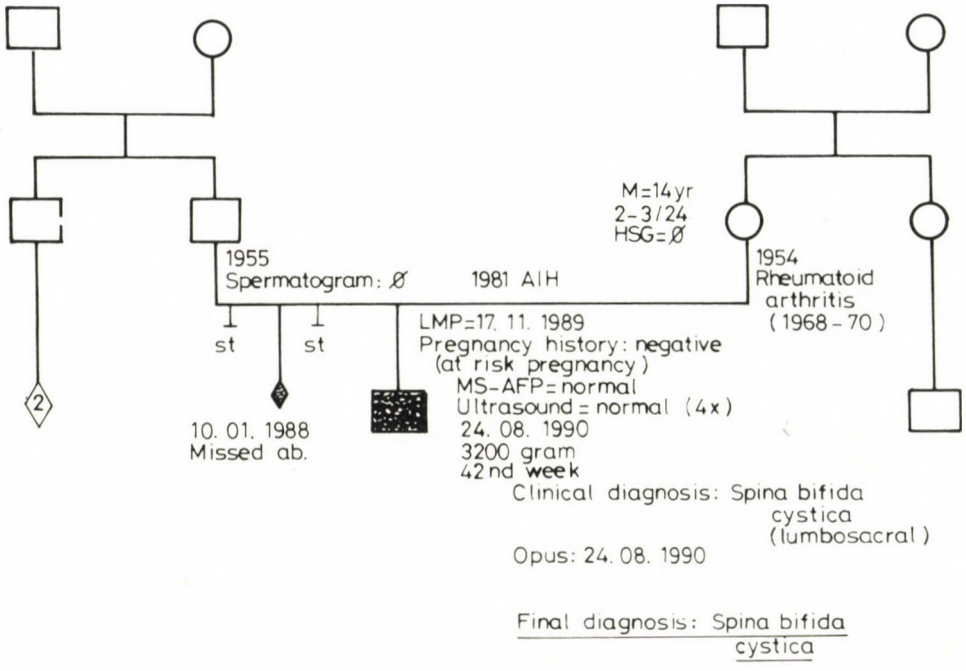


Figure 5: Family and pregnancy history of case 3963

Placebo I

5331
07. 03. 1989

Capsule use: fully supplemented.
One day omission before conception and one or two days after conception, but after the 8th week of gestation.

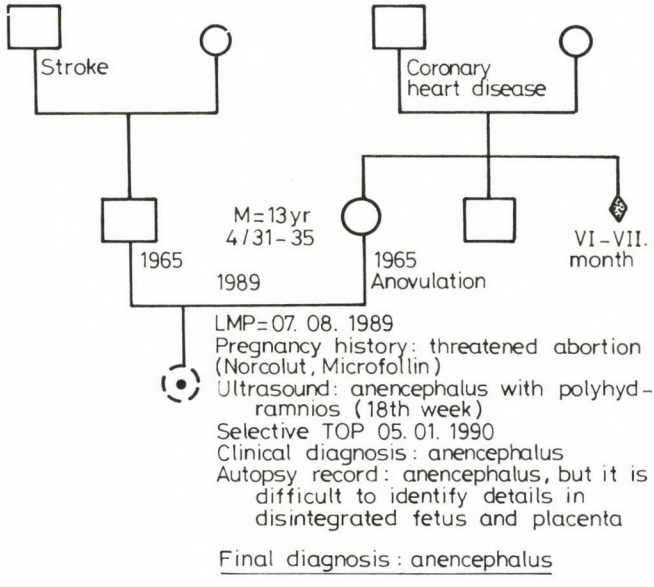


Figure 6: Family and pregnancy history of case 5331

while the expected number of spina bifida was 4 instead of the observed 2, but these differences might be caused by chance.

TABLE I

The data base of congenital abnormality (CA) groups/types in full course (I), partial course (II), no supplementation (III) and total (T) material in the multivitamin and trace element groups

CA types/groups	Multivitamin				Trace element			
Isolated	I	II	III	T	I	II	III	T
Neural-tube defect	0	0	0	0	4	1	1	6
Microcephalus	1	0	0	1	1	0	0	1
Hydrocephalus	0	0	0	0	1	0	1	2
Other CA of nervous system (cerebellar agenesis, porencephalic cyst in brain)	1	0	0	1	1	0	0	1
CAs of eye (buphthalmos, coloboma)	2	0	0	2	1	0	0	1
Cardiovascular CAs	9	1	0	10	14	4	2	20
CAs of respiratory system (tracheal stenosis, bronchial stenosis)	2	0	0	2	0	0	0	0
Cleft palate	0	0	0	0	0	1	1	2
Cleft lip+palate	3	1	0	4	1	2	0	3
Cong. hypertrophic pyloric stenosis	2	0	0	2	6	1	1	8
Other CAs of digestive system (colon malformation due to mesenterium commune, anal atresia)	1	0	0	1	1	0	0	1
Undescended testis	2	4	0	6	8	2	0	10
Hypospadias	5	1	0	6	5	1	0	6
Renal agenesis	0	0	0	0	0	2	0	2
Obstructive CAs of urinary system	1	0	0	1	4	0	0	4
Other CAs of urinary system (cystic kidney II, dystopia renis, exstrophia vesicae)	1	0	0	1	2	0	0	2

TABLE I Cont.

CA types/groups Isolated	Multivitamin I	II	III	T	Trace element I	II	III	T
Torticollis	0	0	0	0	1	1	0	2
Cong. dislocation of hip	28	9	3	40	19	4	3	26
Deformities of feet	10	2	0	12	14	1	0	15
Reduction CA of limb	1	0	0	1	4	1	0	5
Arthrogryposis	0	0	0	0	1	0	1	2
Pectus excavatum	3	0	0	3	0	0	0	0
Foramina parietale permagna	0	0	0	0	2	0	0	2
CAs of abdominal wall (gastroschisis, omphalocele)	1	0	0	1	0	1	0	1
Faciocranial hemangioma or portwine stain	2	1	0	3	3	0	0	3
Cong. inguinal hernia	22	9	0	31	22	7	0	29
Other CAs (non-immun-hydrops, polydactyly in foot, syndactyly in foot, dermoid cyst, hymen imperforatus, craniosynostosis)	0	0	0	0	6	0	0	6
Multiple								
Down syndrome	2	0	0	2	3	1	1	5
Other chromosome CA-syndrome (Turner)	0	0	0	0	1	0	0	1
Monogenic CA-syndromes (Allagille, collodium)	1	1	0	2	0	0	0	0
Cong. postural deformity association	2	2	0	4	6	0	0	6
GAM (genital anomalies of male)	2	1	0	3	3	1	0	4
Unidentified multiple CAs	5	1	1	7	4	1	1	6
Total	109	33	4	146	138	32	12	132

TABLE II

Data of offspring with neural-tube defect (NTD) in the trace element (TE) group

Year		NTD	Associated defects	Outcome	Sex	Supplement
Entry	Birth					
1985	1986	Anencephalus with lumbal rachischisis	Dextrocardia	TOP	girl	TE-I
1986	1987	Thoracolumbal (Th4-L2) spina bifida cystica	Arnold-Chiari, hydrocephalus rib defects, bilat. pyelectasia and hydroureter, bilat. clubfeet	Livebirth (infant death)	girl	TE-I
1986	1987	Anencephalus	Eventration of abdominal wall	TOP	girl	TE-I
1987	1990	Sacral spina bifida cystica (4 cm)	Hydrocephaly, spontaneous recovery (strabismus)	Livebirth	boy	TE-II
1989	1990	Anencephalus		TOP	girl	TE-I
1990	1991	Anencephalus with thoracal rachischisis	-	TOP	girl	TE-III

TOP = termination of pregnancy
F = female
M = male

TR I = full supplementation
TR II = partial supplementation
TR III = no supplementation

TABLE III

Data of liveborn cases with oral cleft in the multivitamin (MV) and trace element (TE) group

Birth year	Oral cleft	Comments	Sex	Birth weight (g)	Gestation age (wk)	Supplement
1985	Left cleft lip	Closed spontaneously	boy	3150	40	TE-II
1985	Bilateral cleft lips with cleft palate	-	boy	3200	40	TE-II
1986	Right cleft lip	Epicanthal fold in the infant	boy	2450	37	MV-I
1986	Right cleft lip with cleft palate	Father is affected with cleft lip with cleft palate	boy	3800	40	TE-I
1987	Bilateral cleft lips with cleft palate	-	boy	3000	39	MV-I
1988	Right cleft lip with cleft palate	-	boy	4000	41	MV-I
1988	Bilateral cleft lips with cleft palate	Epileptic mother without anticonvul-sant treatment during pregnancy	girl	2950	40	MV-II
1987	Cleft palate	-	girl	3250	40	TE-III
1990	Cleft palate	-	girl	3200	41	TE-II

TABLE IV

The data base of cases with congenital cardiovascular malformation (CCM) in the multivitamin (MV) and trace element (TE) groups

Group	Birth year	CCM	Diagnosis time	Diagnosis method	Outcome	Sex	Birth weight (g)	Gestation age (wk)	Supplement	Family history
Multivitamin	1986	Left heart hypoplasia	At birth	Autopsy	LB (ID)	girl	3000	39	MV-I	Situs inversus with dextrocardia in mother
	1987	Ventricular septal defect* (small)	Follow-up	Cardiol	LB	girl	3700	40	MV-I	-
	1988	Double onset of pulmonary artery with pseudovalves and stenosis	At birth	Autopsy	SB	boy	2700	42	MV-I	-
	1988	Stenosis of aortic valve	Follow-up	Cardiol	LB	boy	4000	39	MV-II	-
	1989	Pulmonary stenosis (min. grad.)	Follow-up	Cardiol	LB	girl	2300	38	MV-I	-
	1990	Atrial septal defect, type II	At birth	Surgery	LB	girl	2800	39	MV-I	Aortic stenosis in mother
	1990	Atrial septal defect, type II	At birth	Surgery	LB	boy	3900	38	MV-I	-
	1991	Atrial septal defect, type I, ventricular septal defect	At birth	Autopsy	SB	boy	2250	34	MV-I	-
	1991	Ventricular septal defect	Follow-up	Cardiol	LB	boy	3350	36	MV-I	-
	1989	Stenosis of aortic valve	At birth	Cardiol	LB	girl	2950	39	MV-I	-

* Closed spontaneously

** It was confirmed by the cardiological institute but the family moved to an unknown address later.

LB = Livebirth; SB = Stillbirth; ID = Infant death

TABLE IV Cont.

Group	Birth year	CCM	Diagnosis time	Diagnosis method	Outcome	Sex	Birth wight (g)	Gestation age (wk)	Supple-ment	Family history
Trace-element	1987	Left heart hypoplasia (aortic atresia, hypoplastic mitral valves)	At birth	Autopsy	LB (ID)	girl	2350	40	TE-III	-
	1986	Tetralogy of Fallot	At birth	Surgery	LB	boy	4100	40	TE-I	-
	1986	Ventricular septal defect*	At birth	Cardiol	LB	girl	2950	38	TE-I	-
	1987	Aortic stenosis	At birth	Cardiol	LB	girl	3100	39	TE-I	-
	1987	Ventricular septal defect (moderate)	Follow-up	Cardiol	LB	boy	3150	39	TE-II	WPW syndrom in mother
	1987	Unspecified CCM**	Follow-up	Cardiol	LB	girl	2500	37	TE-I	-
	1987	Ventricular septal defect (small)	Follow-up	Cardiol	LB	boy	3950	41	TE-I	-
	1988	Atrial septal defect, type II	Follow-up	Surgery	LB	girl	3250	39	TE-I	Mitral prolap-sus syndrome in mother
	1987	Ventricular septal defect	Follow-up	Surgery	LB	boy	3650	40	TE-III	-
	1989	Transposition of great vessels	At birth	Autopsy	LB (ID)	boy	3300	40	TE-I	-
	1989	Aortic stenosis	Follow-up	Cardiol	LB	boy	3050	41	TE-I	-
	1989	Atrial septal defect, type II	At birth	Surgery	LB	boy	3150	38	TE-I	-
	1989	Patent ductus arteriosus	Follow-up	Suregery	LB	girl	3000	40	TE-I	-
	1990	Ventricular septal defect*	At birth	Cardiol	LB	boy	3610	40	TE-I	-
	1990	Ventricular septal defect	Follow-up	Cardiol	LB	girl	3100	40	TE-I	-
	1990	Aortic stenosis	Follow-up	Cardiol	LB	boy	3950	41	TE-II	-
	1990	Left heart hypoplasia	At birth	Autopsy	LB (ID)	boy	2300	35	TE-I	-
	1990	Atrial septal defect, type II	Follow-up	Surgery	LB	boy	3550	39	TE-I	-
	1991	Ventricular septal defect*	At birth	Cardiol	LB	girl	3230	40	TE-II	-
	1991	Ventricular septal defect	At birth	Cardiol	LB	boy	2600	37	TE-II	-

TABLE V

Data of cases with defect of urinary system in the multivitamin (MV) and trace element (TE) groups

Birth year	Urinary defects	Time of diagnosis	Outcome	Sex	Birth weight (g)	Gestation age (week)	Supplement
1985	Right renal agenesis Left ectopic kidney	Follow-up	LB	Girl	3050	39	TE-II
1986	Left stenosis of pyeloureteral junction, pyelectasia - caly-cestasia, ren duplex	At birth	LB	Boy	3050	41	TE-I
1986	Hydronephrosis (poly-cystic kidney type IV) Potter sequence)	Prenatal	FD	Girl	-	19	TE-I
1987	Left ureter stenosis with pyelectasia	Follow-up	LB	Girl	3800	40	TE-I
1987	Urethral atresia with bilateral hydronephro-sis	Prenatal	FD	Boy	-	19	MV-I
1987	Hydronephrosis*	Prenatal	FD	Girl	-	22	TE-I
1988	Bilateral renal agenesis (Potter sequence)	Prenatal	FD	Girl	-	23	TE-II
1988	Dystopia renis (hospitalised)	Follow-up	LB	Boy	3400	40	TE-I
1990	Exstrophia vesicae urinariae	At birth	LB	Boy	3300	40	TE-I
1991	Left cystic kidney, type II.	At birth	LB	Girl	4870	40	MV-I

FD = fetal diagnosis * Clinical diagnosis was false hydrocephalus
LB = live birth

TABLE VI

Data of infants with congenital hypertrophic pyloric stenosis in the multivitamin (MV) and trace element (TE) groups

Birth year	Sex	Birth weight (g)	Gestation age (week)	Day of surgery	Other defects and family history	Supplement
1986	boy	3150	41	28	-	TE-I
1988	girl	3000	41	No surgery, (hospitalisation in two occasions)	Alopecia loc.	TE-I
1987	boy	3550	39	58	Pectus excavatum in father	TE-I
1987	boy	3400	41	29	Cong. dislocation of hip and inguinal hernia in father	TE-I
1987	boy	2900	31	15	Twin A is healthy	TE-III
1990	girl	3650	40	94	-	TE-I
1991	boy	3350	38	67	-	MV-I
1992	boy	3850	39	64	Cong. dislocation of hip in mother	TE-I
1992	boy	3200	41	21	-	MV-I
1991	girl	3000	41	28	Right choanal stenosis was diagnosed, however, it had a spontaneous recovery	TE-II

TABLE VII

DATA of cases with congenital limb deficiency in the multivitamin (MV) and trace element (TE) groups

Birth year	Outcome	Sex	Birth weight (g)	Gestation age (week)	Congenital limb deficiency	Supplement
1986	LB	boy	3350	40	Femur-fibula-ulna complex, atypical (left femoral hypoplasia and missing of left fibula)	TE-II
1986	LB	girl	3700	41	Terminal transverse (left acheria with finger buds)	TE-I
1987	LB	boy	2100	36	Femur-fibula-ulna complex (missing of IV-V fingers in left hand, left femoral hypoplasia)	TE-I
1988	LB	boy	3350	40	Terminal transverse (left adactylcy I-V)	MV-I
1990	LB (ID)	girl	1300	37	Split hand/foot (severe hypoplasia of right III finger, adactyly of right III-IV toes, syndactyly of left III-IV toes)	TE-I
1990	LB	boy	4000	42	Terminal transverse (lack of two-thirds of left forearm)	TE-I

LB = livebirth
ID = infant death

TABLE VIII

Data of liveborn infants weith Down syndrome

Birth year	Birth weight (g)	Gestation age (week)	Maternal age (yr)	Karyotype	Supplement	Comments
1987	2850	38	25	47,XY,21+	TE-I	Maternal smoking
1987	3100	38	28	47,XY,21+	TE-I	-
1988	3150	39	27	47,XX,21+	MV-I	Large congenital hemangioma in lumbosacral region
1988	2630	39	34	47,XX,21+	TE-I	-
1991	2850	41	21	47,XX,21+	TE-II	Atrial septal defect type I (other CAs, pregnancy history)
1990	2650	40	25	47,XX,21+	MV-I	Condyloma in mother
1989	3200	38	22	47,XX,21+	TE-I	-

TABLE IX

Data of offspring with unidentified multiple congenital abnormality in the multivitamin (MV) and trace element (TE) groups

Birth year	Outcome	Sex	Birth wight (g)	Gestation age (wk)	Component defects	Group	Time of diagnosis	Comment
1985	LB	boy	2550	36	Hydrocephalus, atrial septal defect type II, bilateral cong. inguinal hernias, minor anomalies (e.g., lowset ears), somatic retardation (46,XY)	TE-I	At birth	-
1986	LB	boy	3300	39	Left bronchial stenosis, pectus excavatum	TE-II	Follow-up	Sequence (?)
1987	LB (ID)	girl	920	28	Cleft palate, micrognathia (Robin sequence), absence of ribs	MV-III	At birth (autopsy)	-
1987	LB	boy	2100	39	Malrotation of right kidney, right cong. inguinal hernia, right undescended testis	MV-I	Follow-up	Congenital postural deformity association [18]
1987	LB	boy	4040	40	Obstructive defect of urinary system (urethral stenosis), undescended testes	MV-II	Follow-up	-
1987	SB	girl	1200	36	Bilateral cleft lips with cleft palate, spinabifida occulta, bilateral pos equinovarus	MV-I	At birth (autopsy)	Schisis association [18]

TABLE IX Cont.

Birth year	Outcome	Sex	Birth weight (g)	Gestation age (wk)	Component defects	Group	Time of diagnosis	Comment
1988	FD (ID)	boy	1550	34	Esophageal atresia, annular pancreas with duodenal atresia, anal atresia	MV-I	Prenatal	Multiple intestinal atresia of autosomal recessive origin
1989	SB	?	1990	35	Hermaphroditism, bilateral clubfeet, minor anomalies, e.g., hypertelorism	TE-I	At birth (autopsy)	No chromosomal analysis
1990	LB	girl	4400	40	Syndactyly complete, preauricular tag, cong. dislocation of hips	TE-I	At birth	-
1991	LB	girl	3100	40	Dermoid cyst, left cong. inguinal hernia	TE-I	Follow up	-
1991	LB (ID)	boy	770	30	Ventricular septal defect, congenital inguinal hernias	MV-I	Follow-up (autopsy)	Richard, the III association [18]
1992	LB	boy	3900	38	Right pyelon-ureter duplex, bilateral cong. dislocation of hips	TE-III	Follow-up	-
1993	FD	girl	800	26	Hydrocephalus, bilateral hydronephrosis	MV-I	Prenatal	-

LB = livebirth ID = infant death
SB = stillbirth
FD = fetal diagnosis

The expected and observed numbers of anencephalus showed a good agreement (2.2 versus 2).

Other CA-groups were not related to the main hypothesis of this trial.

Isolated oral clefts were differentiated in two groups. Four newborn infants with cleft lip with or without cleft palate were found in the multivitamin group and three in the trace element group (Table III). Two children with cleft palate occurred in the trace element group and none in the multivitamin group.

Table IV shows the data of cases with cardiovascular CAs. There were 10 cases with cardiovascular CAs in the multivitamin group and 20 in the trace element group (χ^2_1=3.69; p=0.055), relative risk is 0.48 (0.23, 1.03). The difference is mainly explained by two cases of ventricular septal defect in the multivitamin group and 8 cases in the trace element group (χ^2_1=3.81; p=0.051). However, their diagnosis was based only on clinical findings in nine cases.

It is interesting to see the distribution of offspring with the CAs of the urinary system (Table V). The difference in their number (2 versus 8) is very near to the level of significance (χ^2_1=3.81); p=0.051). It is worthwhile differentiating the group of renal agenesis (0 versus 2) and obstructive CAs of the urinary system (1 versus 4) in the multivitamin and trace element groups.

The number of clinical diagnosis of congenital hypertrophic pyloric stenosis indicated a surprising difference (2 versus 8) between the study groups (χ^2_1=3.81; p=0.051) (Table VI). However, one case had no surgery in the trace element group, thus it is better to diagnose it as pyloric spasm. After the exclusion of this case the difference is not significant (χ^2_1= 2.95 %; p=0.086).

One offspring with congenital limb deficiency was found in the multivitamin group, while there were five in the trace element group (Table VII). The difference is not significant (χ^2/Yates = 1.60; Fisher p=0.12). There was a 6th case with hypoplasia of toe IV with flexion contracture in the trace element group, after its inclusion of the data base, the difference is near to the level of significance (χ^2_1=3.74; p=0.053). However, this case had also a torticollis, thus it was considered as a congenital postural deformity association /14/.

Two multiple CA groups are worth mentioning. The number of offspring with Down syndrome was two in the multivitamin group and five in the trace element group. All cases had trisomy 21 (Table VIII). The data of unidentified multiple CAs are summarised in Table IX. Of 13 cases, 8 had only two component CAs, if minor anomalies and functional defects (e.g., somatic retardation) were not considered. Five cases had a putative multiple CA-entity but without evidence. Two offspring had obstructive CAs of the urinary system, it was associated with hydrocephalus in one

case and with ventricular septal defect in another case in the multivitamin group. These seem to be against the trends of isolated CAs. However, the origin of multiple CAs differs from that of isolated developmental disturbances.

DISCUSSION

The rate of CAs diagnosed from the second trimester of pregnancy until the age of 1 year is 65/1000 in Hungary /7/. The total rate of CAs was 59/1000 in the multivitamin group, while 76/1000 in the trace element group. The latter surprising high rate is probably due to the complete ascertainment and the inclusion of some borderline defects between mild CAs and minor anomalies (e.g., deformities of feet, torticollis, pectus excavatum, faciocranial hemangioma).

Our trial has resulted in three main findings. First, the periconceptional multivitamin supplementation including 0.8 mg of folic acid can reduce significantly the first occurrence of NTD. This was the first intervention study to demonstrate this important preventive effect. Previously our preliminary results were published /8/. Second, our finding did not confirm the results of Tolarova /20/, who found that periconceptional multivitamin supplementation with a dose of 10 mg folic acid per day protected against cleft lip. It was the case in other nonneural midline CAs /5/ and it is in an agreement with the report of Bower and Stanley /1/. Third, some other CA entities had a lower rate in the multivitamin group than in the trace element group. The difference was at the 0.05 level of significance in ventricular septal defect, the CAs of urinary system and congenital hypertrophic pyloric stenosis.

In 1964 Hibbard /12/ reported a higher rate of CAs (3%) in the offspring of folate-deficient mothers than in controls (1.6%). Later Hibbard and Smithells /13/ showed a relationship between CAs and a defect of folic acid metabolism based on FIGLU (formiminoglutamic acid excretion) test. This test was positive in 62% of mothers with malformed infants and in 15% of mothers with normal infants. This 4 times difference was significant. However, later this line of research was concentrated only on NTD and other CAs were neglected.

Folic acid acts as a co-factor for enzymes involved in DNA and RNA biosynthesis and is also involved in the supply of methyl groups to the so-called methylation cycle which converts homocysteine to methionine /17/. However, folic acid, vitamin B12, vitamin B6, vitamin C and zinc interact with one another in many metabolic pathways. Thus, the decreased rate of CAs may also be related to both folic acid and other vitamin intakes. Cell division is exceptionally rapid at the critical

stages of specific developmental fields in embryos. The cell`s ability to increase the synthesis of nuclein acids and to methylate important compounds such as proteins and lipids could be compromised by the deficiency of folic and other vitamins resulting in impaired cell function and subsequently CAs. Genetically determined vitamin-dependency rather than vitamin-deficiency may have some causal role in the origin of NTD and some other CAs.

A further cohort study is ongoing to differentiate the chance effect and effect of multivitamins in the origin of these CAs and to clarify the mechanism(s) of this primary preventive method.

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INFLUENCE OF PARENTAL BIRTH WEIGHT ON BIRTH WEIGHT OF THE OFFSPRING

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The birth weights of 660 newborn infants of various intrauterine growth were related to the birth weight of their parents. The findings offer further support for a maternal regulation of fetal growth in small-forgestational age infants. This regulation is less effective in true prematurity where pathological and environmental factors seem to prevail over familial features.

INTRODUCTION

The role of intergenerational factors in pregnancy outcome has often been investigated. As recently reviewed by Emanuel /3/, both direct and indirect evidence document the importance of pre- and postnatal growth of females to the quality of their reproductive experience as adults.

Ounsted and Ounsted /10/ claimed that through maternal regulatory genes the mother's own intrauterine experience affects her reproductive performance. This theory was supported by two Hungarian studies, also showing that the maternal regulation was less effective in true prematurity where the role of environmental and actual pathological factors seemed to prevail over the familial/genetic features /2, 12/.

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MATERIALS AND METHODS

In the neonatal units of the Baranya County Hospital, Pécs and Department of Pediatrics, University Medical School, Pécs, gestational age, birth weight, length and head circumference of a total of 660 newborn infants were determined. Only singletons were included, babies of gipsy or other ethnic origin as well as infants with malformations were excluded from the study. The mothers and fathers of the infants with malformations were excluded from the study. The mothers and fathers of the infants were personally interviewed and their age, height, profession, social status were registered. Inquiries were also made about the mothers previous diseases and pregnancies. Gestational age of the family members could not be detected. Birth weight of the parents could be checked from medical records in one third of families: the oral information proved to be highly reliable in these cases.

The newborn infants were grouped according to gestational age and birth weight as follows:

1. Full-term appropiate-for-gestational age (AGA) neonates with a gestational age from 37 to 42 weeks, and with a birth weight between the 10th and 90th percentile values of the local standards.
2. "Mature" small-for-gestational age (SGA) newborn infants with a gestational age of 37 or more weeks, whose birth weight was under the 10th percentile.
3. True premature infants with a gestational age under 37 weeks, whose birth weight fell between the 10th and 90th centile curves of the local chart.
4. Premature SGA neonates with a gestational age of less than 37 weeks, and with a birth weight under the 10th percentile value.

Large-for-gestational age babies were not involved in this study.

RESULTS

Table I shows the mean age, height and weight values of the parents. Both mothers and fathers of mature SGA infants were slightly younger, smaller and lighter than those of mature AGA neonates. The parental age and birth rank of premature SGA infants were somewhat higher than in the other groups, but the parental height and weight values of premature AGA and SGA babies were very similar both to each other and to the values of the mature AGA group.

Analysis of medical history of the mothers and social status of the families did not result in relevant differences.

The mean birth weights are summarized in **Table II.** As shown by the figures, the birth weight of the mothers of mature SGA neonates was lower than that of the AGA infants, the difference being more expressed among the mothers of boys. The

TABLE I

Birth weights (g) of the index neonates and their parents
(mean ± S. D.)

	MATURE NEONATES (gest.age≥37 weeks)				PREMATURES (gest.age<37 weeks)			
	Birthweight centiles				Birthweight centiles			
	10 - 90		< 10		10 - 90		< 10	
	Boys n=218	Girls n=202	Boys n=29	Girls n=38	Boys n=79	Girls n=69	Boys n=11	Girls n=14
Index neonate	3555 ±428	3368 ±434	2426 ±286***	2222 ±330***	2250 ±665***	2039 ±649***	1216 ±389***	1228 ±188***
Mother	3199 ±562	3162 ±566	2626 ±511***	2957 ±590***	3104 ±702	2955 ±635*	2593 ±519***	2925 ±494***
Father	3412 ±616	3429 ±568	3310 ±637	3001 ±496*	3168 ±615*	3339 ±581	2989 ±643**	3036 ±480**

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$ against the corresponding value of the mature AGA (10-90 centiles) group

TABLE II

Parental age, height and parity of the newborn infants examined (mean±S.D.)

	MATURE NEONATES (gest.age≥37 weeks)				PREMATURES (gest.age<37 weeks)			
	Birthweight centiles				Birthweight centiles			
	10 - 90		< 10		10 - 90		< 10	
	Boys n=218	Girls n=202	Boys n=29	Girls n=38	Boys n=79	Girls n=69	Boys n=11	Girls n=14
Mother								
Age (year)	25.5±5.2	25.0±4.7	24.8±4.2	23.5±6.5*	23.2±4.0*	26.0±6.2	27.1±3.8	30.1±4.4*
Height (cm)	164.3±6.1	163.6±6.1	161.6±5.8*	161.1±5.9*	163.7±6.1	162.8±6.5	160.7±4.7*	163.8±7.6
Father								
Age (year)	28.5±6.7	28.4±6.0	27.7±7.5	25.7±8.0*	25.0±4.3*	27.6±5.3	29.3±5.0	30.2±2.5*
Height (cm)	176.6±6.4	177.5±6.2	172.0±7.6*	173.8±7.2*	175.6±6.7	177.1±7.1	175.9±8.9	176.7±5.8
Parity	1.6±0.7	1.5±0.6	1.5±0.9	1.5±0.8	1.7±0.8	1.7±0.9	2.1±1.1*	1.9±0.9

* $p < 0.05$ against the corresponding value of the mature AGA (10-90 centile) group

paternal means of mature AGA and SGA boys did not significantly differ, whereas the birth weights of fathers of SGA girls proved to be slightly lower.

The birth weight of mothers of premature SGA neonates was significantly lower than those of the mothers of premature AGA infants, which were very similar to the values in the mature AGA group. The differences were greater among the mothers of boys. The paternal birth weights were slightly lower in the case of premature SGA infants.

DISCUSSION

The aim of the present study was to reinvestigate the relation of birth weights in two generations in a new series of Hungarian infants. Unfortunately, the effect of parental gestational age on birth weight and duration of gestation could not be examined, although this could have contributed to a better understanding of intergenerational factors in pregnancy outcome /1, 5/. It should be mentioned, however, that parent-children and marital correlations in gestational age are rather difficult, if not impossible, to obtain /7/.

The relative role of intrinsic and extrinsic factors /3/ could not be evaluated either. Thus, smoking, dietary habits, alcohol consumption, triceps skinfold thickness, and several other factors including possible secular trends /4, 9/ were disregarded in this study.

At the same time, parental age, height, parity, pregnancy history and social class were considered. Apart from a certain variation, the differences in birth weights could probably not be attributed to these factors.

In spite of the limitations, in accordance with earlier studies /2, 4, 5, 10, 12/ the present results offer further support for an intergenerational influence on birth weight through the maternal line. Our findings seem to confirm the assumption that maternal regulation plays a major role in intrauterine growth retardation but is less significant in prematurity which is caused rather by various other biological and environmental factors /12/. From a merely practical point of view this means that women who had been SGA should be considered at increased risk to give birth to SGA infants /6, 10/. The findings are also in harmony with the conclusion by Magnus

et al. /8/ who claimed that, in contrast to birth weight, human variation in gestational age does not appear to be influenced by genetic factors to any large degree.

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URINARY ENDOTHELIN-1 EXCRETION IN FUROSEMIDE-TREATED HUMAN NEONATES

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The present study was carried out to determine the response of urinary ET-1 excretion to furosemide administration in human neonates. Ten newborn infants with mean birthweight of 2752 g and mean gestational age of 37.1 weeks were given furosemide in a dose of 1 mg/kg. Prior to and following furosemide therapy urine was collected for a period of 12 hours and analyzed for creatinine, osmolatity, sodium and potassium, as well as for AVP, aldosterone and ET-1. In response to furosemide administration urine flow rate and urinary osmolar, sodium and potassium excretion increased significantly, whereas creatinine excretion remained unchanged. Furthermore, following furosemide therapy there was an increase in AVP (19.5 ±5.4 vs 28.7 ± 7.8 pg/kg/h, $p = 0.06$, NS), aldosterone (507±120 vs 751 ± 203 ng/kg/h, $p < 0.05$) and ET-1 (36.0 ± 5.6 vs 61.4 ± 8.7 fmol/kg/h, $p < 0.05$) excretion, respectively. Urinary ET-1 excretion was found to correlate positively with diuresis ($r = 0.75$, $p < 0.001$), sodium ($r = 0.53$, $p < 0.0025$), osmolar ($r = 0.73$, $p < 0.001$) and AVP excretion ($r = 0.72$, $p < 0.001$) but not with aldosterone excretion ($r = -0.10$, $p = 0.96$). It is concluded that the furosemide-induced diuresis and natriuresis is associated with significantly increased urinary ET-1 excretion which may further inhibit sodium and water reabsorption in the distal nephron. The enhanced generation of ET-1 in the renal medulla appears to be related to decreased medullary tonicity and AVP stimulation.

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INTRODUCTION

Endothelin-1 (ET-1) originally isolated from the culture media of porcine aortic endothelial cells /31/ has been considered to play an important role in the renal control of salt and water metabolism /24/.

ET-1 administration in a high dose produced marked reduction in renal blood flow, glomerular filtration rate, urine flow and sodium excretion /5/. In low dose, however ET-1 induced profound diuresis and natriuresis without affecting renal circulation and glomerular filtration /23/. Several lines of evidences indicate that the physiological responses to ET-1 in the kidney are likely due to locally generated peptide rather than circulating hormone /4/. In support of this contention renal epithelial cells, in particular cells from the inner medullary collecting ducts are capable of high rates of ET-1 synthesis /12, 28/, exhibit abundance of ET-1 receptors /17, 27/ and have high cellular levels of ET-1 /15, 30/. The locally produced ET-1 functions as an autocrine/paracrine factor to modulate renal tubular transport of sodium and water, either directly or indirectly through interacting with other regulating hormones.

The involvement of endogenous ET-1 in the regulation of renal tubular sodium and water reabsorption during the neonatal period is not clearly defined.

However, recent studies from our laboratory have shown that urinary ET-1 excretion, an estimate of renal ET-1 production /1, 3, 4, 18/, is flow-dependent and higher in preterm than in term neonates (26) and it can be markedly suppressed by giving NaCl supplement /21/.

The present study was undertaken to determine whether the increased diuresis and natriuresis in furosemide-treated neonates is causally related to changes in renal ET-1 production and whether the response of renal ET-1 if any, is mediated by volume regulatory hormones i.e. AVP and RAAS, or by reduction in renal medullary tonicity.

MATERIALS AND METHODS

The study was performed in 10 newborn infants with mean birth weight of 2752 g (range: 1920-3670 g) and mean gestational age of 37.1 weeks (range: 32-41 weeks) at the age of 2 to 5 days (means: 3.4 days). Male infants were selected for the study to overcome the technical difficulties in urine collection. The infants were fed pooled breast milk when necessary completed with 10% glucose in water of formula (Prematil, Milupa) to provide daily fluid intake of 80 to 130 ml/kg. The indication for furosemide administration was cardiopulmonary fluid retention in five infants, symptoms of increased intracranial pressure in four infants who recovered from perinatal asphyxia and oliguria with moderate peripheral edema in one infant. Prior to

furosemide therapy plasma electrolyte concentrations and blood acid-base parameters were within the normal range and the respiratory support could be terminated.

Before furosemide administration urine was fractionally collected for a control period of 12 hours then furosemide was given i.m. in a single dose of 1 mg/kg and urine collection continued for another 12 hours. The specimens were refrigerated, pooled and stored at -20 °C until analyzed for creatinine (modified Jaffe's method), osmolality (vapor pressure osmometer, Wescor Co, Utah, USA), sodium and potassium (ion-selective electrodes) as well as for AVP, aldosterone and ET-1. AVP /2/ and 18-aldosterone-glucuronide /29/ were measured by radioimmunoassays. For the measurement of ET-1 radioimmunoassay was also applied using specific antibody (RPA 555, Amersham, Braunschweig, Germany) after extraction which was performed on Am prep 500 mg C2 columns according to the protocol provided by Amersham. The detection limit was 1.0 pmol/l with 50% binding at 4 pmol/l. The intra- and interassay coefficients of variation were 8.1 % (n = 10) and 13.9% (n = 24), respectively.

Data were evaluated by Student's paired t-test and by least squares linear regression analysis. Results are expressed as the mean ± SEM. Approval of the institutional ethical committee and informed parental consent were obtained for the study.

RESULTS

Table I shows that in response to furosemide administration there was a marked increase in urine flow rate and in urinary excretion of sodium and osmolality ($p < 0.001$). Urinary potassium excretion double ($p < 0.05$), whereas creatinine excretion remained practically unchanged.

TABLE I

Changes in urine volume and urinary excretion of creatinine, osmolality, sodium and potassium in newborn infants treated with furosemide

	volume (ml/kg/h)	creatinine (mg/kg/h)	osmolality (mosm/kg/h)	sodium (mEq/kg/h)	potassium (mEq/kg/h)
before furosemide	2.46 ±0.41	0.42 ±0.03	0.41 ±0.07	0.04 ±0.02	0.02 ±0.01
after furosemide	5.41*** ±0.24	0.50 ±0.07	1.05*** ±0.07	0.34*** ±0.04	0.04* ±0.01

* $p < 0.05$
*** $p < 0.001$

The furosemide-induced alterations in urinary AVP, aldosterone and ET-1 excretion are shown in Figure 1. AVP excretion increased from the baseline value of 19.5± 5.4 pg/kg/h to 28.7±7.8 pg/kg/h after furosemide, this increase however, just fell short of statistical significance ($p = 0.06$). Furosemide administration resulted in a significant rise in urinary aldosterone and ET-1 excretion from the control values of 507±120 ng/kg/h to 751±203 ng/kg/h ($p < 0.05$) and from 36.0±5.6 fmol/kg/h to 61.4±8.7 fmol/kg/h ($p < 0.005$) following furosemide therapy, respectively.

Urinary ET-1 excretion was found to correlate directly with urine flow rate ($r= 0.75$, $p < 0.001$) and sodium excretion ($r = 0.53$, $p < 0.0025$). Furthermore, there was a significant positive correlation between urinary ET-1 and AVP excretion ($r = 0.72$, $p < 0.001$), and ET-1 and osmolar excretion ($r = 0.73$, $p < 0.001$) but such a relationship between ET-1 aldosterone excretion could not be established ($r = 0.10$, $p = 0.96$) (Fig. 2).

DISCUSSION

The present study provides evidences that in newborn infants the marked increase of sodium and water diuresis following furosemide administration is associated with a significant rise in renal ET-1 production which may contribute to the complex pharmacological actions of furosemide.

Since furosemide inhibits sodium and water reabsorption in the thick ascending limb of Henle's loop, it is conceivable to assume therefore that the flow-dependent increase of renal ET-1 production can be localized mostly in nephron segments distal to the sites of furosemide action. This notion is consistent with the observations that the highest rate of ET-1 synthesis /12, 28/ and the most abundant ET-1 binding sites have been detected in the inner medullary collecting ducts further augments sodium and water excretion by inhibiting Na^+-K^+ATPase activity /32/ as well as vasopressin-stimulated osmotic water permeability and cAMP accumulation /16, 19/.

The mechanisms of enhanced renal ET-1 production in furosemide treated neonates is far from clear. Furosemide-induced volume depletion tended to increase urinary AVP excretion and there was a strong, positive relationship of AVP to ET-1 excretion. Moreover, both AVP and ET-1 receptors have been identified in the inner medullary structures of developing kidney /9, 20/. In this regard it is to be noted that AVP has been shown to stimulate ET-1 release in a variety of experimental

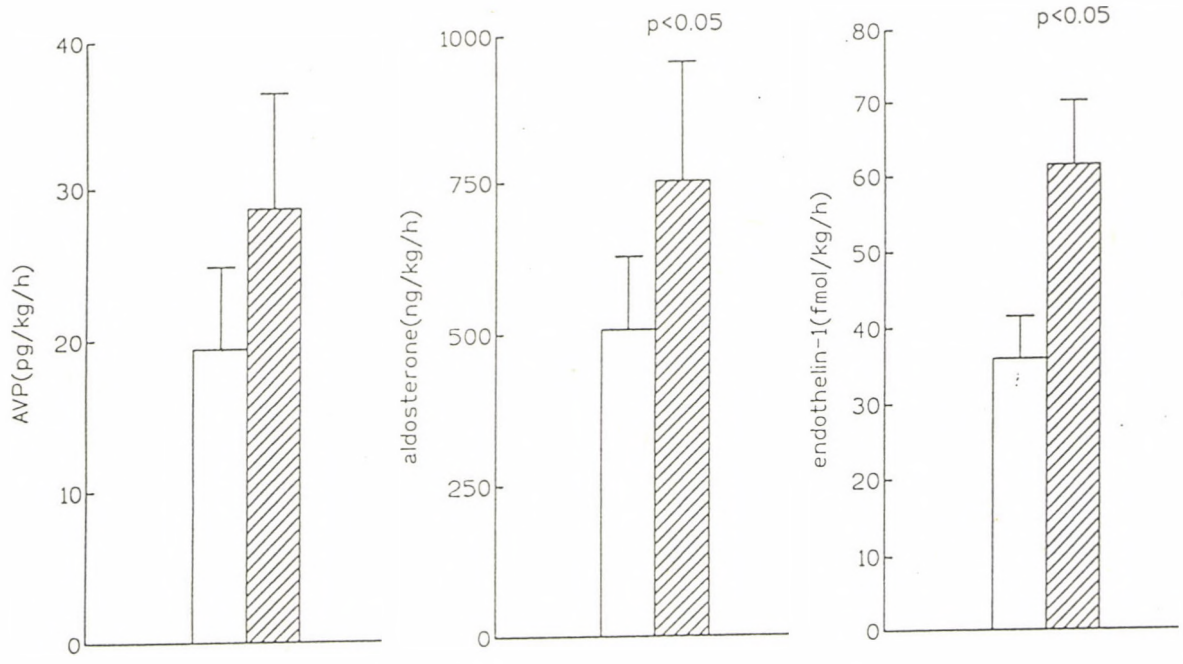

Fig. 1. Response of urinary AVP, aldosterone and ET-1 excretion to furosemide administration in newborn infants

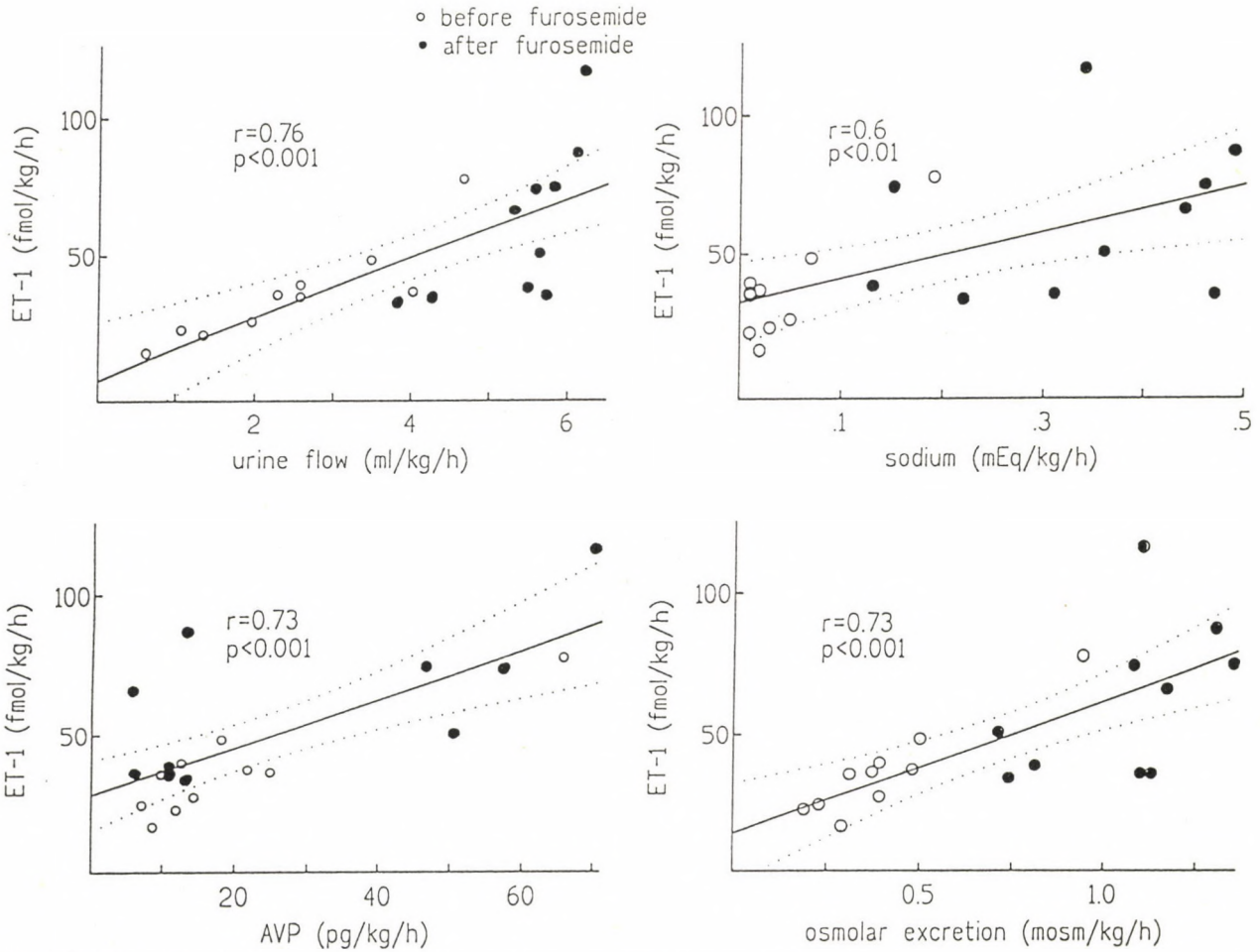

Fig. 2. Relationship of urinary ET-1 excretion to urine flow rate and urinary sodium AVP and osmolar excretion in newborn infants treated with furosemide

conditions via a mechanism possible involving receptor-mediated mobilization of intracellular Ca^{2+} and activation of protein kinase C /7, 8, 11/.

Reduced tonicity in the renal medulla as reflected by the markedly increased osmolar excretion may also account for the higher rate of ET-1 secretion and may explain the close relationship between urinary osmolar and ET-1 excretion. In good agreement with this notion Kohan and Padilla most recently published that increasing media osmolality from 300 to 450 mosm/kg with NaCl or mannitol caused a dose- and time-dependent reduction in ET-1 mRNA in cultured rat inner medullary collecting duct cells. Similarly, induction of low or high medullary tonicity by volume expansion or depletion in vivo was associated with significantly elevated or reduced urinary ET-1 excretion and medullary ET-1 mRNA production, respectively. In addition, the authors provided evidences that the osmolar regulation of ET-1 production is unique to cells in the medullary collecting duct /13/.

As an alternative possibility it is also to be considered that some of the excreted ET-1 derive from the proximal tubules. Furosemide administration to human neonates in a dose of 1 mg/kg resulted in an increased activity of RAAS; plasma renin activity doubled and there was an about 50 percent increase in plasma aldosterone level and urinary aldosterone excretion /25/. Estimated by the response in urinary aldosterone excretion, RAAS in the present study was similarly activated. The elevated angiotensin II simultaneously stimulated proximal tubular sodium reabsorption, aldosterone production and the release of ET-1-like immunoreactivity in endothelial cells through immediate and dose-dependent induction of the ET-1 gene expression /11/. Sparsely distributed ET-1 binding sites and low rate ET-1 synthesis /12, 17, 27, 28/ have been demonstrated in the proximal tubule and ET-1 has been shown to specifically increase the activity of proximal tubular sodium transporters /6/.

It has been claimed therefore, that the angiotensin II-induced ET-1 acts in concert with angiotensin II to stimulate proximal tubular sodium reabsorption and aldosterone production /10, 22/.

As a result of the combined effects of furosemide and the related endocrine reactions profuse diuresis and natriuresis occurs in association with significantly increased urinary ET-1 excretion. Urinary ET-1 appears to be released by the distal nephron which is the major site of its production and the main target of its action. The contribution of the proximal tubules is most likely insignificant at this level of RAAS stimulation because the ET-1-mediated proximal tubular sodium reabsorption lags far behind the distal tubular sodium loss that is strongly related to the locally generated ET-1.

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MATERNAL COCAINE USE AND NEONATAL PATHOPHYSIOLOGY

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Infant mortality rate in the United States is higher than in many other developed countries. Substance abuse in the United States is one of the major causes of premature deliveries and increased infant morbidity, and thus of infant mortality. Although no specific syndrome results from perinatal cocaine exposure, the impact of cocaine on intrauterine development and perinatal events results in adverse effects on the neonate. Maternal cocaine abuse is expected to become more frequent in the Central European countries in the near future. To draw the attention of Central European medical communities to fetal cocaine exposure, maternal and fetal pathophysiologic changes associated with cocaine abuse are discussed in view of a few selected cases from recent admissions to the Neonatal Intensive Care Unit of the Medical Center of Louisiana at New Orleans.

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INTRODUCTION

In 1993, the United States ranked 16th in the world in infant mortality, far behind many other developed countries /27/. Several studies have attempted to try to determine the major factors involved in the etiology of the high infant mortality rate. Most studies suggest that *1.* -lack of prenatal care, *2.* -high rate of teen pregnancies, and *3.* -substance abuse alone or in combination are the most important factors. Research on substance abuse in the United States continues to focus on crack cocain. Although alcohol is still the most frequently abused substance, the prevalence of cocaine use by pregnant women has been estimated by most studies to range from 5.5-18% and more than 100,000 crack babies are born each year in the United States. The annual medical cost of the consequences of in utero exposure to cocaine in the neonatal period is estimated to exceed $500 million dollars in the United States /21/. Although no definitive unique syndrome results from prenatal cocaine exposure, cocaine has a significant impact on child health and development /9, 20, 21/. Cocaine use during pregnancy correlates strongly with a number of other maternal characteristics such as alcohol and other drug abuse, smoking and malnutrition. Women who use cocaine during pregnancy are usually older and black and use other drugs as well. Because the use of cocaine is illegal, maternal self-report alone will fail to identify many exposed neonates, however, cocaine and its metabolite (benzoylecgonine) can be detected in amniotic fluid, fetal and maternal urine samples, hair, and meconium /10, 12, 13, 16/.

An increased occurrence of premature labor, premature rupture of membranes (PROM), stillbirth, abruptio placenta, and meconium stained amniotic fluid have all been observed among women who use cocaine. The cocaine exposed infant is at risk for a variety of complications including fetal distress, prematurity, small length, height and head circumference for gestational age, cerebral infarction, neurobehavioral disturbances, and congenital malformations /9, 20, 21/. Because cocaine readily crosses the placenta and the blood-brain barrier, its primary neonatal effects could be explained by its direct action on catecholamine synthesis /18, 19, 26/. Secondary effects are those attributable to changes in maternal physiology with subsequent alterations in fetal perfusion and transfer of nutrients and oxygen to the fetus /30/.

Since it is expected that maternal drug abuse will be more frequent in the Central European countries in the near future, this article discusses selected cases observed in the United States in an attempt to draw attention of Central European medical communities to this issue.

MATERIALS AND METHODS

The Medical Center of Louisiana at New Orleans is an inner city hospital facilitated by two universities (Tulane University Medical Center and Louisiana State University) and represents predominantly low-income black population. In 1993 4,186 babies were born and 392 were admitted to the level II and III Neonatal Intensive Care Units (NICU) in this hospital. The rate of premature deliveries was 6.2%, and the neonatal mortality rate was 13.0/1000 live births. Because of the high frequency of drug abuse (mostly crack cocaine) during pregnancy, urine analysis for maternal drug abuse is routinely performed using commercially available RIA kits. Twelve percent (12%) of mothers admitted in labor had positive urine toxicology screen for cocaine (Table I). We selected the following representative cases for publication to illustrate the most common consequences of maternal substance abuse.

TABLE I

Rate of maternal cocaine abuse and neonatal mortality in the Medical Center of Louisiana at New Orleans in 1993

Number of deliveries	4.186
Admission to level II + III NICU	392
Premature rate	6.2%
Neonatal mortality rate	13.0/1000 live births
Positive maternal cocaine urine test rate at admission	12%

Patient 1

1228 g black female was born to a 28-year old G3P2 who had no prenatal care. Mother presented to the Emergency Room with profuse vaginal bleeding and admitted to using crack cocain in the evening of delivery. There was no placenta previa, and abruptio placentae was diagnosed. An emergency Cesarean section was performed, and patient emerged crying with Apgar score 7 at one minute and 8 at five minutes. She was intubated and transported to the NICU, where umbilical artery and venous catheters were placed. Percentiles for body weight, length, and head circumference were appropriate for the estimated gestational age of 28-29 weeks. Both the maternal and neonatal urine samples were positive for cocaine. She required minimal ventilatory support. Ampicillin and Gentamicin were started for presumed sepsis. Antibiotics were discontinued after 3 days since cultures remained negative. She advanced to full feedings without difficulties. Repeated ultrasound examinations showed no intraventricular or periventricular hemorrhage. During her hospital course no retinopathy of prematurity or bronchopulmonary dysplasia developed. Her brainstem evoked auditory response study was within the normal limits at discharge.

Patient 2

2807 g black female was born to a 29-year-old G6P3 mother who had no prenatal care with a history of two previous premature deliveries. She admitted to using crack cocaine the day prior to delivery. There was thick meconium upon rupture of membranes. The baby was delivered via precipitous vaginal delivery with Apgar scores of 2 and 6. The estimated gestational age was 41 weeks; percentiles of body weight, length, and head circumference were appropriate for gestational age. There was thick meconium below the vocal cords, and the baby was intubated and suctioned. Following intratracheal suctioning, she required a brief period of bag ventilation with 100% oxygen for bradycardia. On arrival to the NICU, the patient was noted to be jittery. She was given lorazepam (0.1 mg/kg). She did not develop clinical seizures, but she continued to be jittery and tremorous. The urine samples of the mothers and the newborn proved to be positive for cocaine. The infant was discharged without symptoms on the 5th postnatal day.

Patient 3

1205 g black female was born via vaginal delivery at 28 weeks estimated gestational age to an 18-year-old G2P1 mother who had no prenatal care. She admitted to marijuana, cocaine and alcohol abuse. Apgar scores were 7 at one minute and 8 at five minutes; the

infant was appropiate for gestational age for birth weight, length, and head circumference. The baby was initially intubated for less than 12 hours. She was kept on antibiotics for three days until cultures taken at delivery proved to be negative. The results of maternal and neonatal urine toxicology were positive for cocaine. On the second day of life gavage feedings were introduced with 3 mls of Similac Special Care formula on 3-hour schedule. By the 5th postnatal day she tolerated full feedings taking 180 ml/kg/day. On postnatal day 6, bilious emesis developed without evidence of necrotizing enterocolitis (NEC) or obstruction of other etiology. The enteral feeding was suspended until the 10th day of life. Then bolus feeds were once again attempted, but two days afterwards abdominal distension developed. Her repeated evaluation was again negative, so on the 12th postnatal day she was started on continuous feeds of Preterm Enfamil formula containing 81 cal/100 ml. After she tolerated feedings, the rate was advanced slowly until she met caloric requirements via the enteral route. The remaining neonatal course was uneventful.

DISCUSSION

In 1985 *Chasnoff et al.* suggested that a mother's cocaine use during pregnancy is associated with significant adverse effects in the newborn infant /5/. However, cocaine use in pregnant women has continued to increase substantially in the United States. Cocaine abuse is associated with the use of other substances and high risk life style, making the mother prone to multiple infections, trauma, neglect, and malnutrition. The effect of cocaine on the fetus is determined by the pattern of abuse. Cocaine has a half-life of about 40 to 60 minutes after intravenous or intranasal administration. Crack cocaine is the alkaloidal form, that, when smoked, produces a rapid increase in blood concentration and a half-life similar to those obtained after intravenous administration. *In vivo* animal studies have shown cocaine to cross the placenta freely /29/. *In vitro* perfusion of the human term placental cotyledon provided evidence that the steady-state maternal-to-fetal transfer of cocaine is significantly greater than benzoylecgonine transfer. Since the placenta serves as a depot for large amounts of cocaine, it offers some degree of fetal protection after bolus administration /23/. Cocain-binding protein has also been described in the placenta, but its role in the regulation of placental cocaine transport is not known /1/. Benzoylecgonine, which was thought to be a pharmacologically inactive metabolite of cocaine, has recently been shown to have a greater contractile effect than cocaine on isolated cerebral arteries of the lamb /22/.

As a stimulant drug, cocaine affects multiple neurotransmitter systems in the central nervous system (CNS) including the dopaminergic and norepinephrinergic systems. Cocaine blocks the re-uptake of these neurotransmitters. Cocaine also stimulates dopamine synthesis and causes an up-regulation of postsynaptic dopamine receptors. During pregnancy the norepinephrine-mediated vasoactive consequences of cocaine exposure in animals include decreased uterine blood flow and constriction of umbilical arteries leading to fetal hypoxemia and decreased nutrient transfer /30/. Blood levels of the norepinephrine precursor dihydroxyphenylalanine were higher in prenatally cocaine exposed than in unexposed newborns. The effects of cocaine on the dopaminergic, norepinephrinergic system may be due entirely to chronic stress associated with the cocaine-induced vasoconstriction and hypoxia in utero /18)/ In the cerebrospinal fluid (CSF), cocaine exposed infants had significantly lower levels of homovanillic acid, one of the principal metabolite of dopamine, when compared with unexposed infants /19/. In rabbit pups, cocaine exposure reduced striatal dopamine content and also affected the trophic activity in this region /26/.

A large variety of pathological conditions during pregnancy, delivery, and the neonatal period are thought to be associated with maternal cocain abuse /9, 20, 21/. Namely, PROM, abruptio placentae, meconium stained amniotic fluid, premature delivery, stillbirth, fetal distress, intrauterine retardation and failure to thrive, cerebral infarctions, neurobehavioral defects, and congenital malformations (especially genitourinary tract, cardiovascular, and limb deformities) are the most significant. However, meta-analysis of 45 articles on the fetal effects of cocaine exposure /14/ suggests that there may be less reproductive risks associated with fetal cocaine exposure than generally believed. For instance, only genitourinary malformations, premature birth, and spontaneous abortions could be shown to be significantly associated with cocaine use in polydrug users when compared to control groups of polydrug users not using cocaine. Comparison of users of cocain alone with no drug users revealed a higher risk for in utero death, in addition to genitourinary tract malformations /14/.

Complex methodologic issues contribute to scientific uncertainty regarding the possible effects of prenatal cocaine exposure. These include difficulties in accurate identification of users, uncertain measurement of dose and gestational timing of exposure, sample selection bias, failure to control for confounding variables, identification of appropriate control populations, and selection of sensitive outcome measures /32/.

During normal early neonatal transition, the changes in the function of cardio-respiratory system are the most striking events. Intrauterine cocaine exposure

significantly affects these aspects of neonatal adaptation. It is associated with transient ST segment abnormalities in the infants and these abnormalities postnatally suggesting consistent and transient myocardial ichemia /17/. On the first day of life, cardiac output and stroke volume were lower, and arterial blood pressure was higher in infants exposed to cocaine in utero /25/. These infants are also at increased risk of intraventricular hemorrhage, periventricular leukomalacia /24/, and NEC /7/ signifying the importance of the vasoconstrictive actions of cocaine in the development of neonatal pathology. There is a decreased incidence of respiratory distress syndrome and neonatal jaundice among premature infants prenatally exposed to cocaine /28, 31/. This may be related to the observation that chronic intrauterine stress enhances maturation of enzymes including those involved in surfactant production and bilirubin metabolism. Infants prenatally exposed to cocaine have a higher incidence of apnea and sudden infant death /6/, have increased tremulousness and startles, and state stability, decreased interactive behaviors /5/, and have higher incidences of cognitive and motor delays at follow up /24/. Furthermore, cocaine exposed infants had significantly lower cortisol levels postnatally when responding to stress. These infants have decreased modulation capability to normally stressful events /15/. Indomethacin treatment may also enhance the adverse effects of intrauterine cocaine exposure on renal, cardiovasular, and platelet function /4/. Finally, hyponatremia was noted to be associated with regular cocaine use during the last stages of pregnancy /8/.

The primary mode of cocaine action is maternal and fetal vasoconstriction. Therefore a well-defined fetal cocaine syndrome does not exist. Most fetal defects - including the birth defects - may be related to vasoconstriction, hypertension, and infarcts at any time during gestation in any structure. Subsequent loss of vascular supply and tissue necrosis produce fetal damage that is beyond capacity for repair.

The social and financial impact of maternal cocaine abuse needs to be further clarified. In the United States neonatal hospital cost was by $5200 more for cocaine-exposed infants at the time of medical discharge readiness than for unexposed infants. Fetal exposure to crack was associated with much larger cost increases. The cost of infants remaining in the nursery while awaiting home and social evaluation or foster care placement further increased this cost difference /21/. These infants continue to be at risk because of the parents' life style. The inappropriate home environment and improper care contribute to delayed cognitive and motor development. Postnatal exposure to cocaine has been reported via breast-feeding, by direct ingestion, and by passive inhalation. Of interest, parents' cocaine use during the year preceding their child's birth may increase the risk of rhabdomyosarcoma by 5 fold in their children /11/.

In 1993, the provisional infant mortality rate in the United States was 8.3/1000 live birth. In Louisiana it is estimated to be 9.8/1000 live birth, higher than the national average /27/. In the level II and III NICU at the Medical Center of Louisiana at New Orleans the neonatal mortality rate was 13.0/1000 live births and 12% of the mothers admitted in labor have positive urine toxicology screens for cocaine. These represent the women who have used cocaine within 48 hours of the test and thus probably significantly underestimates the existing rate of abuse. Our first case presented an abruptio placentae with severe maternal bleeding, emergency Cesarean section and, as it is commonly seen, a completely asymptomatic infant. The mother admitted to using cocaine and both the mother's and infant's urine sample were positive for the substance. Although premature birth is a major risk of maternal cocaine abuse, even the fullterm infant could be adversely effected as shown in case 2. Thick meconium below the vocal cords and signs of early withdrawal required medical attention. The most classic presentation of consequences of maternal cocain use is an infant who is very irritable and difficult to feed in the initial days of life. With appropriate differential diagnosis and treatment the irritability gradually declines, and the infant's feeding pattern improves. Maternal methyldopa treatment may result in an excessive tremor in neonates which was thought to be related with striking depression of CSF noradrenaline level /3/. In our last case, the feeding intolerance was prolonged but physical exam, radiologic, and laboratory tests were unremarkable. Since neonates exposed to cocaine in utero are at significantly elevated risk for the development of NEC /7/, this must always be first considered in the differential diagnosis when those infants present with signs of feeding intolerance. However, in the last case, besides maternal cocaine abuse, several other factors may have been also involved in the pathomechanism of feeding difficulties including prematurity, and alcohol and marijuana abuse. Prenatal care and maternal nutritional supplementation may decrease the risk of adverse neonatal outcome, even among women who continue to use cocaine. Health care providers should approach addicted women with empathy and concern, emphasizing the woman's real potential to improve the future for herself and her children if she receives appropriate drug rehabilitation treatment and medical care.

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PET FOOD AS AN UNUSUAL SOURCE OF INDOOR POLLEN ALLERGY

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The authors prove by pollen analytical examinations that the commercially available unwashed pet food: parrot, canary, rodent food, canary grass (seed and seed mixtures) contain several seriously allergen pollen as grass, weed (ragweed, pigweed, mugwort) pollen and moulds' spores. In the available pet food 37 types of seeds and stuck to these seeds 23 types of pollen grains could be identified. It was observed that 3 grass pollen allergic children who showed asthma, allergic rhinitis, urticaria, Quincke edem in winter time were not allergic to either the feathers or the fur of their pets. After removing the pets from the patients' flats, and stoping to store pet food, the symptoms disappeared. Pet food unproperly cleansed can prove to be an indirect indoor source of allergy. It is advisable for pollen allergic people not to keep grain consuming pet animals.

INTRODUCTION

It is not unusual for the allergic patients or their families to keep a pet at home. Over 60% of the households in the United States have animals /1/. Dogs, cats and small mammals are far more common in families having children. For instance dog ownership in families with no children is 33.1%, once there is at least one child over six in the family, dog ownership jumps to 56.1% /2/. Caged birds' ownership occurs in 5.0 percent of households /1/. A preliminary survey conducted by Herring /6/ suggests that the incidence of pet ownership may be even higher among the families of allergic children than among families of non-allergic children.

Our attention was drawn by the phenomenon that pollinotic children showed allergic symptoms even out of the pollen season. For example children allergic to grass pollen suffered from allergic symptoms in the winter months also without infection. Searching

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for allergens, it became clear that in the home of these children pets (e.g. caged birds, hamsters) fed with seeds were kept.

Since the children did not show hypersensitivity to feathers and fur, the animals must have caused the allergy in some other ways. It was suggested that the food of the animals, containing pollens could be the pathogenetic factor.

PATIENTS AND METHODS

We observed three pollinotic children who suffered from allergic symptoms in the winter without sensibilisation against perennial allergens and without having positive responses to their pet's fur. Skin prick tests were performed with Bencard (Beecham) and Pharmalgen allergens. The positive control was 1 mg/ml Histamine solution.

Nasal challenge was performed with Pharmalgen allergens. The allergen was diluted in albumin. We counted the number of sneezes, the drops from nasal discharge and measured nasal inspiratory peak flow with a Youlten (Clement Clark) Instrument.

Pollen and seed identification in the pets' food: after extraction, filtration, centrifugation the microscopic elements (pollen and spores) were acetolysed by Erdtman's method and embedded in a mixture of glycerine-water.

The animal food was also simultaneously analysed and identified by seed experts (P. Erdős and Z. Madas). As control examination pet food originating from different sources and different times were also studied.

RESULTS

The three case reports are summarised in Table I. All the patients had grass pollen allergy but did not have positive results in the house dust mite and feather skin prick tests, nor did they have positive response to their pet's fur. After the removal of the pet all the children became symptom free. Two of them later had symptoms in the summer period as well, thus proving grass pollen sensitivity.

TABLE I

Data of the three patients

Patients	No. 1	No. 2	No. 3
allergic family history	+	-	-
age at examinations	10.5	15	5
symptoms (in winter)	rhinitis urticaria Quincke edema	rhinitis urticaria	asthma
pet in the flat symptoms ceased	parrot	hamster	parrot
after pet elimination	+	+	+
symptoms at summer	+	-	+
skin prick pos.	grass cladospora	grass	grass
Spec. IgE positivity	grass Alternaria	not done	grass
nasal provocation positive with	grass	not done	grass

The skin prick tests of the three pollen sensitive children are summarised in Table II.

Analysis of the pets' food:

A. Parrot food

1 kg of parrot food contained an average of 1200 pollen grains. Most of them belonged to the goose foot family and grasses, but also a quite a large number belonged to the ragweed (Table III/A). No seeds of Ambrosia (ragweed), garden sorrel or Artemisia (mugwort) were found in the parrot food while their pollen and even fern spores were stuck to the other seeds.

TABLE II

The skin prick tests of three pollen sensitive children keeping pets
(the crosses indicate the level of skin sensitivity)

Allergen	case 1.	2.	3.
PHARMALGEN			
gm4 (grass mixture)*	++	+++	+++
g1 (Anthoxanthum odoratum)	+++	+++	+++
g8 (Poa pratensis)	+++	neg.	+++
g12 (Secale cereale)	++	neg.	+++
w1 (Ambrosia artemisiifolia)	++	neg.	neg.
w6 (Artemisia vulgaris)	neg.	neg.	neg.
w9 (Plantago lanceolata)	neg.	neg.	neg.
arborpollen **tm	neg.	neg.	neg.
m2 (Cladospora)	+++	neg.	neg.
BENCARD			
feathers (mixture)	neg.	neg.	neg.
canary feathers	neg.	neg.	neg.
budgerigard feathers	neg.	neg.	neg.
hamsterfur		neg.	
rabbit fur		neg.	
house dust mite	neg.	neg.	neg.

* gm4 (g5,6,12,13) Lolium perenne, Phleum pratense, Secale cereale, Holcus lanatus.

** tm Betula verrucosa, Corylus avellane, Alnus incana, Quercus alba.

TABLE III

Seeds and pollen grains with allergic character in parrot food (A); in canary food (B); in hamster food (C) and stuck to the panicle of Phalaris canariensis (D)

FAMILY Genus	POLLEN A	 B	 C	 D	SEEDS A	 B	 C	 D
CHENOPODIACEAE								
-AMARANTHACEAE	+++	+++	+	++				
Chenopodium album					+	-	+	-
Amaranthus retroflexus					+	-	+	-
Amaranthus albus					-	+	-	-
COMPOSITAE								
TUBULIFLORAE	+	++	+	+				
Ambrosia artemisiifolia	++	++	++	+++	+	-	-	-
Artemisia sp.	+	-	-	++	-	-	-	-
Arctium sp.	-	-	-	-	+	-	-	-
Helianthus annuus	-	-	-	-	+	-	+++	-
PLANTAGINACEAE								
Plantago sp.	+	+	-	+	-	-	-	-
POACEAE-CEREALIA	+++	+++	++	+++				
Avena fatua					-	-	+	-
Avena sativa					+++	+++	+++	-
Agropyron repens					+	-	-	-
Echinochloa cruss-galli					+	+	+	-
Hordeum vulgare					-	+	-	-
Panicum sp.					+++	++	+++	-
Phalaris canariensis					+	+	-	+++
Secale sp.					-	-	+	-
Setaria italica					+	+	+++	-
Setaria pumila					+	+	-	-
Sorghum sp.					-	-	+++	-
Triticum aestivum					+	+	+++	-
Zea mays					+	-	+++	-
POLYGONACEAE	+	-	-	-				
Polygonum aviculare					-	+	-	-
Polygonum convolvulus					-	-	+	-
Polygonum lapathifolium					+	+	-	-
Rumex sp.	+	-	+	-	-	-	-	-
FUNGI	+	+++	+++	+				
Claviceps purpurea					-	+	-	-

+++ = dominant ++ = frequent + = sporadic

B. Canary food

1 kg of canary food contained an average of 3500 pollen grains. The prevailing pollen were those of mild grasses (Table III/B). The canary food was the richest in pollen and mould per unit of surface. The canary food contained ragweed pollen, although among the seeds no Ambrosia seed was detected.

C. Rodent food (guinea-pig, hamster)

This mixture contained the least amount of pollen but the highest of mould spores (both protophytes and polycellular organisms) (Table III/C).

D. Canary grass

More kinds and a larger amount of pollen stuck to the grass were found than expected. The majority of them were the very allergenic ragweed, grass, pigweed and mugwort (Table III/D).

DISCUSSION

Beck /2/ acknowledged that pet owner experience is so pervasive and of such importance in the lives of people that many, especially the young, have more contact with animals than even those who work with animals. Nearly 25% of the allergic population are sensitive to dogs and cats /5/.

By keeping pets one has to count both with direct and indirect consequences. All animals lose their epithel or feathers, therefore the flat would contain more mites. The allergologists are aware of the fact that the fur or feathers of animals may be allergen sources and try to convince their patients not to keep animals at home. It happens quite often, that this request is denied by the patient and/or his family, thus causing serious disputes between the doctor and family, and this can even influence their relationship /6/, as we experienced in our third case. That is why we consider it very important to make it clear for the parents, that not only the animal presents a potential danger for the allergic patient, but also the food that it is fed with, and other substances used for caring /7/, may provide an allergen source being responsible for the disease.

The mixed grass pollen found in pet food can be responsible for the severe allergic complaints that occur out of the pollen season.

Our pollen analytical examination proved that the commercially available unwashed pet food contains several pollen and mould spores. In the case of Patient 1 the moulds can also be considered as allergy inducing agents. It has to be emphasized that even pet food which is not a mixture consists of the fruitful clusters of canary grass, contains 9 kinds of pollen and moulds stuck to the plant (Table III/D).

In several flats dry products of plants are tied in bunches as decoration in flower pots which can also be a source of pollen dispersion in the air of the flat.

One can also consider that it is possible for workers in agriculture to have allergic symptoms in the winter when they feed their animals with pollen containing seed mixtures. In conclusion it can be stated that the pet food examined contained a great number of various allergenic pollen grains and mould spores which by getting into the ambient air may provoke allergic complaints. Accordingly, pollinotic individuals are advised against keeping seed consuming animals.

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DOES DEXAMETHASONE TREATMENT IMPROVE THE OUTCOME OF BACTERIAL MENINGITIS?

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Although steroids show marked modulation in inflammatory processes in experimental meningitis, their use in clinical field remains controversial. This study deals with 89 cases of bacterial meningitis in children treated between 1983 and 1993 in Saint László Hospital. Patients younger than 2 months of age were treated with cefotaxime, while older infants and children with ceftriaxone as a presumptive therapy. Dexamethasone as an adjunctive therapy was administered in 32 cases while in 57 cases only antibiotic was given (historical control). The causative agent (H. influenzae) was prevalent in the dexamethasone treated group, and N. meningitidis in the historical control group. The mortality rate after 24 hours of hospitalization was O in the dexamethasone treated group, while 11 died in the historical, not dexamethasone-treated group. Hearing impairment and other sequelae were nearly similar in both groups. Authors think that this can be explained by the fact that even severe bacterial meningitis cases remain alive by the dexamethasone therapy. Sequelae can be improved by appropriate therapy so these children can live a relatively normal life.

INTRODUCTION

The study of molecular pathophysiology of experimental meningitis showed that cerebral damage is partly due to the direct impact of bacterial components (polysaccharides, cell-wall components, endotoxin, etc.). On the other hand the host's inflammatory pathway activation is probably more important. This is manifested by release of the cytokines like interleukin-1 and tumor necrosis factor (TNF) and other

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mediators. These mediators lead to the alteration of the blood-brain barrier, cerebrospinal fluid dynamics and brain metabolism. These changes cause vasogenic cerebral edema, increased intracranial pressure with consecutive decrease of cerebral perfusion, regional hypoxia and focal ischemia of the brain tissue. Steroids have been shown to block the release of cytokines "in vitro" /1, 2, 3, 4, 5, 6, 7, 8, 9/. They have also potent anti-prostaglandin E2 effect /3, 4, 10/. On the other hand, it was also suggested that corticosteroids may potentiate ischemic injury of neurons in vitro /10/.

In the following we present the data of a retrospective study which we undertook in order to decide whether the use of dexamethasone is a useful additional therapy in bacterial meningitis of infants and children.

PATIENTS AND METHODS

Data were collected from case reports of children with bacterial meningitis hospitalized in Hungary /Saint László Hospital, Budapest/ during the period between January 1983 and June 1993.

The diagnosis of bacterial meningitis was confirmed by the examination of CSF including bacteriological culture. Quick diagnostic test (latex particles agglutination) was performed in most of the cases.

The empirical antimicrobial therapy was generally cefotaxime (Claforan®) under two months of age and ceftriaxone (Rocephine®) for older children.

Dexamethasone was administered in the second half of the investigation period (32 patients), while 57 patients served as historical control. The dose of dexamethasone was 0.6 mg/kg devided in four doses and given through the first four days of the disease. The first dose was administered one hour before the presumptive antibiotic treatment.

Results were analyzed according to the average time of the sterilization of CSF; average duration of fever; mortality rate; frequency of sequelae. Sequelae were checked by neurological examination and by BERA audiometry.

RESULTS

Table I presents the distribution of patients according to the causative agents. Table II shows the distribution of patients according to age. It is clear that in the second half of the decade the H. influenzae became the most frequent causative agent of

TABLE I

Etiology of bacterial meningitis treated and non-treated with dexamethasone as adjunctive therapy

Pathogen	Number of patients	
	Treated with dexamethasone	Non-treated with dexamethasone
H. influenza	24	16
N. meningitidis	6	18
S. pneumoniae	2	11
Gram negative bacteria*	-	9
Others	-	3

*E coli, Salmonellae

TABLE II

Distribution of patients with bacterial meningitis treated and non-treated with dexamethasone as adjunctive therapy

Age	Number of patients	
	Treated with dexamethasone	Non-treated with dexamethasone
< 1 year	22	36
> 1 year	10	21

TABLE III

Outcome of bacterial meningitis of children treated and non-treated with dexamethasone as an adjunctive therapy

	Treated with dexamethasone	Non-treated with dexamethasone
Average time to sterilize CSF/day	1.8	1.8
Average duration of fever/day	5.0	6.5
Number of death after 24 hours of hospitalization	0	11
Number of patients with hearing impairment	7	9
Number of patients with other sequelae*	6	5
Total number	32	57

*Muscular hypertonia or hypotonia, ataxia

bacterial meningitis in Hungary. At the same time no changes can be observed in the age distribution of bacterial meningitis.

Table III shows the results of adjunctive dexamethasone therapy. There was no difference between the dexamethasone-treated and non-treated groups as far as sterilization of the CSF is concerned. Fever lasted for somewhat longer in the dexamethasone non treated group, however not significantly.

The mortality rate (after 24 hours) was significantly lower in the dexamethasone treated than in the non-treated group.

The rate of sequelae was similar in both groups.

DISCUSSION

In spite of literary data /10/, dexamethasone therapy had no deleterious effect on the course of bacterial meningitis. The sterilization of the CSF was not influenced by the dexamethasone therapy. The most striking effect of the dexamethasone is that no child with bacterial meningitis died after 24 hours of hospitalization, while the mortality was 19 per cent in the dexamethasone non-treated historical group.

The similar rate of sequelae can be explained by the fact, that even more severe cases remained alive. Authors think that dexamethasone therapy along with appropriate antibiotic treatment is indicated in all cases of bacterial meningitis, though there are authors, who indicate it only in H. influenzae-caused meningitis and not for infants under 2 month of age /11/.

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CARNITINE DEPENDENT CHANGES OF THE PLASMA LEVELS AND URINARY OUTPUT OF AMINO ACIDS IN PIVAMPICILLIN TREATMENT

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Pivampicillin can cause carnitine depletion because the xenobiotic acid pivalate is liberated from the drug which forms an acyl ester with carnitine. The sustained urinary elimination of this ester can produce carnitine depletion. In this study the effect of pivampicillin treatment on amino acid metabolism in two groups of children with different carnitine reserves was investigated. In one group six children were treated with pivampicillin and with an equal molar amount of L-carnitine (group A), the second group received a 5.7-fold molar excess of carnitine to pivampicillin (group B) for a week. In group A a partial carnitine depletion developed, while the plasma level of valine (122%), isoleucine (121%), leucine (116%), alanine (121%) and glycine (125%) were elevated compared to control levels on the last day of treatment, which was accompanied by increased urinary output of glycine. In group B no carnitine depletion was detected, and the higher urinary carnitine ester output than group A showed a more efficient elimination of the administered xenobiotic acid. In group B only alanine (153%) and glycine (136%) levels in plasma were elevated compared with the control levels, urinary glycine output also increased. The results suggest that the pivampicillin induced carnitine depletion could affect the metabolism of branched chain amino acids in vivo.

INTRODUCTION

The primary biochemical function of carnitine is associated with the ester forming capacity of its ß hydroxyl group /1-3/. In the different organelles and/or compartments of the tissues numerous carnitine acyltransferase activities having

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distinct characteristics are described /2/. Similarly, as products of these enzymes numerous aliphatic carnitine esters have been identified in the tissues and biological fluids /2, 3/.

With the ester forming capability carnitine plays a regulatory role in the ß oxidation of the long-chain fatty acids. Besides this function the esterification process involves many endogenous or exogenous short- and medium-chain acyl residues /2, 3/. Amongst them a special point is the proposed role of carnitine in the oxidation of the carbon skeleton of the branched chain amino acids /3-9/. After converting to-2-oxo acids the acyl moiety undergoes an oxidative-decarboxylation by a common branched chain 2-oxo acid dehydrogenase intramitochondrially resulting in the generation of branched-chain acyl-CoA esters /10, 11/. Products of the degradation pathway have been identified as carnitine esters /2, 3/, moreover, in different tissues or in isolated mitochondria a stimulatory effect of carnitine on oxidation process has been described /5-9/. However, as a marker of the biological significance the opposite possibility, the degradation process in carnitine deficiency has not been investigated.

After pivampicillin is absorbed, pivalate is liberated from the drug which then is activated to a CoA ester /12/. Sequestrating the free CoA pools /12/ as pivaloyl-CoA can impair those metabolic processes in which CoA is an acyl acceptor or in which the ratio of free/ester-CoA is regulatory /13/. Thus, the pathway of degradation of branched chain amino acids may interact with both of the above possibilities /3/. Since carnitine can accept the pivaloyl moiety from CoA, pivampicillin can cause carnitine depletion due to the enormous urinary loss of pivaloylcarnitine /14, 15/. The above metabolic events induced by pivampicillin treatment in humans provided a useful model for study the possible role of carnitine availability in the preservation of amino acid metabolism.

MATERIALS AND METHODS

Patients. *Pivampicillin and lower dose of carnitine treated group (group A).* Six female children were selected for the study. The mean age was 10 yrs (range 8.13 yrs), the mean body weight was 35 kg (range 25-48) at the start of the study. The study period was 8 days. After a control day (day 0) the patients were treated for seven days with pivampicillin (average dose 1250 mg, range 1000-2000 mg) and an

equal molar quantity of carnitine (for each mg of pivampicillin, 0.35 mg L-carnitine internal salt was used), the dose was divided into two or three equal doses (one tablet contains 500 mg pivampicillin which corresponds to 1.08 mmoles pivalate).

Pivampicillin and higher dose of carnitine treated group (group B). Seven children (3 males, 4 females) participated in the study. The average body weight was 40 kg (range 14-87), the mean age was 11.3 yrs (range 5-17 yrs). The dose of pivampicillin was 1500 mg with 3000 mg L-carnitine (this dose is within the clinically recommended dose range, average 75 mg/kg body weight) divided into three doses in all cases. The duration of treatment was seven days as in group A.

Procedures. The current study design was constructed with the acceptance of the following generally approved principles: 1, the plasma levels of free amino acids reflect the tissue levels, and 2, an overnight fast is adequate to reach a steady state concentration which is not affected directly by the last food intake but reflects the intracellular metabolic state. Normally the children were fed with a standardized isocaloric clinical food. Before (day 0) and on the last day (day 7) of treatment urine was collected over 24 h, started at 8:00 AM. On the same days blood was taken into heparinized tubes between 8:00 and 9:00 AM. Before the days of blood collections the children were requested to fast overnight to reach definitive steady state metabolite levels (the last meal was before 9:00 PM, and after this only water was given on request by the supervising nurses). The plasma and the urine samples were stored at -80 °C until analysis. The study design was approved by the local Ethical Committee. Informed consent was obtained from the parents of all participants. The treatments were indicated by clinical decision based on the development of infection caused by ampicillin sensitive bacteria. The history of children was negative for serious illness and they were healthy with good general condition.

Methods. Plasma acid soluble and urinary carnitines were measured by a radiochemical assay as described /15, 16/. Presence of pivaloylcarnitine in the urine was determined in random samples by gas-chromatography /15/. Amino acids were quantitated by a Biotronic LC 2000 amino acid analyzer using ninhydrin derivatization /17/ according to the method recommended by the manufacturer (Maintal, Germany).

Statistics. Because within the groups relationship of means at different times was tested, for statistical comparisons the Student's t-test for paired samples was used.

RESULTS

Plasma and urinary carnitine levels are shown in Table I. In both groups increase was found in plasma acid soluble carnitine esters due to the presence of the xenobiotic pivaloylcarnitine /15/. The urinary output of carnitine esters was

significantly increased on the last day of treatment (Table II). The increase was primarily due to the excreted pivaloyl-carnitine as it was determined by gaschromatography (not shown). The daily excreted amount of carnitine esters was higher in group B. Different results were obtained in the two groups regarding the plasma levels and urinary output of free carnitine. In group A the plasma level and urinary output of free carnitine was low, while in group B an increase was found in plasma free carnitine level with unchanged urinary output of free carnitine (Table I).

TABLE I

Plasma levels (μmol/l) and urinary output (μmol/day) of carnitine and carnitine esters in the two groups of pivampicillin and carnitine treated children

	Plasma		Urine	
	Day 0	Day 7	Day 0	Day 7
Group A				
total	44.0±3.58	30.4±3.55*	334.2±197.3	2243.5±579.4*
acyl	11.4±1.97	18.9±1.92*	211.7±94.3	2238.8±560.8*
free	32.6±3.43	11.5±1.79*	122.5±103.7	4.27±4.65*
Group B				
total	42.7±1.58	57.0±8.04*	298.1±68.1	3389.7±647.5*
acyl	9.60±1.20	16.1±3.39*	158.0±54.1	3161.3±586.5*
free	33.1±2.23	41.0±5.52*	140.1±41.8	128.4±49.1

* $p<0.05$ vs day 0 of the same group

Plasma levels of free amino acids in the two groups of children are shown in Tables II and III. In group A a statistically significant increase was found in the levels of glycine, alanine, valine isoleucine and leucine (Table II), whereas in group B the levels of glycine and alanine were elevated on the last day of treatment compared

with the original values (Table III). Comparing the daily excretion rates of amino acids in all groups the output of glycine was increased on the last day of treatment as compared to the initial values (Tables IV and V).

TABLE II

Levels of plasma free amino acids (μmol/l) in patients treated with pivampicillin and equal molar carnitine, group A

(means ± SEM * $p<0.05$ vs day 0)

	day 0	day 7
aspartate	26.3±2.86	26.4±5.80
hydroxyproline	12.4±1.30	14.5±1.13
threonine	129.9±8.91	139.4±14.6
serine	154.9±6.25	152.8±10.4
asparagine	21.7±3.96	23.6±4.90
glutamate	210.6±12.6	189.6±14.4
glutamine	233.6±19.7	215.9±19.9
proline	197.3±24.7	218.0±16.6
glycine	204.8±17.4	256.4±18.2*
alanine	308.6±35.6	372.4±23.4*
citrulline	12.7±1.48	15.5±1.57
valine	216.6±11.2	263.3±25.0*
methionine	10.3±0.88	10.6±1.36
isoleucine	109.5±4.95	132.1±8.40*
leucine	132.7±5.24	153.5±5.40*
tyrosine	54.2±2.91	55.8±3.26
phenylalanine	53.0±3.70	52.4±4.68
ornithine	59.1±3.96	72.7±9.04
lysine	172.4±8.20	169.0±13.5
histidine	68.2±2.57	72.2±3.02
3-methylhistidine	2.71±0.43	3.68±0.54
tryptophane	39.3±1.34	41.9±3.41
arginine	110.1±12.1	115.2±21.4

TABLE III

Plasma level of free amino acids (μmol/l) in children treated with pivampicillin and elevated molar dose of carnitine, group B

(n=7, means ± SEM, * $p<0.05$ vs day 0)

	day 0	day 7
aspartate	14.2±1.91	15.1±1.85
hydroxyproline	15.1±2.49	17.4±2.79
threonine	130.1±12.0	138.9±12.0
serine	135.6±10.3	143.9±7.25
asparagine	23.5±4.86	37.8±4.76
glutamate	180.1±22.7	228.2±30.4
glutamine	263.1±31.2	277.6±18.0
proline	263.3±37.1	291.9±23.8
glycine	184.7±18.2	251.4±16.6*
alanine	283.7±47.1	433.0±41.2*
citrulline	11.1±1.06	16.3±1.66
valine	257.1±27.9	267.1±26.0
methionine	21.8±2.48	27.3±2.66
isoleucine	133.6±11.0	145.6±9.69
leucine	158.4±22.4	157.3±15.8
tyrosine	58.3±6.08	59.9±6.00
phenylalanine	57.6±5.92	55.9±4.76
ornithine	53.4±4.11	65.6±4.71
lysine	154.2±18.1	176.4±11.5
histidine	59.9±4.26	73.3±3.49
3-methylhistidine	3.77±0.76	3.21±0.33
tryptophane	43.1±1.72	48.9±1.52
arginine	90.2±7.87	106.4±6.67

TABLE IV

Urinary excreted amounts of amino acids (μmol/l) in combined pivampicillin and equal molar carnitine treated group, group A

(n=6, * $p<0.05$ vs day 0)

	day 0	day 7
aspartate	18.7±3.71	15.7±3.06
threonine	67.0±8.97	58.5±16.6
serine	173.8±32.4	152.0±40.8
asparagine	36.4±7.81	42.5±10.3
glutamate	25.0±8.21	21.5±12.6
glutamine	155.0±42.7	172.3±62.3
glycine	715.3±152.5	854.3±225.0*
alanine	126.2±17.3	116.3±29.6
citrulline	8.17±2.67	7.17±1.74
valine	27.9±6.60	27.4±6.01
methionine	27.9±6.63	27.4±6.01
isoleucine	6.54±2.53	9.96±2.48
leucine	22.7±5.45	30.0±7.70
tyrosine	50.2±21.5	46.9±9.93
phenylalanine	31.5±9.19	27.7±7.02
ornithine	4.36±0.69	5.33±1.44
lysine	46.3±15.3	33.1±10.3
histidine	376.0±89.3	304.7±65.5
3-methylhistidine	139.1±28.0	135.1±27.4
tryptophane	5.78±1.14	4.67±1.14

TABLE V

Urinary excreted amounts of free amino acids (μmol/day) in children treated with pivampicillin and elevated molar dose of carnitine, group B

(n=6, * $p<0.05$ vs day 0)

	day 0	day 7
aspartate	12.3±3.79	12.8±3.32
threonine	50.5±15.4	55.5±29.6
serine	139.3±43.9	155.2±93.8
asparagine	45.7±12.1	38.8±7.99
glutamate	17.3±3.81	12.5±3.45
glutamine	178.3±21.8	154.6±56.1
glycine	578.5±217.5	899.3±396.4*
alanine	103.3±13.2	115.3±63.3
citrulline	3.98±2.41	7.36±5.75
valine	12.2±3.32	12.6±2.99
methionine	12.2±3.32	12.5±2.99
isoleucine	3.78±1.43	3.80±1.64
leucine	11.0±2.69	10.7±3.10
tyrosine	39.0±14.7	35.8±12.3
phenylalanine	23.3±7.54	19.7±5.18
ornithine	7.10±2.29	4.00±1.25
lysine	43.1±18.1	38.1±18.7
histidine	333.0±98.9	291.8±100.4
3-methylhistidine	101.6±30.7	82.7±22.0
tryptophane	4.34±0.35	6.19±1.68

DISCUSSION

The results presented herein are consistent with previous studies with pivampicillin treatment that demonstrated variability of carnitine reserves depending on the amount of the carnitine supplement given /14, 15, 18/. In this study, while in group A the given lower dose of carnitine was not enough to reserve the free carnitine stores, in group B the elevated intake resulted in elimination of the majority of the given xenobiotic acid load (3.24 mmoles/day pivalate) and there was no decrease in circulating free carnitine levels and urinary output of free carnitine. In addition, taking also into consideration that the plasma level of carnitine can reflect the changes of the tissue concentration /19/, the data of the current work show different carnitine reserves of the body in the two groups.

So far cumulative data show an effect of carnitine in the metabolism of the branched chain amino acids /3-9/. Derivates of the catabolism of these amino acids have been identified as carnitine esters (propionyl-, isovaleryl carnitine) in tissues and body fluids /3, 16/. Furthermore, carnitine could stimulate the oxidation of branched chain α-ketoacids in different tissues and in mitochondria having different origin /4-9/. However, the biological significance of these observations have not been established in humans, no data have been available demonstrating that carnitine is required for the normal oxidation process of these amino acids. A reason for this is that useful model for human carnitine deficiency syndrome has not been available.

In the current work, different changes of amino acid profiles were observed in the two groups. In group A increase was found in the levels of glycine, alanine, valine, isoleucine and leucine, whereas in group B only the levels of glycine and alanine were elevated on the last day of treatment. Since a basic difference between the two groups was the altered carnitine status, the differing results of the two groups suggest a role of carnitine in the maintenance of normal flux in the catabolic pathway of branched chain fatty acids.

Theoretically the above role of carnitine can be explained by at least three ways /3/. First, carnitine may be required for shuttling the activated acyl groups from the cytosol into the mitochondria across the membrane barrier for subsequent metabolism. Second, via accepting the acyl groups from acyl-CoA it regenerates the free CoA reserves required at the branched chain α-ketoacid dehydrogenase step.

Pivalate administration is known to increase the ratio of acyl/free CoA ratio in rat hepatocyte decreasing the level of free- and some of short-chain (acetyl and succinyl) CoA esters accompanied by the formation of pivaloyl CoA /12/. Third, pivalate or its CoA ester is inhibitory to transport and/or metabolic steps of branched chain amino (or keto) acids.

It is noteworthy, that the increase of two amino acids (glycine and alanine) seems to be independent from the carnitine status since increase was observed in both groups. The background of the altered metabolism of these amino acids is not known. As analogy, an other branched chain xenobiotic acid, the valproate (dipropyl acetate) is known to affect the metabolism of glycine /20, 21/ via inhibition the glycine cleavage enzyme system /22/, which leads to increased plasma levels and urinary output of this amino acid. Similarly, in normal humans administration of valproate inceases plasma alanine concentrations /23/.

The daily urinary output of amino acids was similar in the two groups of children. Except the elevated output of glycine on the last day of combined treatment in both groups, excretion of other amino acids remained unchanged, however, in some cases a trend to increase was found (isoleucine and leucine in group A). This disassociation between the plasma levels and urinary output of amino acids suggests, that except glycine, the plasma level did not elevate above the normal boundary of tubular reabsorption threshold. However, in the case of glycine even altered kidney metabolism or transport of this amino acid cannot be ruled out.

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NEONATAL MULTICYSTIC DYSPLASTIC KIDNEY TOGETHER WITH AN OVARIAN CYST DIAGNOSED ANTENATALLY: A CASE REPORT

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We report on a neonate with multicystic dysplasia of the right kidney together with a left ovarian cyst. The prenatal diagnosis of both anomalies was accurately made using ultrasound. The infant was treated surgically.

INTRODUCTION

Multicystic dysplastic kidney is the most common renal cystic disease encountered in the newborn /1/. The routine use of ultrasonography in pregnancy facilitates the diagnosis of these lesions more often in utero /2/. Associated congenital anomalies are frequent. On the other hand, it is also associated with extrarenal congenital anomalies such as oesophageal atresia, cardiac, muscular, skeletal, neural and gastrointestinal anomalies /3/. Up to now, multicystic dysplasia together with an ovarian cyst has not been reported.

CASE REPORT

A woman (gravida 3, para 2) was at 36 weeks gestation when a prenatal ultrasonogram showed multicystic dysplasia of the right kidney and an intraabdominal cyst measuring 6x5 cm (Fig. 1). Fetal movement and amniotic fluid volume were normal. The fetus appeared to be female and it was felt that the cyst was mesenteric or ovarian. The fetus was followed with occasional ultrasonic evaluation.

Physical examination following normal vaginal delivery revealed a large, uniloculated and mobile intraabdominal cystic mass. Right kidney was palpable. There were no audible bruites and no cardiac murmurs. Blood pressure was normal. Urinanalysis, serum creatinin, electrolytes and bilirubin were normal. Ultrasonographic examination of the abdomen demonstrated multicystic dysplasia of right kidney, normal left kidney and large abdominal cyst but its origin could not be identified. An intravenous urogram showed no function of the right kidney with normal function in the left kidney.

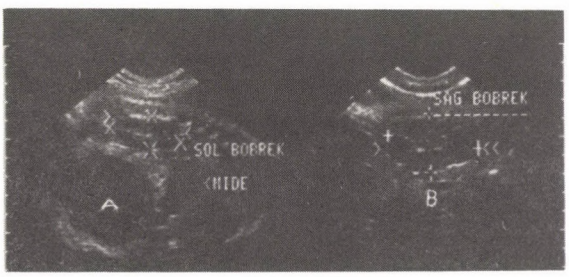

Fig. 1: Antenatal ultrasound scan shows, A: left ovarian cyst and B: multicystic dysplasia of right kidney

The infant was operated on the third day of admission. A laparatomy was performed through an intraumbilical transverse incision. A left ovarian cyst measuring 9x7 cm and multicystic dysplasia of the right kidney was observed (Fig. 2). Nephrectomy and oophorectomy were performed.

Histopathological examination of the specimens demonstrated multicystic dysplasia and follicular cyst.

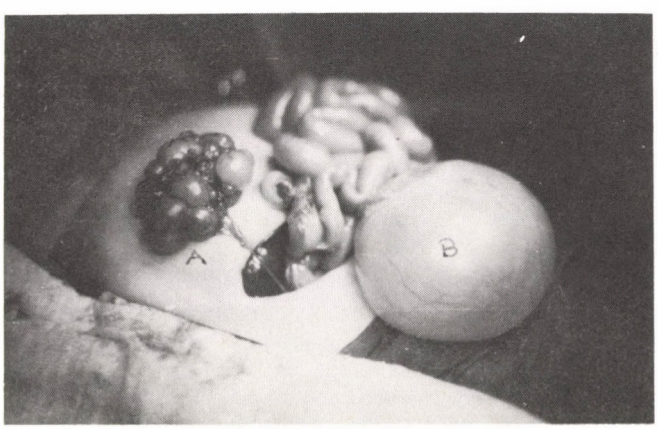

Fig. 2: Intraoperative photograph shows, A: multicystic dysplastic kidney and, B: left ovarian cyst

DISCUSSION

Multicystic dysplastic kidney is a commonly occurring condition now frequently identified prenatally. It is a developmental anomaly of the kidney that can be distinguished readily from other forms of cystic renal diseases in childhood /4/. The renal parenchyma is replaced by tense noncommunicating cysts and the proximal ureter is atretic or nonpatent. In the course of time multicystic dysplasia may reduce in size or it may fully disappear /4, 5/. Malignancy, hypertension, pain, hematuria and infection have been reported as late complications of multicystic kidneys /3-5/. Some authors have suggested routine prophylactic nephrectomy to prevent these complications, but others preferred conservative treatment /3-5/.

Cystic and solid tumors of the ovary are rare during the newborn period. The most frequent tumor is ovarian follicular cyst which can be diagnosed prenatally /6/. Ovarian cysts are thought to be the result of excessive stimulation of the fetal ovaries by human chorionic gonadotropin /7/. When the fetus is removed from the maternal influence of these hormones, spontaneous resolution of the cyst can occur. It is suggested that conservative management with sonographic reevaluation is an acceptable alternative to surgical therapy in uncomplicated cases /8/. Complications of large ovarian cysts include torsion and rupture. Thus ovarian masses with a solid or complex component are treated surgically /8, 9/.

In this patient, multicystic dysplastic kidney and an abdominal cyst were diagnosed in utero. The origin of the abdominal cyst could not be defined at this stage. Following her birth, control ultrasonographic examination demonstrated that the cyst was ovarian or mesenteric. It may be difficult to differentiate between mesenteric, enteric and ovarian cysts even via ultrasonography. She was operated due to this reason.

There should not be a relationship between multicystic dysplasia and ovarian cyst because multicystic dysplasia develops due to intrauterine vascular catastrophe or ureteral obstruction /3/ and ovarian cyst occurs due to excessive human chorionic gonadotropin.

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MIDGUT DELETION: A CASE REPORT AND LITERATURE REVIEW

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An unusual case of midgut deletion secondary to intrauterine midgut volvulus with total and irreparable ischemia and sloughing is reported.

INTRODUCTION

Deletion of the midgut was first reported by Moore in 1986 /1/. The patient had no intestine from just beyond the ligament of treitz to the mid-transverse colon. Up to now, two additional, somewhat similar cases have been reported /2/. Here a fourth case of midgut deletion will be presented.

CASE REPORT

A 1.200 g boy was born by normal vaginal delivery at 28 weeks's gestation to a 22-year-old (gravida 2, para 2) mother, and the mother did not have any antenatal check-up. The infant was admitted to Faculty of Medicine, Trabzon, with bilious vomiting and no meconium passage of the anus. Physical examination showed upper abdominal distension and rectal irrigation provided passage of small pellets. Abdominal plain film demonstrated double-bubble sign of duodenal obstruction (Fig. 1). His serum bilirubin was 5 mg/dl. Following preoperative preparation with nasogastric tube and intravenous fluids, laparatomy was performed through a right transverse supraumbilical incision. Distended stomach and three parts of duodenum, 5 cm of atretic jejunum just beyond the ligament of Treitz and entirely unused and edematous colon were found. The colon had malrotation but no fixation. The remaining jejunum and ileum were absent (Fig. 2).

Duodeno-jejuno-cecostomi was performed and abdominal wound was closed in a single layer.

On the first postoperative day hyperalimentation treatment and third day rectal irrigation were started. On the sixth day postoperatively a passage of the anus was observed. Eighth day, oral liquid nutrient was started and continued with semiliquid oral infant formula. On the 27th postoperative day the general status of the patient deteriorated and 28th day he died of septicemia. The blood culture grew pseudomonas aeruginasa resistent to all antibiotics.

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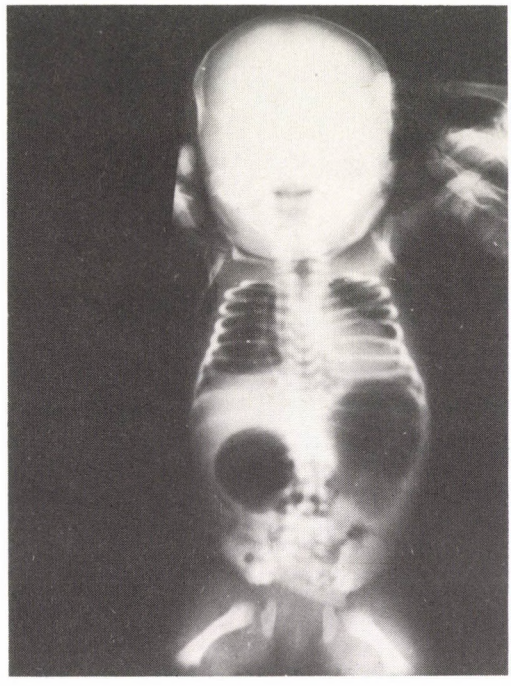

Fig. 1. Plain erect X-ray film demonstrates double-bubble sign of duodenal obstruction

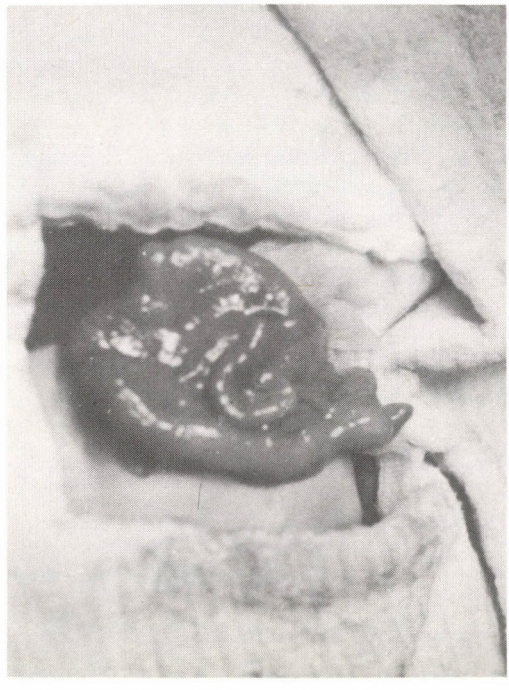

Fig. 2. Operative photograph showing atretic proximal jejunum and unused and edematous entire colon. There is no remaining jejunum and ileum

DISCUSSION

Intestinal atresia is a significant cause of neonatal intestinal obstruction. The experimental works demonstrated that intestinal atresia is an acquired disease and likely the result of late intrauterine mesenteric vascular catastrophe, commonly a volvulus /3/. If volvulus occurs in utero, it will produce ischaemic necrosis of different degree, resulting in single or multiple short segment or extensive atresia of the jejunum and/or ileum /4, 5/. Further experimental studies showed that if an intestinal loop was isolated, resorption of the loop occurred if its blood supply was poor /3/.

Grosfeld and Clatworthy /6/ observed the occurrence of jejunal atresia with infarction of the entire midgut in a tight gastroschisis defect. It can be presumed that if entire midgut is suffered by volvulus in utero and the superior mesenteric vessels will become occluded, the midgut will undergo infarction /1, 2/. This is the most likely cause of midgut deletion.

Our patient had midgut deletion with intact right colon and proximal atretic jejunum in a length of 5 cm. It is described that intact right colon is due to the presence of postaxial branches of the superior mesenteric artery and intact proximal jejunum is due to presence of inferior pancreatic artery /2/. He had no meconium peritonitis. It is demonstrated that healed intrauterine perforation might or might not be associated with the meconium peritonitis /3/.

Patients with midgut deletion have bad prognosis because there is no intestine to handle. In these patients hyperalimentation treatment and small bowel transplantation may be suitable as an alternative treatment /7, 8/.

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FATTY ACID COMPOSITION OF HUNGARIAN INFANT FORMULAE REVISITED

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The fatty acid composition of three infant formulae available in Hungary for feeding healthy, term infants was analysed by high-resolution capillary gas-liquid chromatography. Percentage contribution of linoleic acid (C18:2n-6) was higher, while that of saturated fatty acids was lower in the formula with the highest contribution of vegetable fat to total fat content than in the other products. No other difference of considerable extent was seen between the fatty acid composition of the formulae investigated. Concentrations of linoleic acid, the precursor essential fatty acid for omega-6 long-chain polyunsaturated (LCP) fatty acids, in the three formulae were higher than the median value in mature human milk. In contrast, percentage contribution of alpha-linolenic acid (C18:3n-3), the precursor essential fatty acid for omega-3 LCP fatty acids, in all formulae was less than half of the median value of breast-milk. Percentage contributions of the principal omega-6 LCP fatty acid, arachidonic acid (C20:4n-6), corresponded to 26 to 32% of the median value of human milk. None of the products contained detectable amounts of docosahexaenoic acid (C22:6n-3), the major omega-3 LCP metabolite. Percentage contributions of other omega-3 and omega-6 long-chain polyunsaturates were also markedly lower in the formulae than the values characteristic to mature human milk.

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INTRODUCTION

Polyunsaturated fatty acids play an important role in early postnatal growth and development /3, 9/, and the awareness of the quality and composition of fats supplied to infants increased considerably during the past decade. Composition of human milk is often used as a model for artificial feeding. It has been demonstrated in a number of investigations that human milk contains considerable amounts of long-chain polyunsaturated fatty acids (LCP), and the milk content of 20 and 22 carbon LCP fatty acids remains surprisingly consistent with different self-selected maternal diets at different geographical locations /12/. In contrast, infant formulae usually contain the precursors of omega-6 and omega-3 LCP fatty acid synthesis, linoleic (C18:2n-6) and alpha-linolenic (C18:3n-3) acids, in amounts comparable to that measured in human milk, but contain little 20 and 22 carbon LCP fatty acids /7, 8, 10, 15/.

In Hungary, the contribution of three infant formulae (Mildibé, Robébi A and Robébi B, EGIS, Hungary) to the nutrition of formula-fed, healthy, term infants is overwhelming. In 1992, 1 058 229, 222 028 and 248 470 units (0.5 kg boxes) of these three formulae, respectively, were purchased through Hungarian pharmacies (Annual Report on the Pharmaceutical Market, data source available in Hungarian alone). The three formulae in question amounted to about 95% of all term infant formulae distributed through Hungarian pharmacies in 1992. If one assumes that the purchased amount was utilized completely, it can be concluded that in 1992 these three products represented substitute for 5 801 242 liters of human milk.

The fatty acid composition of two of these three formulae has been analysed by Gere and coworkers, and the results have been published in this journal /6/. However, the technical facilities available at that time rendered possible the indentification of only seven different fatty acids, including no long-chain polyunsaturate. Therefore we determined the fatty acid composition of these three Hungarian infant formulae by using high-resolution capillary gas-liquid chromatography and compared the LCP content to data on the fatty acid composition of mature human milk in Hungary and in Europe.

MATERIALS AND METHODS

Two-two units of the three formulae (Mildibé, Tobébi A and Robébi B, EGIS, Hungary) were purchased through the Pharmacy of the University Medical School of Pécs and stored at room temperature until analysis. All products were well within the guaranteed shelf-live at analysis. Prior to analysis, products were reconstituted with tap water according to the manufacturer's declaration.

Total lipids were extracted from 4 ml of formula with methanolcloroform (2:1, vol/vol) /2/. (Previous analysis revealed that in infant formulae, just as in human milk, almost all fatty acids were present in triglycerides, and only minor amounts in sterol esters and phospholipids; therefore, we measured fatty acids in formula total lipids). Fatty acids were transesterified with methanol and hydrochloric acid /16/ and dissolved in hexane including 2 g/l butylated hydroxytoluene as an antioxidant. Fatty acid composition was analysed by high/resolution capillary gas/liquid chromatography using a Hewlett-Packard Series II 5890 gas chromatograph with on column injection and flame ionisation detection. Technical details of chromatography have been described elsewhere /4/. Fatty acid results are expressed as percentage (wt/wt) of all fatty acids detected with a chain length between 10 and 24 carbon atoms (mean of 2 measurements). The precision of fatty acid quantification with this methodology has been previously described /11/.

RESULTS

Fat content (according to manufacturer's declaration) of the three formulae is shown in Table I. The contribution of vegetable to total fat was identical (21%) in two products, while it was markedly higher (35%) in the third one. Percentage contributions of 21 fatty acids which were present in more than 0.1% concentration in at least one of the formulae investigated are given in Table II. (Data of three of the lower than 0.1% concentrated LCP fatty acids (C20:2n-6, C22:4n-6 and C20:5 n-3) are additionally shown in Table III, whereas data for three other lower concentrated fatty (C20:3n-9, C22:1n-9 and C24:1n-9) are not shown.)

The formula with the highest contribution of vegetable fat to total fat content (Robébi A) had markedly higher linoleic acid (C18:2n-6) content and showed moderately lower values for the principal saturated fatty acids (lauric /C12:0, palmitic /C16:0/ and stearic /C18:0/ acids) than the other two formulae. No other difference of

considerable extent was observed between the fatty acid composition of the three formulae.

TABLE I

Fat content (according to manufacturer's declaration) of the three infant formulae investigated

	Mildibé	Robébi A	Robébi B
Fat content			
Milk fat (g/l)	2.6	2.2	3.0
Vegatable fat (g/l)	0.7	1.2*	0.8*
Contribution of vegetable to total fat (%)	21.0	35.0	21.0
Total fat (g/l)	3.3	3.4	3.8

* Sunflower oil

When data were compared to the median value of 14 Europen studies on fatty acid composition of mature human milk /12/, lower value for monounsaturated fatty acids (human milk median: 38.8%) and, with the exception of the formula with higher vegetable fat content, higher values for saturated fatty acids were seen (human milk median: 45.2%). Concentrations of linoleic acid, the precursor essential fatty acid for omega/6 LCP synthesis, in all the three formulae investigated were higher than the mdian value (11%) of mature human milk in Europe /12/. In contrast, percentage contributions of alphalinolenic acid (C18:3n:3), the precursor essential fatty acid for omega:3 LCP synthesis, in all formulae was less than half of the median value (0.9%) characteristic to mature human milk /12/.

TABLE II

Fatty acid composition in the three infant formulae (% wt/wt)

	Mildibé	Robébi A	Robébi B
Saturated fatty acids			
C10:0	1.47	1.20	1.60
C12:0	2.54	2.04	2.49
C14:0	9.08	7.17	8.93
C16:0	29.35	25.46	30.01
C17:0	0.76	0.52	0.62
C18:0	9.91	8.49	9.56
C20:0	0.26	0.35	0.38
C22:0	0.26	0.34	0.25
C24:0	0.13	0.13	0.11
Total	53.81	45.68	54.04
Monounsaturated fatty acids			
C14: 1n-5	1.03	0.81	1.01
C15: 1n-5	0.30	0.24	0.31
C16: 1n-7	1.41	1.27	1.52
C18: 1n-9	25.51	24.98	25.55
C18: 1n-7	0.68	0.65	0.64
C20: 1n-9	0.11	0.10	0.09
Total	29.45	28.37	29.50
Polyunsaturated fatty acids			
C18: 2n-6	15.43	25.10	15.47
C18: 3n-6	0.15	0.13	0.16
C18: 3n-3	0.44	0.20	0.24
C20: 3n-6	0.11	0.08	0.10
C20: 4n-6	0.14	0.13	0.16
C22: 5n-3	0.11	0.06	0.08
Total	16.62	25.84	16.32

TABLE III

Omega-6 and omega-3 long-chain polyunsaturated fatty acids (LCP) in the three infant formulae investigated compared to human milk in Hungary[1] and to average values in 14 studies reported on fatty acid composition of mature human milk in Europe[2]

	Mildibé	Robébi A	Robébi B	Human milk in Hungary	Human milk in Europe*
Omega-6 LCP					
C20: 2n-6	0.02	0.02	0.03	0.3	0.3 (0.2-0.5)
C20: 3n-6	0.11	0.08	0.10	0.3	0.3 (0.2-0.7)
C20: 4n-6	0.14	0.13	0.16	0.5	0.5 (0.2-1.2)
C22: 4n-6	0.06	0.03	0.03	0.1	0.1 (0.0-0.2)
Total	0.44	0.33	0.36	1.2	1.2 (0.4-2.2)
Omega-3 LCP					
C20: 5n-3	0.05	0.02	0.02	n.d.	0.2 (0.0-0.6)
C22: 5n-3	0.11	0.06	0.08	0.1	0.2 (0.1-0.6)
C22: 6n-3	n.d.	n.d.	n.d.	0.3	0.3 (0.1-0.6)
Total	0.16	0.07	0.10	0.3	0.6 (0.3-1.8)

[1] Drury et al., Prog Lipid Res 25: 235, 1986

[2] Koletzko et al. J Pediatr 120: S62, 1992

* Median (ranges)

The long-chain polyunsaturated fatty acid content in the three formulae investigated is compared with published data on fatty acid composition of mature human milk in Hungary /5/ and in Europe /12/ in Table III. Percentage contribution of LCP fatty acids was similar in the three formulae, and the values detected were markedly lower than the values characteristic for human milk. Percentage contribution of the principal omega/6 LCP fatty acid, arachidonic acid (C20:4n-6), corresponded to 26 to 32% of the median value of human milk. None of the formulae

investigated contained detectable amounts of docosahexaenoic acid (C22:6n-3), the principal omega-3 LCP fatty acid in human milk and infant tissues.

DISCUSSION

The quality and composition of dietary fat supplied to infants is of concern because fatty acids have important structural and functional effects on the developing organs, especially on lipid-rich neuronal tissues, such as the brain and retina /9/. Lipid deposition in developing cerebral tissues is closely linked to the vulnareble period of neural differentiation with rapid neuronal cell multiplication, their dendritic arborization and formation of synaptosomes, all processes that require sufficient availability of polyunsaturated fatty acids /9/. Lipids of the central nervous system contain in the neonatal period only minor proportions of the precursor essential fatty acids, linoleic (C18:2n-6) and alpha-linolenic (C18:3n-3) acids, but almost all polyunsaturated fatty acids in the neonatal brain are LCP fatty acids with 201 and 22 carbon atoms, mostly arachidonic (C20:4n-6), cervonis (C22:4n-6) and decosahexaenoic (C22:6n-3) acids /11, 17/. Three LCP fatty acids, namely dihomo-gamma-linolenic acid (C20:3n-6), arachidonic acid (C20:4n-6) and eicosapentaenoic acid (C20:5n-3), are also needed as indispensible precursors for the synthesis of biologically active eicosanoids.

The foetus appears not do depend on active endogenous synthesis of LCP, since active placental transport of LCP fatty acids seems to cover the needs of fetal growth. After birth, the breast-fed infant receives considerable amounts of preformed LCP with human milk. The average LCP fatty acid intake of breast-fed infants is about 100 mg/kg body weigh/day, with an approximately 2:1 ratio of omega-6 to omega-3 fatty acids /11/. The exogenous LCP supply to formula-fed infants depends, however, on the composition of the formula administered.

Both fat content and long-chain polyunsaturated fatty acid composition of the three formulae investigated in the present study were similar, i.e. feeding of any of them provides approximately similar exogenous LCP supply to the formula-fed infant. Higher contribution of vegetable fat (sunflower oil) to the fat content of one of the

formulae resulted in increased percentage contribution of linoleic acid, but did not influence the availability of LCP fatty acids.

As to omega-6 LCP metabolites, the exogenous LCP intake of infants fed one of the formulae investigated can be estimated to approximate one third of the intake of the breast-fed infant. Nevertheless, the precursor omega-6 essential fatty acid, linoleic acid (C18:2n-6), was present in two formulae in higher, and in one formula in substantially higher concentration than in human milk. It is not known, however, to which extent the elevated linoleic acid intake can facilitate endogenous omega-6 LCP synthesis and, thus, compensate for the lower exogenous omega-6 LCP supply. As to omega-3 metabolites, however, the differences between intakes with breast-milk or with formula were unequivocal. Not only omega-3 LCP values, but also the percentage contributions of the precursor essential fatty acid, alpha-linolenic acid (C18:3n-3), were considerably lower in the formulae than the data reported for mature human milk.

The markedly lower omega-3 polyunsaturated fatty acid intake with formula feeding than with breast-feeding is of concern, since sufficient omega-3 fatty acid supply seems to be of functional importance in infancy. On the one hand, docosahexaenoic acid (C22:6n-3) levels were found to be lower in formula-fed than in breast-fed term infants in several comparative studies /3/. On the other hand, recent observational studies on the development of visual functions in term infants suggested possible functional deficiencies related to biochemical deficiency of omega-3 long chain polyunsaturated fatty acids /1, 13/. These data strongly suggest that the role of preformed dietary LCP in the composition of infant formulae for term infants should be reevaluated.

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PROCEEDINGS OF

IV. INTERNATIONAL POSTGRADUATE COURSE AND WORKSHOP OF THE EUROPEAN CHILDHOOD OBESITY GROUP (ECOG)

HELD IN PÉCS, HUNGARY, 3-5 NOVEMBER, 1994

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FOREWORD

Paediatricians and researchers unanimously believe that obesity is a hazard to health and well-being. It is one of the most important public health problems of the westernised societies as shown by shorter expectation of life, increased morbidity, or cost to the community in terms of money and anxiety. The atherosclerosis, hypertension and metabolic dysfunctions leading to serious diseases in adult life have their origins in childhood obesity. Recognition of the significance of this problem on the one hand and its underrepresentation in national and international obesity conferences on the other, led to the foundation of The European Childhood Obesity Group (ECOG) in 1990 at a meeting on the Obese Child in Ancona, Italy, with the following main purposes:

1. to bring together professionals who are clinically involved in the treatment of childhood obesity

2. to improve clinical and scientific knowledge of obesity in childhood

3. to increase understanding of childhood obesity through promotion of studies, research and professional publications

4. to develop programmes for the prevention and treatment of childhood obesity

5. to provide facilities for the interchange of views and experience so as to improve knowledge, skills and clinical practice in all aspects of childhood obesity

6. to encourage training for health professionals and others in all fields of the management and prevention of childhood obesity

The prevention and treatment of childhood obesity is particularly important in Hungary, where the incidence of overweight is around 14% among the 6 - 18 years old population. Unfortunately the undergraduate and postgraduate medical university curricula in Hungary do not emphasise this problem according to its importance. There is a growing concern for obesity in children among paediatricians, general practitioners and other health professionals. However, actually there is a lack of knowledge, skills and clinical practice. To fill the gap, the 4th ECOG Workshop organised in Pécs was combined with a postgraduate course in accordance with the

aims of ECOG. The lectures of 11 invited speakers reviewed up to date information on nearly all aspects of childhood obesity and demonstrated the applicability of recent results to everyday practice for paediatricians, general practitioners, nutritionists and dieticians.

The workshop (with two main topics - "Prevention of childhood obesity" and "Important (nonanthropometric) medical investigations in the assessment of the obese child") tried to bring different approaches closer and to provide guidelines concerning clinical and laboratory investigations essential for the assessment of the obese child and to define the target population for prevention programmes.

It was gratifying to welcome more than 70 active participants representing 11 European countries. I would like to thank once more all the participants for their enthusiasm and activity throughout the two-day meeting.

I thank Dr. Miklós Miltényi, editor-in-chief of the Acta Paediatrica Hungarica, for providing the opportunity to publish the postgraduate lectures and abstracts of the free oral papers and posters. And last but not least I thank the financial support of ACCORD (Assistance of the Community in Co-operation in R&D).

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GENETIC AND FAMILIAL ENVIRONMENTAL INFLUENCES ON CHILDHOOD OBESITY

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It has been known for long time that fatness and its extreme variant-obesity-aggregates in some families and not in others /1/. The obese parents presenting their obese children is a classical paediatric problem. The frequently seen addition to this picture of an obese pet dog reveals the widespread belief that the problem in the family is their environment, namely their shared habit of overeating or their shared physical laziness. However, the scientific basis for this belief is very scanty. The obese subjects may eat a lot, but they may do so to satisfy their current needs, and it does not at all imply that their obesity is due to a preceding overeating. They may not move their bodies a lot because this may be rather unpleasant and exhausting, and this does not imply that laziness preceded the development of their obesity. Development of obesity of course requires a positive energy balance, which however in any case is rather tiny (less than 5%) compared to the total energy turnover per time unit. This positive energy balance may not necessarily be enforced by increased energy intake or reduced energy expenditure. The primary disturbance may as well be a tendency to accumulate energy as fat in the fat cells, which then creates the positive energy balance by compensation via a variety of feed-back systems influencing energy intake and/or expenditure. The familial aggregation of obesity may be due to the shared environment, but also to the genes they have in common, and the environmental factors and the gene products may operate primarily on any of the components of the energy balance equation. The observation of familial aggregation of obesity therefore immediately raises the question about the role of the genes common to the family members.

In human beings, there are two classical ways of answering this question, namely the twin method and the adoption method. The technology of molecular genetics now allow for search for polymorphic DNA markers of the genome possibly associated with the phenotype in the family (quantitative trait linkage). However, it may be more rational to restrict the use of this technique to the search for sites of the genome possibly containing important genes for phenotypes, in which the classical methods have demonstrated a genetic influence.

The overall conclusion from many different studies is now that the familial resemblance in fatness and obesity among adults is due to the genes they have in common rather than to persisting influences of the rearing family environment they shared in childhood. The question regarding childhood fatness and obesity is then whether or not this conclusion applies at that age and, if not, what the roles then are of the genes and of the family environment they live in.

In the twin method, the evidence for genetic influence is obtained by comparing the resemblance of monozygotic twins with the resemblance of dizygotic twins. Monozygotic twins have identical genes and dizygotic twins have, as other full siblings, on average half of their genes in common Therefore, the extent to which the resemblance of monozygotic twins exceeds the resemblance of dizygotic twins can be taken as a measure of the genetic influence. Several such twin studies have been carried out for adults, adolescents and children /1/, and they all support that genes play a very important role for fatness and obesity. Most of them even suggest that all resemblance of siblings can be attributed to the genes they have in common.

The inference from the twin method assumes that any important environmental influences on the phenotype are similar for monozygotic twin pairs and for dizygotic twin pairs. This may not be true. Common experience shows that monozygotic twins because of their considerable similarity in physical appearance often are treated much more alike than are dizygotic twin pairs. Such greater similarity in environment may contribute to increase resemblance in the phenotype under study and therefore blas the inference about genetic influence upwards. One possible way of avoiding this bias is by studying twin pairs separated early in life. The separation happens, however, so rarely that it is very difficult to establish sufficient samples, and there is, moreover, in these samples often concern about how effective the separation has been. A few studies have been carried out in adults, and they support the conclusions drawn from the use of the classical twin method /1/.

Another way of removing the possible bias of the classical twin method is by studying subjects adopted away from their biological family early in life. Two methods have been employed - the complete and the partial adoption method - that differ with regard to whether or not there is access to information about the biological family of the adoptees. In the complete adoption study, genetic influences are assessed by the resemblance of the adoptee and their biological family members (assuming that the preadoptive - usually only prenatal - environment are unimportant for the familial resemblance of the phenotype). The influence of the family environment is assessed by the resemblance of the adoptee and the members of the adoptive family. In the partial adoption study, the influence of the family environment is assessed in the same way as in the complete adoption study, but there

is not direct way of assessing the genetic influence. This has been performed by comparing the resemblance of the adoptee and the adoptive family members with the resemblance observed in natural families (which have been other families or the adoptive parents and their own biological children).

The first series of adoption studies of fatness and obesity were partial adoption studies with adoptees in childhood or adolescence /1/. They produced a very heterogenous set of results ranging from almost no genetic influence to a strong genetic influence explaining all familial resemblance. In studies where both parent offspring and sibling-sibling comparisons were used, the two types of analysis differed with more support for genetic effects among the latter. It may have been quite critical for the results how the adoptive parents with their adoptees were selected for the study. Any tendency to selective recruitment among those resembling each other in the fatness would inflate the estimate of the effects of the family environment.

One complete adoption study of chilhood fatness (assessed by BMI) has been carried out in Denmark /3/, and another one in Colorado, USA /2/. Both studies included the biological parents, adoptive parents and adoptive siblings of the adoptee, but only the former also included the biological full and half siblings of the adoptee. Both studies clearly supported that the genetic influence is important already in childhood. The Danish study supported some weak influence of the shared family environment, but this was not found in the study from Colorado.

It is important to notice that the traditional question about the magnitude of the heritability (proportion of the total varience of the phenotype in the population that can be ascribed to genetic variance) has not been discussed. Twin studies consistently produce much higher heritabilities than adoption studies, possibly because of complex gene-gene and gene-environment interactions and correlations. Moreover, the magnitude of the heritability will depend on the variation of environmental influences as well (heritability is 1 if there is no variation in exposure to relevant environmental factors).

In conclusion, both twin and adoption studies strongly support that most if not all familial resemblance in fatness and obesity in human beings is due to the genes they have in common. There may be some weak contribution to the resemblance of the shared family environment as long that they live in it. On the other hand, the twin and adoption studies as well as other epidemiological studies leave no doubt that, despite the clear role of the genes, the environment - not assessed as the shared family environment - play as important a role as the genes. In addition to the obvious need of search for the specific genes involved, there is an obvious a need for more detailed

studies of specific environmental factors, and how they may interact with the genes in producing obesity.

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GENETIC, NUTRITIONAL AND SOCIOCULTURAL ASPECTS OF OBESITY

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Obesity is an excess of body fat. In childhood most obesity is associated with increased lean body mass (LBM) for age, although pathological conditions such as Prader-Willi syndrome, can have normal or low LBM with excess fat. If obesity is by definition excess stored fat and in normal circumstances LBM is not reduced, obesity must have resulted from an excess of energy intake over energy expenditure. Such imbalance could have occurred in the past so that nutritional status is stable when the child is assessed and energy intake balances expenditure.

The study of energy balance in obesity is full of controversy and contradiction. It has long been debated whether there are physiological differences in the ways the obese deal with ingested energy and mobilise stored energy for expenditure when compared with similar processes in the nonobese /1/. Are the obese simply those who consume more energy than they need? Are they individuals who have poor appetite control or an appetite centre set 'too high' for their nutritional status? Much effort has been spent in studying appetite regulation in obesity. Areas of the brain can be related to initiation and cessation of eating in experimental animals. Problems in similar areas of the human brain are sometimes related to abnormalities of appetite and nutritional status in clinical practice. Is the 'appetite centre' the main regulator of energy intake in those populations where food is available in excessive amounts /2/? It seems surprising when we consider how easily food intakes and 'appetite' are influenced by family and peer group activities, by environmental pressures such as food presentation and availability, by emotional states and by social conditioning. The role of appetite in balancing energy intake with expenditure must be seen in the context of wider sociocultural and environmental issues.

Concepts become fashionable yet often later decline in support as scientific knowledge changes and advances. Current views are that underlying most 'simple' obesity there is a strong familial, and now presumed genetic, predisposition for obesity. Environmental factors influence this predisposition by encouraging or inhibiting the manifestation of this predisposition. The strength of the inherent predisposition and the frequency of environmental features which encourage excess of energy intake over expenditure, lead to high or low prevalences of obesity in communities.

It used to be thought that the number of fat cells was largely set in the first year of life and the predisposition to obesity determined in early life. It is now recognised that the number of fat cells is determined by the size and fat content of existing cells rather than by the age of the individual /3/. A need to store fat recruits potential adipocytes from connective tissue stroma. Current evidence shows little to support an influence of early infant feeding practices on later obesity in terms of persisting abnormal nutritional status /4/. However, if early feeding sets styles of feeding and attitudes to food which encourage disorganised eating habits and excessive energy intakes, these could lead to later obesity.

GENETIC INFLUENCES IN OBESITY

Fat children commonly have fat parents /5, 6/. In my experience with children attending obesity clinics attached to children's hospitals, only about twenty percent of obese children did not have at least one parent who was overweight or obese. Thirty to forty percent of children had both parents overweight or obese. In many cases other children in the family were also significantly overweight. Since families tend to eat and exercise together especially when the children are quite young, familial obesity need not indicate genetic determinants for obesity. Nevertheless, studies of monozygotic and dizygotic twins /7, 8/ and of adoptees /9/ in relation to their biological and adoptive parents suggest that even in different environments, similarities in genetic makeup lead to similarities in body composition.

How might genetic influences determine fatness or leanness? We do not know. For a condition as common in the western world as obesity and so variable in time of development, in degree and in complications. A single gene effect is unlikely. More likely is a variety of genetic factors influencing the intake, partition and utilisation of energy. Such factors may include faulty appetite control; variation in the thermic response to food; excessively efficient fat deposition; less ready fat mobilisation; variable metabolic efficiency. A variety of degrees of difference between individuals, rather than an 'all or nothing' risk also seems likely for such fundamental physiological processes. Together genetic factors may account for 40% of the metabolic differences recorded between individuals /10/.

Are there data to support any of these suggested genetically determined differences? Some families have resting metabolic rates that tend to be in the lower range of normal for age and lean body mass and others tend towards the higher range of normal /11/. Such differences do not correlate with relative fatness or any familial predisposition to obesity. Nevertheless, if we consider obesity the consequence of a

variety of genetic and environmental factors, a relatively low resting metabolic rate may be one contributing genetic factor which predisposes a family to the development of obesity.

Other studies suggest some individuals store ingested fat more readily than others. Overfed individuals store fat at varying rates even with the same excess of intake over expenditure. Monozygotic twins show similarities in the rate at which they store fat which are much greater than similarities between unrelated individuals /12/. If a tendency to store fat readily is also associated with more difficult mobilisation of stored fat, obesity is a likely result.

Some obese children have very high LBM as well as fat mass for age. They also have tall, large, parents. These children may be high birth weight infants who have increased LBM from birth and a genetic propensity for large lean and fat mass. Growth is exuberant and obesity seems almost inevitable in westernised environments where food is readily available /13/.

ENVIRONMENTAL INFLUENCES ON THE DEVELOPMENT OF CHILDHOOD OBESITY

The prevalence of obesity is increasing in most westernised and westernising countries today despite the fact that in many of these countries mean energy intakes for both children and adults have dropped markedly in the past forty years /14/. It would seem unlikely that genes predisposing to obesity have become suddenly more prevalent in these societies, particularly as the pattern of developing obesity is common to geographically remote westernising societies. A westernised environment encourages the development of obesity in those who are genetically predisposed.

Nutritional aspects

There have been many efforts to characterise diets of the obese and to distinguish 'at risk' eating habits. No one finding explains obesity. It is our experience that many obese children have relatively undisciplined eating and often long lists of food dislikes, including particularly meat, wholemeal cereals, fruit and vegetables. Do these 'fads' reflect a reluctance to chew due to poor weaning practices? Whole foods require more chewing to consume and usually take longer to eat than their refined or prepared forms. They seem more filling because of greater bulkiness. Non starch polysaccharides may slow energy absorption in comparison with more refined versions of the same food. Insulin responses are less because glucose is more slowly

released during digestion. Reactive hypoglycaemia is thus less likely following ingestion and absorption resulting in less need to eat again quickly.

We can only speculate on factors in the western lifestyle which predispose to the development of obesity. In adult societies improved income leading to greater consumption of alcohol may be one cause. But this does not explain the increase in childhood obesity. High fat intakes leading to greater energy density of foods result in loss of some of the satiety introduced by the volume of food consumed. Fat may be more readily deposited as fat in certain 'at risk' individuals than the same amount of spare energy ingested as carbohydrate /15/.

Patterns of eating may be very relevant to the development of satiety signals in response to food. A meal enjoyed and prolonged with the family or in pleasant company is likely to engender a greater feeling of satiety than a meal of similar energy content eaten alone in front of the television when little thought was given to what or how much was eaten.

Modern methods of marketing foods have significant effects on consumption. Foods are presented in different attractive packets and in different flavours so that satiety with one variety may be alleyed by the use of different flavours or presentations. Vigorous advertising at, for example, peak child viewing time on television, leads to peer group pressures on children to eat when they do not need food. Foods eaten under those circumstances are commonly high in energy and of low satiety value.

Socioeconomic aspects

In developing societies it is the affluent who tends towards obesity. In most westernised societies it is children of the disadvantaged and of ethnic minorities who seem most at risk of obesity. Studies from Copenhagen /16/ suggest that the environment in which children are reared rather than the social class or education level of the parents is the main environmental factor predisposing to obesity in later childhood or adult life. Disadvantages such as lack of safe play areas and easily available, cheap, good quality fresh food may combine with parental depression from unsatisfactory housing, to encourage obesity.

Childhood obesity is common amongst children of single parent families (which may reflect socioeconomic deprivation), and single children within a family. Why the latter group should be at risk is not clear unless this reflects either overindulgence of single children or the energy consuming effects of living with brothers and sisters.

Psychological characteristics

There are no precise psychological habits which define obese children. Nevertheless there are some attitudes which seem common to many of the very obese who have presented at my clinics in the past. These characteristics may be helpful in indicating what might go wrong in the environment to predispose to obesity.

Children are often referred to obesity clinics because poor school progress is attributed to their size. Such children rarely make much effort to slim and give the impression of children who have a lot of self pity, poor peer group relationships and who have developed obesity as a consequence or association of their psychological problems, rather than as a precursor to their problems. Other obese children are well integrated with their friends and have few school problems despite their great size. They may or may not succeed with slimming depending on whether they perceive successful slimming as a high priority.

Some obese children are remarkable in their dependence on their parents. They expect to be dressed and undressed in the clinic at an age when most children would be doing these things for themselves. They do little to help with running the home and appear to expect parents to do everything for them. When confronted by dietary and lifestyle recommendations, comments such as 'I don't like it' and I don't want' are regarded as sufficient reason for failure to make efforts over changes in lifestyle. By contrast, other obese children meet the challenge of slimming by overcoming some dislikes to try and attain their objectives. Unfortunately slimming is neither easy nor quick even amongst those who make great efforts. Positive approaches to slimming need great support if they are not to lead to disillusion.

Some obese are clearly very inactive but many are not more obviously lazy than their non obese peers. Fat boys, because of their large size, may be very successful at sports. It is difficult to gauge whether fat children are using less or more energy than their peers in activities. Altered body composition makes overall energy consumption of the obese greater than that for their leaner peers, but difficulty estimating LBM accurately makes any estimate of energy consumption/kg LBM imprecise.

There seems good evidence to incriminate the popularity of television as entertainment for children in the modern epidemic of obesity /17/. Activity levels tend to be very low when watching; eating is common; sweets, crisps and other snacks may be consumed almost unnoticed; and frequent food advertisements can have subconscious influences.

Formal exercise in the form of sports and walking is important in prevention or reduction of fatness. However, most of the day is spent at relatively low levels of activity /18/. If a child uses little more than basal activity because of time spent watching television or sitting inactive at home, energy consumption overall may be

considerably less in twentyfour hours than for a child who moves around the home, helping the rest of the family, taking an interest in others' activities and generally trying to adopt an active lifestyle without necessarily being very sporting. An outward looking attitude and the encouragement of responsible independence may be good preventives against the insidious development of obesity.

No one cause can usually explain obesity in an individual. Subtle genetic and environmental influences which induce high energy intakes and low energy expenditures have combined effects in obese individuals. These may be compounded by family or medical inaction over children's obesity because of despair or acceptance of other obesity within a family. Children only present when obesity is excessive and difficult to reverse. These varied factors together result in the disturbing increase in childhood obesity that is common in so much of Europe today.

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THE ROLE OF ENERGY EXPENDITURE IN THE DEVELOPMENT AND MAINTENANCE OF OBESITY IN CHILDREN

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Genetic, environmental, and behavioural factors produce a positive energy balance which leads to the progressive increase of fat mass up to obesity. The etiopathogenesis of the defect in the regulation of energy balance which causes obesity has not been defined, in particular for the difficulty to obtain a reliable and valid assessment of the energy intake in free-living conditions /1, 2, 3/. On the contrary, the use of new techniques (doubly labelled water: $^2H_2{}^{18}O$), or the improvement of methods already available (indirect calorimetry and heart rate monitoring method), to assess the 24 h energy expenditure (TEE) and its main components (Basal metabolic rate [BMR], thermogenesis [T], energy expenditure for activity [EE_A], and the energy expenditure for growth [EE_G]) allowed a significant improvement of the knowledge on the other element of the energy balance, i.e., the energy expenditure.

Total energy expenditure. The TEE was found to be significantly higher in obese than in nonobese children and adolescents, both in males and in females /1, 3/. An index of activity, i.e., the ratio TEE/MR, was comparable in obese and nonobese children /3, 4/.

BMR. In a large number of studies, a significantly higher BMR in obese than in nonobese children and adolescents was found. While no difference between the two groups was found when BMR was adjusted for fat free mass [FFM] by ANCOVA, using FFM as the covariate /5, 6/. BMR adjusted for FFM was comparable in obese after weight loss and nonobese children /6, 7/. Weight loss induced a reduction of BMR which was directly proportional to the loss of FFM /6, 7/. In adult Pima Indians, a reduced BMR adjusted for FFM significantly correlated with subsequent weight gain /8/. However, no longitudinal data are available in children.

Thermic effect of food (TEM). Obese children (at least part of them) and adolescents showed a slightly but significantly lower TEM than nonobese children /9, 10, 11/. After weight loss, TEM increased to values comparable to those of nonobese children, suggesting that the reduction of TEM was subsequent and not preceding obesity. However, the real impact of the energy saving due to the reduction of the TEM have to be evaluated in the context of the total 24 h energy expenditure.

Energy expenditure for activity. The results of a study of Roberts SB et al. /12/, suggested that "reduced energy expenditure, particularly on physical activity, was an important factor in the rapid weight gain during the first year of life in infants born to overweight mothers", underlining the importance of the EE_A in the pathogenesis of obesity. Data on children and adolescents showed that the daily EE_A (+ thermogenesis or: TEE-BMR) was comparable or higher in obese than in nonobese subjects /3, 4/. The assessment of the patterns of activity showed that obese children spent significantly more time in sedentary activities than nonobese children /13/. The higher energy cost of activity, due to the necessity to move a heavier body, may explain the discrepancy between a shorter time spent in activity and a comparable energy expenditure due to activity in the two groups /14/.

Nutrients balance. The quantity and composition of nutrient intake and oxidation may affect the regulation of energy intake and impaired regulation of energy intake may predispose to obesity. In particular, a key role seems to be played by fat oxidation /15/. Studies performed in adults showed that a lower 24 h fat oxidation rate was a predictive factor for subsequent body weight gain /16/ and that a lower 24 h fat oxidation rate is a risk factor for body weight regain after weight loss /17/. Recent studies in children and adolescents showed higher postabsorptive fat oxidation rate in obese than in nonobese children /18, 19/. In obese children the rate of fat oxidation correlated with fat mass which was able to explain an additional part of the variance of fat oxidation not already explained by FFM /19/. Therefore, in already obese children, a metabolic attempt to achieve fat balance, i.e., increasing fat oxidation, is reported, at least in postabsorptive conditions. At the present time, longitudinal data on the nutrients oxidation rate of children in the dynamic phase of obesity are not available.

CONCLUSIONS

On the basis of the results of the above mentioned studies, we may conclude that some progress on the role of energy expenditure in the genesis and maintenance of obesity in children have been achieved. Further investigations are needed to define the role played by the EE_A, which is the only discretional component of TEE, in the prevention and treatment of obesity, especially in children.

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METHODS TO EVALUATE BODY COMPOSITION

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Body composition is often used as an indicator of nutritional status. It is influenced by age, sex, food intake, physical activity and diseases. The method used to measure body composition depends on the variable to be quantified. It may also depend on the practical conditions of the study. Elaborated methods give more accurate information, but they have a high cost and they are often based on hypotheses established in adults. Anthropometry remains the most widely used method. Measurements can be used directly. Various indices give complementary information on body composition /9/, such as the weight/height^2 or body mass index (BMI), trunk/extremity skinfold ratio, waist/hip ratio, upper arm muscle area (UMA) and upper arm fat area (UFA), based on skinfolds and arm circumference. Body density and percentage body fat can be predicted from anthropometric measurements (weight, height or skinfolds), using regression equations.

Weight-for-age and height-for-age are the first indicators to be considered for growth surveillance. To assess under or overweight, weight-heigth indices are necessary. At adolescence, the Body Mass Index is preferred to weight-for-height as age can be taken into account. In addition, the BMI pattern reflects real changes in body shape and fatness (Figure 1), and early in life it is an indicator of later development. Changes which appear at adolescence actually have their origins much earlier, during the first years of life. This is clearly observed monitoring the BMI curves in individuals (Figure 2) or in populations.

Measures of weight and height should be augmented by skinfolds. The triceps skinfold is usually recommended and widely used, but trunk skinfolds, such as the subscapular, are better on many counts: association with internal fat, with risk factors and response to nutritional interventions (Tables I and II).

In conclusion, elaborated methods for measuring body composition are useful to obtain accurate information. However, valuable information on body composition is given by the combination of various anthropometric measurements. In addition patterns of anthropometric measurements during growth provide useful information to predict adult measurements.

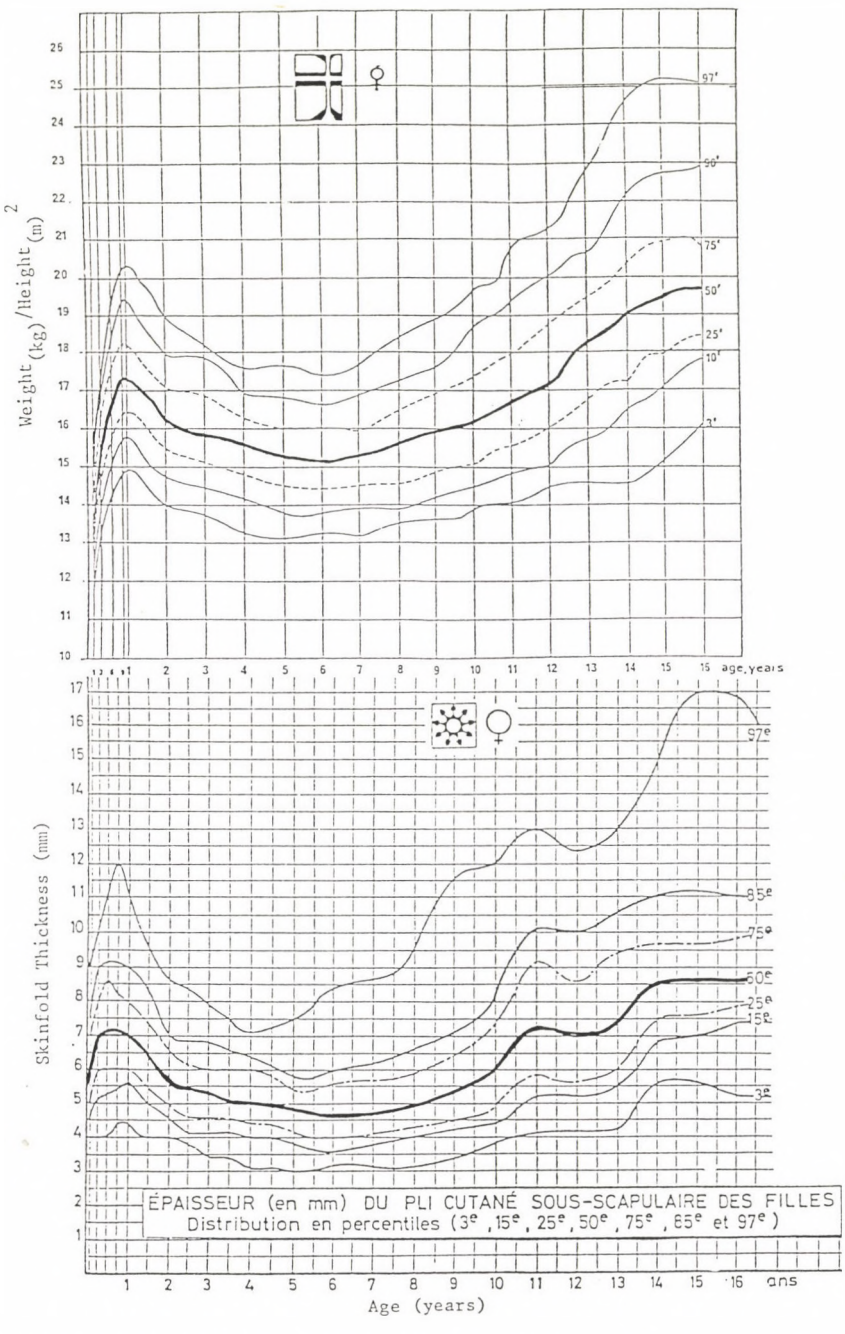

Figure 1: Development of adiposity assessed by the Wh/Ht^2 Body Mass Index and by subscapular skinfold in girls (after Rolland-Cachera, 1993)

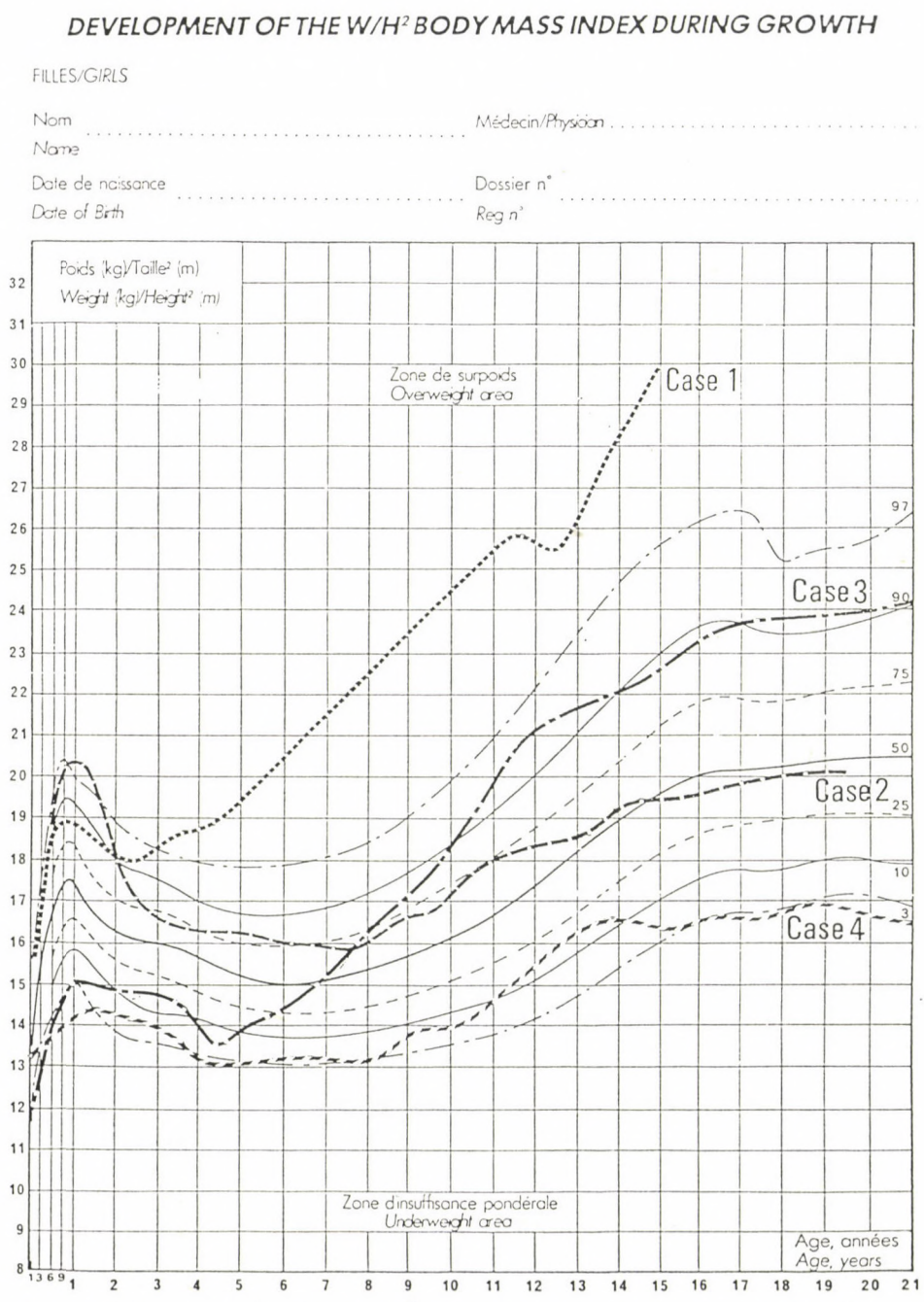

Figure 2: Examples of weight/height^2 monitoring on BMI reference charts in girls. Case 1: fat at one year, remained fat after early rebound (2 years); case 2: fat at one year, did not stay fat after a late rebound (8 years); case 3: lean at one year, did not stay lean after an early rebound (4.5 years); case 4: lean at one year, remained lean after late rebound (8 years) (after Rolland-Cachera, 1993)

TABLE I

Selection of Anthropometric Measurements According to Various Characteristics
(Out of SF and BMI)

Characteristics	Age	Males	Females
Relationship with Body	6-13 yrs	TRI	TRI
Composition	13-18 yrs	TRI	TRI
% BODY FAT (density) [7]	Adults	W/H^2	TRI
TOTAL BODY FAT	6-13 yrs	W/H^2	W/H^2
density [7]	13-18 yrs	SS	W/T^2
	Adults	W/H^2	W/H^2
CT Scan [12]	Adults	W/H^2	W/H^2
INTERNAL FAT			
MRI [6]	11-12 yrs	SS	SS
CT Scans [12]	Adults	W/H^2	W/H^2
Specificity [3]	8-19 yrs	TRI	W/H^2
Association with Card Vasc Risk Factors [11]	12-17 yrs	W/H^2	W/H^2
Tracking [10]	Child- Adult	W/H^2	W/H^2
Technical aspects			
Availability, reference data	all ages	W/H^2	W/H^2
Acceptance	all ages	W/H^2	W/H^2
Reliability	all ages	W/H^2	W/H^2

TABLE II

Selection of Anthropometric Measurements According to Various Characteristics
(Out of Trunk & Extremity SF)

Characteristics	Age	Male	Female
Relationship with Body Composition			
% BODY FAT (density) [7]	6-13 yrs	TRI	TRI
	13-18 yrs	TRI	TRI
	Adults	SS	TRI
TOTAL BODY FAT			
density [7]	6-13 yrs	SI	SI
	13-18 yrs	SS	SS
	Adults	SS	all
INTERNAL FAT MRI [6]	11-12 yrs	SS	SS
Response to nutritional intervention [4]	all ages	Trunk SF	Trunk SF
Specificity [3]	8-19 yrs	TRI	SS
Association with Card Vasc Risk			
Factors [11]	12-17 yrs	Trunk SF	Trunk SF
[2]	11-16 yrs	Trunk SF	Trunk SF
[1,5]	Adults	Trunk SF	Trunk SF
Tracking [10]	Child-Adult	Trunk SF	Extr SF
Technical aspects [8]			
Availability, reference data	all ages	TRI&SS	TRI&SS
Acceptance	all ages	TRI	TRI
Reliability (out of 13 SF)	all ages	TRI&SS	TRI&SS

Abbreviations:
SF = skinfold, TRI = triceps SF, SS = subscapular SF, SI = suprailiac SF, W/H^2 = BMI = body mass index

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OBESITY AND TYPE 1 DIABETES MELLITUS (IDDM)

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INTRODUCTION

The onset of obesity in adolescence may have significant adverse effects on health. Indirect evidence that obesity amongst adolescent girls with IDDM may predispose to obesity in adult women is suggested by data collected in the adult diabetes clinic in Ninewells Hospital, Dundee, Scotland (RT Jung, personal communication) which demonstrates that 17% of women (10% of men) with IDDM compared with 12% of non-diabetic women (8% of men) /11/ have a body mass index of 31-40 kg/m^2.

Excess body weight may increase morbidity in childhood. Body weight is a major factor determining blood pressure in young insulin-dependent diabetics /28/. In adolescent girls with IDDM, increased body mass index and poor glycaemic control are associated with menstrual irregularities and features of polycystic ovarian disease /2/. IDDM in the young, particularly females /29/ is associated with atherogenic lipid and lipoprotein profiles. In older patients with IDDM, adverse lipid profiles are associated with known body composition risk factors such as increased waist-hip ratios /27/. However, there are surprisingly few published data on body composition in young people with IDDM.

BODY COMPOSITION IN CHILDREN WITH IDDM

It is a common clinical impression that obesity is a problem in adolescents with IDDM although published data of body weight are inconsistent. Several studies have demonstrated that adolescents with IDDM and girls in particular are heavier than normal. Girls with poorly controlled IDDM are heavier than average, though those with good blood glucose control are of normal weight /7/. Others have shown that diabetic girls over the age of eight and boys over the age of eleven are heavier than local population standards /15/. The author made the inference that girls are more

obese whereas the boys had increased muscle mass though no body composition data was presented to support such a conclusion /15/. Another study has shown that in diabetic patients ranging in age from 3 to 45 years old, females tended to be above average weight but both sexes had thicker than normal subscapular skinfolds /8/.

More recent work from Denmark shows that adolescent girls, particularly those on multiple injection regimens, have a higher body mass index than adolescent boys /20/. However, other uncontrolled studies of body weight suggest that whereas children and adolescents with IDDM are heavier than ideal, they may not be heavier than their non-diabetic peers /1, 10/. These latter studies are contradicted by a prospective study of newly diagnosed children with IDDM which has demonstrated that within two years of diagnosis, diabetic children become significantly heavier than controls /30/.

Obesity is more reliably assessed from measurements of body composition than by inference drawn from measurements of weight and height alone /25/. In adolescents with IDDM, skinfold thickness and bioelectrical impedance techniques have shown that pubertal girls have substantially more body fat than prepubertal girls and pubertal boys. 57% of Scottish pubertal girls with IDDM (compared with 29% of healthy young British adult women /11/, have a body fat in excess of the ideal maximum of 30% of body weight /12/. Further unpublished studies in Newcastle upon Tyne, England and Pécs, Hungary have confirmed these findings with 59% of adolescent girls in Newcastle and 71% in Hungary having body fat in excess of 30% body weight. These findings demonstrate that adolescent girls with IDDM have a tendency to develop excessive body fat during puberty and detailed analysis shows that this is principally a phenomenon of the later stages of puberty coinciding with a time of increasing insulin dosage and poor glycaemic control.

RISK FACTORS FOR THE DEVELOPMENT OF OBESITY IN CHILDREN WITH IDDM

In children with Type I IDDM, it is suggested that because of decreased insulin sensitivity at adolescence, insulin doses need to be significantly increased to

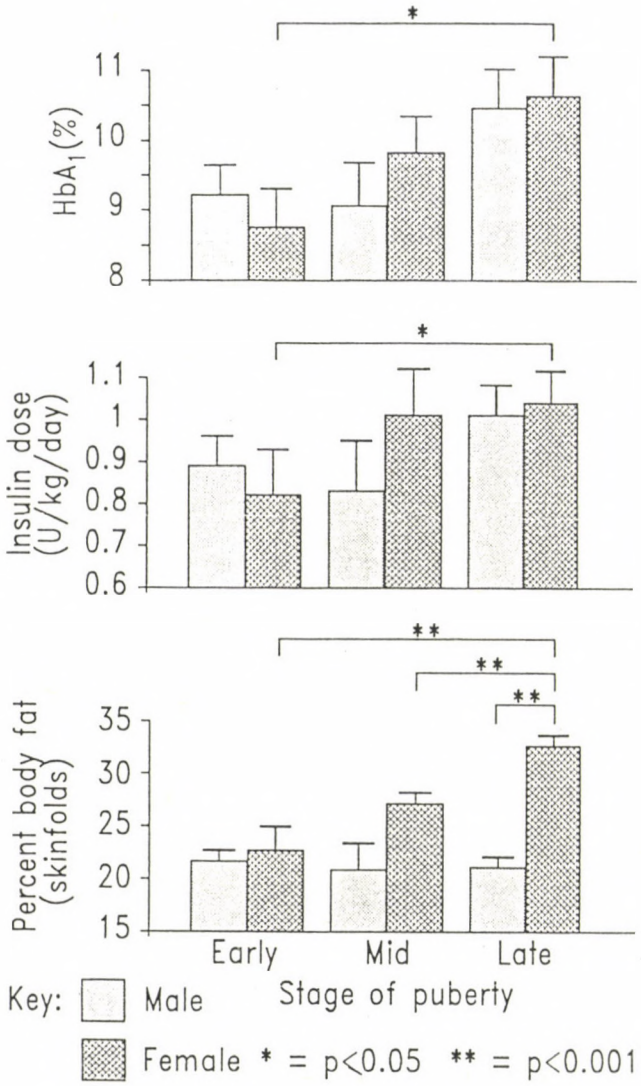

Figure 1: Effect of puberty on body fat, insulin dose and HbA_1

maintain blood sugar control /14/ but despite the larger doses of insulin per kilogram body weight, blood glucose control often remains poor. Insulin has anti-lipolytic properties and in theory, larger doses of insulin may predispose to excess accumulation of fat.

However, although previous research /12/ has shown that girls in later puberty receive more insulin and have greater body fat than those in early puberty, there was no correlation between measures of insulin resistance /26/ or insulin dose (U/kg/d) /12/ and obesity. This finding suggests that failure to decrease insulin doses after the growth spurt is not the major factor predisposing to obesity though numbers in the groups studied were small.

Obesity occurs when energy intake exceeds energy expenditure. Energy expenditure is contributed to by basal metabolic rate (BMR), thermogenic response (e.g. to food and stress) and energy expended in activity. A decrease in any of these may predispose to weight gain and obesity.

IDDM and insulin therapy have significant effects on some components of energy expenditure. It is known that in children with IDDM, increased thermogenic responses to food /19/ and adrenaline occur /21/ compared to controls. In neither study however, were differences in BMR observed between children with IDDM and control subjects. In adults with poorly controlled IDDM, BMR is increased /23/ and a net loss of protein occurs /22/, though improved blood sugar control has been shown to decrease BMR and produce weight gain when no compensatory decrease in energy intake occurs /17/. It would therefore seem that as BMR is unaltered in patients with good glycaemic control and increased with poor control and as thermogenic responses in IDDM appear to be increased rather than decreased, reduced levels of physical activity may be the major mechanism resulting in decreased total energy expenditure and may thus have an important role in the development of increased body fat observed in adolescent girls with IDDM.

Little is known of the levels of physical activity in adolescents with IDDM. It may be hypothesized that levels of physical activity are decreased in these individuals because of concern about the concurrent risk of hypoglycaemic episodes during exercise. Questionnaire based studies have demonstrated that at all ages in healthy children, boys expend more energy than girls and that after the age of 14 years, there is an appreciable decline in physical activity levels in girls /24/. However, physical

activity leading to improved physical fitness is known to alter glucose metabolism in IDDM. In combination with glycaemic control, physical fitness accounts for 73% of the variation of insulin mediated glucose utilization /6/, reducing the level of insulin resistance which occurs in puberty /4, 5/. However, exercise training alone in adolescents, whilst increasing insulin sensitivity and physical fitness, does not necessarily improve blood sugar control though it has been suggested that in association with alterations to diet and insulin, it may be of value in the management of IDDM /16/. Energy intake in adolescents with IDDM appears to be the same as that of healthy children /13/ though assessment of this by dietary recall may be unreliable in those diabetics with a tendency to overweight /3/. Although eating disorders are common in young women, there is no evidence that the incidence is greater in those with IDDM /9/.

FUTURE STRATEGIES FOR THE PREVENTION OF OBESITY IN CHILDREN WITH IDDM

In common with non-diabetics, it is likely that adolescents with IDDM take little physical exercise. They should be encouraged to take part in sporting activities which may be encouraged through participation in residential diabetic camps with an emphasis on outdoor pursuits. Advice on insulin reduction and increased glucose intake is necessary to ensure that such individuals are at minimal risk of hypoglycaemia which might dissuade them from future involvement in these activities.

In addition, it is important that a determined attempt is made to reduce background daily insulin dosages when adolescents approach the end of puberty and a resolution of the transient increased insulin resistance occurs /5/. This may also allow dietary education to focus on decreasing dietary calory intake with consequent benefits on lipid profiles /18/.

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OBESITY AND THE RISK TO PHYSICAL HEALTH

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There are very few useful recent studies on the feelings and attitudes of obese children and their families towards their obesity and the consequences of being obese. The list of consequences for obese children and adolescents is long: girls are worried about figure, clothes, friends and partners, boys about restriction on sport and physical activity. All are teased at school and have higher levels of emotional troubles. Many obese children are characterized by low self-esteem, depression, lack of confidence and poor self-discipline. Misperception of body function and disturbance of body image is a consistent psychopathological feature. Parents feel that they had produced imperfect children by infantile overfeeding. Often there is considerable family conflict in the homes of obese yougsters who were harassed by lean siblings. The families are more often introverted, socially isolated and passive. Generally obese girls are more obsessed by their obesity than boys. Obesity of early onset appears to be associated with most striking body image problems. Those who become fat in childhood and adolescence are at risk of becoming emotionally disturbed as a consequence. Psychosocial problems in childhood persist in adults. however, obese adult persons rationalize the problems and many of them can cope and live with these problems. Obese children and adolescents, however, at least partly may become adult "bing" eaters or restrained eaters with disturbed eating behavior and likelihood of persistence and aggravation of obesity.

Numerous studies have shown that overweight people are at increased medical risk and there is no doubt that obesity in adulthood is strongly associated with a variety of serious diseases and an increased overall mortality rate /1, 2, 3/. Cardiovascular disorders, hypertension, dyslipidemia, cancer, gallbladder disease, gout, arthritis, psychosocial disability, orthopaedic, dermatological disorders, cholelithiasis and others are related to obesity. However, in childhood and adolescence problems for obese children and adolescents primarily result from

psychological and social consequences. Children probably suffer more than adults from the fact "obesity".

For adults obesity generally is accepted to be a more or less serious health risk, the question is, however, whether this is true also for childhood and adolescence. In the short-term, there is little relationship between obesity and morbidity/mortality, whereas in the longer term there is a strong relationship. The Framingham Heart Study (data based on age adjusted rates for 2219 men who at the beginning of the follow-up were from 29 to 61 years of age, free of coronary heart disease and cancer and from whom weight, height, and smoking information was available) clearly demonstrated the increasing risk with the duration of obesity /4/. The relationship is J-shaped, with the lowest mortality occurring around the "desirable" value of 100. The longer the follow up, the stronger the association between obesity and mortality.

The long-term relationship between obesity and risk of cardiovascular disease is strong for both men and women /5/. However, is there any risk for children and adolescents? In terms of acute risk for cardiovascular diseases there is of course no immediate risk, however, even in children and adolescents there are demonstrable subtile metabolic effects of obesity and childhood obesity and in particular obesity of the adolescent tends to persist into adulthood and the likelihood of medical complications increase with duration of obesity. The medical risk of childhood obesity, therefore is a problem of persistence and duration. Nevertheless we should be aware that even in children obesity is associated with a number of risk factors, which are known to promote morbidity and mortality in adulthood.

It is well known that obese adults have high total cholesterol, LDL-cholesterol and triglycerid levels and low HDL-cholesterol levels /6/. Several studies found these adverse effects already present in childhood obesity. Hyperlipidemia occurs in approximately one-third of all adolescents, and there is some suggestion that the prevalence of hyperlipidemia is increased in obese adolescents.

In adults, obesity is the most powerful risk factor for noninsulin-dependent diabetes mellitus, with both its magnitude and duration being important considerations. The American Cancer Society Prospective Study showed that compared with persons of "ideal" weight, those with relative weight equal to or greater than 140% have mortality ratios of 5.2 (men) and 7.9 (women) because of diabetes mellitus. These mortality ratios are greater than for any other disease. In children diabetes mellitus is clearly a risk in patients with Prader Willi's syndrome. Impaired glucose tolerance test and hyperinsulinemia, however, is frequently found already in obese children and adolescents: in a recent study we could find an abnormal glucose tolerance test in

12% of the obese children and increased basal insulin levels in 48% /7/. Although the clinical relevance of these results is not clear, hyperinsulinemia and impaired glucose tolerance are potential risk factors not only for diabetes mellitus but also for hypertension and cardiovascular diseases.

During the last years, body fat distribution has gained considerable interest and besides obesity, different body fat patterns have been related to disease /8/. Several studies showed that upper body fat patterns are associated with diseases typically for obesity (hypertension, diabetes mellitus, hyperinsulinemia, hyperlipidemia etc.). This seems to be true also for adolescents: it is well known that obese children tend to have higher blood pressures than lean and these elevated levels do not appear to be due to increased salt intake or preference. Although hypertension occurs with a prevalence of approximately 1 to 2% in adolescents, obese adolescents account for approximately 50% of all cases of adolescent hypertension. Moreover, in recent studies it could be demonstrated that besides the degree of obesity even in adolescents the body fat distribution plays an importance in regard to systolic and diastolic pressure /6/. Upper body fat distribution is closely and positively associated with higher levels of these risk parameters. Similar results have been found for hyperinsulinemia and dyslipidemia. Therefore, there is increasing evidence that body composition and adiposity localisation play an important role in the development of morbid aftereffects of obesity.

Whereas in adulthood medical consequences are directly threatening the health of obese patients, in childhood and adolescence major problems for obese children and adolescents are arising from psychological and social consequences /9, 10/. At no time persons are confronted so directly and frankly with psychosocial problems arising from being obese than in childhood and adolescence. In examining the world of obese children we must look at peers, family and school. The major problem of these children is not the excess weight alone, but the view of others in the environment. Few problems in childhood have as significant an impact on growth and development and psychosocial functioning as obesity in a child. Early studies demonstrated that children as young as five years of age had learned to associate obesity with a variety of negative characteristics. The images of ideal weight are probably reinforced by images of thinness on television.

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IS "IDEAL WEIGHT" IDEAL FROM EVERY ASPECTS?

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In adult persons body mass index (BMI) is considered as a good indicator of the nutritional status and a reasonable estimate of body fatness. Life expectancy and incidence of major diseases among subjects belonging to different BMI ranges give good opportunity to determine the BMI ranges associated with the lowest health risks, i. e. the ideal weight range for a given height from the point of view of good health.

For adolescents the BMI is not an accepted tool to characterize body fatness. In this age group the assessment of risks for major diseases in later life in relation to fatness is difficult /2/. There are no well elaborated recommendation for the ideal level of fatness in adolescents. To evaluate the health impacts of body fat content in adolescent girls we studied the relationship of body fatness with iron status, skeletal size and serum lipids. Iron deficiency is the most frequent nutritional deficiency among young females in Hungary. It influences physical and mental working capacity and presents major problems during pregnancy. Skeletal size is an important indicator of skeletal development. In adolescents the skeletal size reflects the bone mineral content /3/. A well-developed skeleton is supposed to postpone the osteoporotic fractures characteristic to the postmenopausal years /4, 6/. Although the significance of elevated serum cholesterol in adolescent girls has not yet been fully clarified, higher levels of blood cholesterol may indicate higher risk for cardiovascular diseases in later life /5/.

354 girls aged 16.5-18.5 years, attending secondary schools at Pécs were studied. Standard procedures as described by Cameron were used to measure body mass, height, skinfolds and the wrist diameter /1/. The diameter of the clavicle was measured at the middle of the left clavicle on standing subjects, with shoulders slightly elevated and let forwards. The measurement was taken in the frontal vertical plane. At the same site, above the clavicle the skinfold was measured as well, using Lange caliper. The breadth of the clavicle was calculated by subtracting the skinfold value from the clavicle diameter. Fasting blood was taken from the cubital vein. Serum ferritin was determined with immunoradiometric assay (Izinta Hungary). Blood total cholesterol was determined by CHOD-PAP method (Boehringer). Sums

of 3 trunk skinfolds (subscapular, suprailiac and chest lateral) and BMI were used as indices of obesity.

The sums of trunk skinfolds were positively related with the skeletal size parameters: girls with thin skinfolds had thin bones, girls with thick skinfolds had thick bones (Table I). Similar relationship was observed between BMI and skeletal size.

TABLE I

Relationship between skeletal size and the sum of trunk skinfolds in girls aged 17-18 years

Sum of trunk skinfolds quintiles	Clavicle width mm	Wrist width mm
1	15.5 (SD 2.0)	47.7 (SD 2.9)
2	16.2 (SD 2.1)	47.9 (SD 2.9)
3	16.4 (SD 2.2)	47.9 (SD 2.5)
4	17.0 (SD 2.7)	48.7 (SD 2.8)
5	17.5 (SD 2.4)	49.0 (SD 3.2)

Prevalence of blood total cholesterol levels exceeding 5,2 mmol/L was positively related with the level of fatness: it was highest in the fifth (highest) quintile of trunk skinfolds. Prevalence of low serum ferritin values was negatively related to trunk skinfolds: in the fourth and fifth quintiles of skinfolds the prevalence of low ferritin (< 13 µg/L) values was lower than in the first three quintiles. Both the prevalence of increased total cholesterol and of low ferritin concentrations in the lowest quintile of skinfolds did not fit into the general trend of prevalences (Table II). Similar observations could be made if the prevalences of low ferritin and high cholesterol values were investigated in the different quintiles of BMI.

Our findings indicate that in girls aged 17-18 year it is unwise to recommend strict and narrow ranges of indices for fatness (BMI or skinfold ranges), because the relatively low indices which are the best for healthy blood lipid levels are less favourable from the point of view of skeletal development and iron status. One must consider family history of the girls and nutrition related health risks in the community before making evaluation or giving advice concerning "ideal weight".

TABLE II

Prevalence of low serum ferritin values (< 13 µg/L) and high blood total cholesterol levels (>5,2 mmol/L) in girls groupped according to the sum of trunk skinfolds

Sum of trunk skinfolds quintiles	Prevalence of low ferritin %	Prevalence of high cholesterol %
1	17.5	11.4
2	26.3	9.7
3	19.0	12.1
4	11.6	18.0
5	12.8	19.1

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SECONDARY OBESITY

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Obesity can be a feature of a large variety of diseases even if secondary obesity represents only a small percentage (<5%) in the etiology of obesity. Although rare secondary obesity must be considered separately for its implications in differential diagnosis, clinical features, management and therapy.

DIFFERENTIAL DIAGNOSIS

Most cases of secondary obesity can be classified in two main groups: genetic or polimalformative syndromes (Prader Willi, Bardet-Biedl, Alstrom, Cohen, Down, Carpenter, etc.) and endocrine disorders (hypopituitarism, hypothyreodism, Cushing syndrome, hypothalamic lesions, etc.); others are often part of metabolic abnormalities (i.e. in IDDM).

Some clinical characterist are common and peculiar in the overall group. The presence of short stature, particularly if associated with mental retardation and delayed bone age, strongly suggests a secondary obesity. Furthermore the severe degree of long standing obesity may represent another useful marker in differential diagnosis from primary obesity. The further step is to look for other specific signs of each syndrome or of endocrine abnormalities (Table I).

Late diagnosis is still very common as a consequence of the difficulties in discriminating such cases from simple obesity. In addition in some of these syndromes the onset of excessive weight gain is not early in infancy as in Prader Willi Syndrome (PWS).

Patient history represents another interesting source of suggestions and must be as accurate as possible. Neonatal period, for example, shows additional clarifying details in many of the genetic syndromes. Food behaviour and school performance must be evaluated.

TABLE I

Main clinical features associated with obesity in genetic syndromes

PWS	**Bardet-Biedl**	**Alstrom**
neonatal hypotonia	retinitis pigmentosa	deafness
hypogonadism	plydactilia	diabetes
acromicria	hypogonadism	nephropathy
dysmorphic features		retinitis pigmentosa
chr. 15 deletion		

CLINICAL FEATURES

Accurate clinical evaluation is fundamental in order to distinguish genetic syndromes from endocrine diseases.

Auxologic measurement reveals short stature as well as excessive body weight for height. Moreover dwarfism can be disharmonic in hypothyroidism.

Particular attention has to be dedicated to fat distribution; centrally distrbuted adiposity is characteristic of all the endocrine obesity and some of the genetic syndromes (Cohen, Bardet-Biedl). Dismorphism of the face or extremities are to be looked for. Eye abnormalities are common in genetic obesity, especially retinitis pigmentosa in Bardet-Biedl syndrome.

Hypogenitalism, pubertal delay and menstrual abnormalities are frequent in the majority of the genetic syndromes and in the most of the endocrine diseases; accurate clinical and hormonal evaluation is strongly suggested especially during adolescence. When an endocrine disorder is suspected, clinical examination must evaluate specific signs; for example striae rubre, hirsutism, hypertension suggest cushing's disease. Specific homonal tests suport the diagnosis in this group.

A common feature of all endocrine and some of the genetic syndromes is a reduced muscle compartment, leading to limb hypotrophy and muscle weakness. Bone mineral content is often reduced. This two latter aspects are peculiar to secondary obesity; while in simple obesity the excessive adiposity is generally associated with increased lean mass (muscles, internal organs and bone).

MANAGEMENT

For low prevalence and complexity of secondary obesity, patients are often referred to specialized departments.

Nevertheless, knowledge and information about this rare type of obesity must be increased in order to improve early diagnosis and treatment.

In any case a multidisciplinary approach is needed. Ophthalmologic, radiologic, psychologic, endocrinologic and audiometric cheks are necessary for the correct diagnosis as well as for follow-up management. Psychological support is often indicated for frequent behavioural disorders. Difficulties in coping with abnormal food behaviour request frequent clinical controls with auxological examination and parental counselling. Periodic biochemical investigations on glucose tolerance and lipid profile are crucial, especially in genetic syndromes with higher incidence of cardiovascular diseases, dislipidemia and diabetes.

THERAPY

The causal treatment of the endocrine disorders usually resolves the excessive adiposity in few months. When a hypothalamic syndrome develops after surgery for hypothalamic-hypophyseal tumor (craniopharingioma, germinoma, etc.) obesity is very frequent (50% after 6 months and 90% after 1 year in our Department) and an efficient treatment is still unsatisfactory. Moreover the hypothalamic syndrome shows abnormal food behaviour with bulimia, aggressivity, hyperthermia and electrolyte inbalance which complicate the therapeutical approach. Few cases benefit from fluoxetine therapy even if long term results are still controversial. In any case, compliance in dietary restriction is poor. Even in genetic syndromes a strict diet regimen is difficult.

Recently dexfenfluramine has been proposed in order to control appetite but in these cases benefits are only transient or absent. Physical activity is another potentially useful therapeutic tool: mental retardation as well as muscular hypotonia limit the efficacy of an exercise program is these patients.

New and interesting perspectives seem to derive from growth hormone treament. Despite an irrelevant effect on height, GH has shown dramatic influence on fat reduction and lean mass increase in PWS. Furthermore behavioural disorders improve, showing less aggressivity and autolesionism during GH therapy.

Specific treatment is indicated when ocular, renal or cardiac anomalies are present as well as in overt diabetic patients.

When obesity is severe, or leads to respiratory abnormalities (i.e. obstructive sleep apnea) a surgical approach has been proposed.

CONVENTIONAL TREATMENT OF CHILDHOOD OBESITY

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The last decades, the prevalence of childhood obesity was growing in the industrialized countries /1/. Three questions might be asked: are these children to be treated, at which age and how? Obesity in children is often associated to health hazards: high blood pressure, hyperlipidemia, hyperinsulinism, orthopedic disorders, sleep disturbances and mainly psychological aftereffects /2/. But it is also in many cases the onset of adult obesity /3/. In this regard, treating young obese could be considered a prevention of obesity in adulthood. A precoce development of adiposity in childhood - before the age 5.5 - prognoses the maintaining of an excessive fat mass at the end of growth /4/. Therefore it appears suitable not to delay the management of obesity when developed in young children. In this regard, diet remains a cornerstone even if psychological and behavioral aspects are important and to be managed as well. Several treatment programmes have been described mostly pluridisciplinary involving paediatricians, nutritionists, psychologists and physiotherapists. They reported generally on small samples. Besides, the costs of these programmes, not only in money but also in time and medical staff, seem to be incompatible with the large number of children to be treated. Therefore we tried to develop a baseline therapeutic approach which could be promoted by pediatricians, general practitioners and dietetians.

From 1986 to 1994, about 1000 children attended our outpatient clinic for childhood obesity. Most patients experienced a "precoce adiposity rebound" according to the definition of Rolland-Cachera et al. /4/ and most also exhibited a Body Mass Index (BMI) superior to 150% of the P50 BMI for the age. The schedule of the management programme is summarized in Table I. A general examination was performed and blood biological data were recorded namely in order to exclude a secondary obesity or metabolic abnormalities associated to essential obesity. The daily food intake was recorded by the child and his parents in a three-days diary. This allowed the dietetian not only to evaluate the alimentation in terms of intakes but also to track eventual disorders of the timetable. We found the total caloric intake was close to the Recommanded Dietary Allowances (RDAs) but significantly higher in

children whose BMI was superior to 150% of the P50 BMI for age and in children watching television for more than 15 hours a week - as a result of snacking /5/.

TABLE I

OUTLINE OF THE TREATMENT PROGRAMME

First visit

. interview
. physical examination
. anthropometry

Biological tests

Dietary evaluation

Second visit

. discussion of the dietary evaluation
. presciption of a diet
. physical activity programme
. behavioral aspects
. anthropometry

Next visits (on the 4th week)

. anthropometry
. diet (adaptation)
. discussion

After a 6-month follow-up

. second dietary evaluation
. diet modification

The fat content was high (38.7 and 39.5%, respectively in girls and boys) with a very low polyinsaturated fatty acids to saturated fatty acids ratio (P/S: mean=0.25). The fiber and the water intakes were poor. But this baseline diet was comparable to that we recently studied in young non obese scholars aged 6 to 11 years. We also found that nearly 20% of the obese children had usually no breakfast /5/. Most patients had

lunch at school. School dinners in Belgium are generally delivered by private companies: they are rather fat, filling with sauce, lacking in vegetables and presenting with meat of a poor quality. This was an argument to recommend a "home made lunch". The three days food diary was discussed with the child and his family. We proposed an alternative diet restricted to about 65% of the RDAs but providing enough of all the nutrients allowing a normal growth according to the Committee on Nutrition /6/. The lipids were lowered to 30 of the total caloric intake. In the 50% carbohydrates we reduced the amounts of sucrose and other additive sugars. The fiber intake was significantly increased by the consumption of more vegetables, fruits and cereals. The water intake was prescribed to a minimum of 1.5 ml/kCal/day. The schedule of this new diet is summarized in Table II. We insisted all the nutrients were common available supplies and not so-called "dietary" or "light" products. Only aspartam was authorized as a sugar taste additive. The purpose of such a hypocaloric balance alimentary programme was to offer a realistic and reasonable renewed gastronomy not only to the obese patient but also to all the members of his family. "No more chips, fried potatoes, candy bars, sweets and cola" was a rule but we insisted also on positive arguments: "we are going to help you to eat in a better way". And let us discover new cooking, new choices in nutrients that could promote better familial menus. We found an improvement of the alimentation in 75 children who succeeded in loosing excess BMI for more than 6 months /5/. However there was a difficulty to increase for instance the fiber consumption, mainly in young children who were often "reluctant" to most vegetables. Also the total water intake remained too low.

Besides the dietary prescription, a physical activity programme was proposed: sport (in clubs), summercamps, participation in youth associations, ... Behavioral and psychological aspects were discussed from the first session. Eventually, a specific management was organized with the help of a psychologist working in the team.

In 1993 /7/, we reviewed the course of 395 obese children aged > 6 to < 12 years (group 1) and 240 adolescents aged > = 12 to < 17 years (group 2). After 12 months, 24% of the group 1 were still treated and 15% exhibited a further decrease of their excess BMI. In group 2 only 9% were still followed and 7% were still slimming. It must be emphasized that the adolescents were proportionally more obese than the younger children and had also a longer duration of their obesity: this was of worse prognosis. Also we might consider that young children were more "under the control" of their parents than were the adolescents. In this last group, the personal motivation was probably more determinant requiring a more specific support.

TABLE II

OUTLINE OF THE DAILY REGIMEN

BREAKFAST	- cereals, semi-skimmed milk, no sugar or - slice(s) of bread, bread roll(s), thin scrape of low energy margarine, ham of other low calorie delicatessen or skim-milk cheese - coffee, tea, semi-skimmed milk (if not added in cereals)
BREAK	- a fresh fruit or a juice fruit
LUNCH	- soup (skimmed) or salad vegetables - slide(s) of bread, sandwich(es), low calorie delicatessen or cheese - a fresh fruit
HOME	- low calorie yoghurt of skim-milk white cheese
SUPPER	- soup or salad vegetables - lean meat (grilled or boiled), fish, chicken (without the skin) - vegetables (large amounts), no sauce - small portion of boiled potatoes, rice or noodles - a fresh fruit or a low energy pudding

Home made French dressing with low calorie nutrients (as low energy yoghurt).
No additive sugar-eventually aspartam.
Drink: water, sometimes a "light" lemonade.

We can compare this conventional treatment programme to more sophisticated strategies - very low calorie diet or family behavioral programmes, for instance. A recent study of Figueora-Colon et al. /8/ demonstrated a comparable success of hypocaloric balance diet and very low caloried diet in a small sample of adolescents.

Epstein et al /9/ showed better results in a family trained group on the long term (10 years) than in control groups. But again this was involving a very few patients and a very specialized medical team.

Considering the important and growing number of obese children and adolescents and their large number becoming obese adults, a baseline consensus for management is needed. This conventional therapeutic approach could be promoted as a primary therapy by general practitioners, pediatricians and dieticians. For the very obese children and for most adolescents more specific programmes, prepared by well trained pluridisciplinary teams are certainly needed. We have also to include in this prospect a preventive action towards nutrition in young children and the tracking of early weight excess development.

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DRUG TREATMENT OF OBESITY

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INTRODUCTION

Most of our experience in drug treatment of obesity comes from clinical trials carried out in adult obese patients. The majority of the published studies are carried out in women without reported obesity related complications. Therefore our knowledge on the effect and safety of the use of pharmacotherapy in children and adolescents is modest, and the health benefits of prolonged treatment are unknown. Based on surrogate end-points such as blood pressure, serum lipids and glucose tolerance tests it is obvious that weight reduction assisted by pharmacological agents is expected to reduce risk of atherosclerosis and type 2 diabetes. In addition, quality of life in an emotionally vulnerable period of life is another important parameter to take into consideration.

WHO SHOULD BE TREATED?

Eventually the decision about who to treat should be based on an individual assessment of all available factors. Serious efforts to achieve weight loss may be contraindicated in children where a family history of obesity is lacking, as it is known that about a third of those with childhood overweight and obesity will become normal weight adults, probably spontaneously. Nevertheless, pharmacological treatment should be considered in patients where diet therapy and behaviour modification have failed if:

1/ They have complications of obesity

2/ Abdominal fat distribution and other risk factors are present

3/ Weight loss is critical e.g. pre-surgery.

DURATION OF PHARMACOLOGICAL TREATMENT?

Currently available drugs potentiate an efficient diet by 0.5-1 kg per month for about 6 months. They subsequently prevent relapse. Treatment should continue until a desirable weight loss is achieved, and dietary habits and exercise behaviour are permanently changed. Anorectic agents do not seem to loose their effect during long-term use, so permanent treatment is an option in high-risk patients with complications to obesity. One should be aware that pharmacological agents have no effect after discontinuation.

PHARMACOLOGICAL MANIPULATION OF FAT BALANCE

In the prevention and treatment of obesity it is often stressed that it is important to achieve an increased energy expenditure. This rests on the assumption that energy intake is not adjusted to match expenditure, which would maintain energy equilibrium and keep body energy stores unaltered. This assumption is certainly never entirely fulfilled, and it is more the exception than the rule that an increased energy combustion is entirely covered by oxidation of fat from the stores without any compensation in energy intake. The pharmacological corollary is that any use of thermogenic agents should include a suppression of energy intake, either pharmacologically, or voluntarily by diet. The principle pharmacological agents act mainly as appetite suppressants, but several compounds possess thermogenic properties. The adrenergic acting ß-agonists are probably the most promising of these. Dexfenfluramine (dF) has been demonstrated to exhibit both anorectic and thermogenic properties. Non-selective sympathomimetics possess well documented anti-obesity properties and they represent an alternative to serotonergic agents.

THERMOGENIC DRUGS

While energy expenditure may increase 10-fold during exercise, the thermogenic effect of pharmacological agents is much more modest. Sympathomimetic compounds and ß-adrenergic agonists can increase resting energy expenditure by 10-15%, and slightly potentiate the thermic effect of foods. Energy expenditure may be increased by 5-10% on a 24-h basis. When compared quantitatively with exercise, one realises that it is crucial that drug-induced thermogenesis is not fully compensated by

an increased energy intake. According to the concept of macronutrient balances, compensation could be avoided if the increased energy expenditure increases the proportion of relative fat oxidation (i.e. decreased RQ).

USE OF SYMPATHOMIMETICS IN OBESITY

Ephedrine (E) decreases body fat in obese subjects by a dual action: suppression of appetite and stimulation of energy expenditure covered by fat oxidation. The thermogenic and clinical effects are potentiated by adenosine antagonists such as caffeine (C). The metabolic effects of ephedrine are mediated by beta-adrenergic receptors (ßAR), and recent experimental studies show that not only $ßAR_1$, and $ßAR_2$, but also $ßAR_3$ are involved in its thermogenic effect.

Combinations of E+C seem to maintain their anti-obesity effect during continued treatment to 6 mo, and may subsequently prevent relapse (6-12 mo) /1/. E+C offsets the immediate antihypertensive impact of diet-induced weight loss, but this effect is transient, and after 8 weeks of treatment reduction in blood pressure is indistinguishable from that of a placebo-treated group. Independent of weight loss E+C prevents the decline in HDL-cholesterol associated with weight loss, and increases the ratio of HDL-C to total-C, whereas it has no effect on fasting glucose metabolism /2/. In a double-blind comparison of E+C and dexfenfluramine (dF) in overweight and obese subjects the weight loss after 15 weeks was similar (8.3 vs. 6.9 kg), but in a subgroup (BMI > 30 kg/m^2) weight loss was larger in E+C than in dF (9.0 vs. 7.0 kg) /3/. dF caused an immediate reduction in blood pressure, which was not found with E+C, but after 15 weeks blood pressures were similarly reduced. Whereas E+C may be more effective in more severe obesity, dF has been found to be more effecient in middle-aged and elderly patients, and is preferred for the management of obese hypertensives. With the current pharmacotherapy of obesity there is a need for increased knowledge to allow a more differentiated treatment, tailored individually to age, gender, BMI and metabolic characteristics. This shortcoming may be partly solved by newer, more selective $ßAR_3$ agonists which are promising agents and are presently being examined in obese patients.

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WHAT DOES AN INTERNIST EXPECT FROM PAEDIATRICIANS TO DO IN ORDER TO PREVENT OBESITY?

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According to the Hungarian Annual of Statistics /3/, our population has further decreased in 1993. While mortality is continuously increasing, the number of live births is decreasing in Hungary. These are well-known tendencies. The increasing mortality and morbidity are partly due to cardiovascular diseases which are frequently accompanied, or the consequences of obesity. According to our epidemiological survey /2/ the prevalence of obesity in a cohort of chronically ill patients was 39%. In 1988 others /1/ found the prevalence of overweight in the Hungarian adult population 25%. Obesity is an independent risk factor of coronary heart diseases, hypertension, stroke, diabetes mellitus, dyslipoproteinaemias and gall bladder diseases. In spite of all that, obesity is seldom recognised as a potentially harmful health problem and is not treated according to its importance. Unfortunately most of our treatment-schemes for obesity purely concentrate on weight reduction, which one of the reasons of the poor long-term results. The change of our life-style, our manners is indispensable. The regular and abundant meals (mainly supper), the increasing length of time we spent in the comfortable TV-arm-chairs, in front of the TV, the lack of regular sports activities all lead to energy-storage. Beside genetic components social and cultural factors also worsen the situation. The busy life-style (spare-time jobs, the struggle to earn enough money to meet the social requirements), friends with similar attitude, the general disinterestedness in healthy way of life, are all factors promoting weight-gain. The traditional Hungarian cuisine is very tasty but rich in energy and fat, and poor in fibre. Our energy-rich nutritional habits are the greenhouses of obesity.

If we invited a guest for a cup of tea and some cakes, or children for hot chocolate, we could not stand in front of the world. We generally offer much more to eat. Why can`t we emphasise again conversation, chatting, listening to music or playing with the children instead of showing off with the menu?

Most of the people coming home in the evening open the fridge-door and start to eat immediately. We have forgotten the beautifully laid tables with flowers. Instead of calm family meals, we talk about unpleasant memories of the day, spoiling the mood and forcing the whole family to compensate for it by overeating. We need to pay attention to not only what and how much, but also when and how we eat.

The other important feature of our life-style is the lack of sports activities, while in most of the Western European countries gymnastics, jogging, walking or cycling are quite common (at least in the upper social classes). It is true that sports wear is expensive for most of the Hungarian families. However, this cannot explain why so few tourists are seen during the weekends. Great variety of excuses are found for not cancelling the Sunday hike. We do not even visit museums, how could we think of climbing mountains.

It is no doubt, computers and TV teach the children a lot as they push all day long the remote control, but will they be fit enough to utilise their knowledge? The optimal ratio of physical and mental activities has to be found.

Since obese patients after weight reduction are post obese and not healthy persons with normal body weight, obesity can only be treated but never cured. So it is straightforward that the only possible way of influencing adult obesity is prevention. Intrauterine nutrition, nutrition during infancy and childhood and regular physical training are all of major importance in the prevention of childhood and adult obesity

The most important tasks are the following:

1/ Prevent obesity by educating, teaching children how to live a healthy "preventive" life-style

2/ Treat obese children and follow them up thoroughly.

The obese and non-obese have to learn the magic four: what, how much, when and how to eat. To have a meal instead of just eating. To enjoy the meal even if it is a diet. Let or even encourage them to pursue some sport, since those who are not involved in any kind of sport during in the childhood years would scarcely start it in adulthood. They need to improve their self-esteem and self-discipline so as not to pursue dreams and not to look for resolution in eating. It is also important to teach them how to dress, not to put on old tight clothes in the hope of losing weight but to become too thin for their large dresses.

A close and continuous contact between the child and the doctor, psychologist, dietician, physiotherapist is essential because the key of the successful treatment is the good compliance.

Ensure continuous control for the children up to adulthood. The period of adolescence is extremely dangerous since at this age children`s behaviour changes and their compliance decreases on one hand and this is the time when paediatricians release the hand of the obese child and the internist is unwilling to admit him among his elderly patients on the other.

Well, I know we internists expect too much from paediatricians, but the prevention of adult obesity is almost exclusively in their hands. On the other hand adults who

have already acquired a healthier life-style will show a good example for their offsprings.

If a healthy life-style became natural in childhood it, would be easier to maintain it in adulthood. This work is not an easy task. Decades are needed to cure what decades have spoiled.

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CAN CHILDHOOD OBESITY BE PREVENTED?

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All of us, and the majority of our children, live in an environment that overexposes us to obesity promoting factors (diet, media, advertisements, social eating habits, etc.) and underexposes us to protective physical activities (cars, elevators, few and dangerous and expensive places to perform physical activities). As a consequence, no one is immune to developing obesity in the developed countries. It may even be reasonable at this time to stress a structured preventive porgram to high risk subjects who basically consist of children of obese families. The efficacy of the program directed to high risk subjects should be increased through an informative general program directed to all the population using the mass media. This requires a change in social and economic policies because obesity prevention does not have any economic backing, while food advertising, and food sponsors, and even slimming products for both government and commercial television represent a lot of money.

We must try however to warn people of the risks of obesity in order to set limits for both the quality and the number of food commercials during the day. This is especially important during children's programs. We can accomplish this through the influence of the medical community on our governments, consumer unions and even health food companies. We have seen the success of the method already in other health campaigns for smoking, immunization, and AIDS. Only through a mass media prevention program, directed (openly and/or subliminally) to all the population is it possible to create an opinion movement in order to get a healthier behavior. In the last few years, psychologists and sociologists have gained a good knowledge of some of the factors involved in health-related behaviors. This knowledge is the theoretical base for planning strategies to induce favourable behavioral changes.

Hovewer, developing a preventive program for childhood obesity is not easy becuase of the multiple factors in its genesis. Among these factors the familial ones, both genetic and environmental, have a very strong power on the onset and on the outcome of obesity in childhood. One of the tasks of the family, all over the world, is to be a culture-transmitter through development and/or maintenance of knowledge, attitudes, values and habits. So, before trying to change "bad behaviors and habits", we need to understand why people have certain beliefs and then act in certain ways.

We then need to consider what they get in return, by way of reinforcing factors that cause them to maintain this specific behavior.

The Bandura's conceptual model, called social-cognitive theory, is the theory most used for the development of health behavioral change programs.

This theory states that each subject develops, changes, and maintains positive or negative behaviors on the basis of several personal, behavioral and environmental factors. These factors are seen through direct and/or indirect relationships with parents, peers and media.

In the obesity field, in order to be successfully engaged in a preventive behavior, an individual must have: 1/ knowledge about the associations between certain behaviors (reduced activity and excess of nutrient intake) related to obesity; 2/ belief that he is susceptible of becoming obese and that the consequences of it will be negative; 3/ belief that a preventive behavior will prevent or reduce the onset or severity of obesity (outcome efficacy); 4/ trust in himself that he is capable of performing new preventive behaviors (self-efficacy) and in having or learning the skills required to perform these behaviors successfully; 5/ belief that the benefits of acquiring a different behavior outweigh the cost (benefits vs. difficulties); 6/ Last, he must get behavioral reinforcement from family, society and peers for performing the new behaviors.

Since the parents act as role models of behaviors and are the most important source of reinforcement for children, a family approach is necessary for successful prevention of childhood obesity. However, the role models of parents, which is very strong in early childhood, becomes less evident as the child enters the adolescent years. Then peers and media figures become the main role models, so the approach must be different at different ages.

A related question emerges: "When or at what age is it more convenient to start a preventive program?" We have arguments for and against each age.

Starting a preventive program in early childhood has the following positive arguments: 1/ persistent childhood obesity develops by age 4, 2/ access to food depends on the child's caretakers, so the program could focus only on parents, avoiding the problems posed on the required independence of adolescents. In later years the child's or adolescent's involvement outside the home (school, friends), may reduce parents motivation and power to address the problem.

On the other hand, children's health beliefs begin to be a coherent belief system about 9 years of age and become stable at about 10-11 years. Starting a preventive program at this age could present the positive effect to get an active involvement of the subject, who could also be tracked into the adolescence period of higher risk.

The arguments against the two groups of age are: 1/ for early childhood there is a risk that the preventive effect will be very short and will finish before adolescence; 2/ while it is a fact that the later age group may have health-beliefs and habits which are already too established to be permanently changed. In any case, there is no guarantee that preventive programs will be able to induce and maintain behavior changes until adulthood.

The second question that immediately raises: "When could we stop?"

For the time being there is still no answer. However, since the growing child comes from a simple environment, family, and goes into a more complex psycho-social environment of family, peers, school, media, the program should be established in the early childhood or childhood. Probably the best thing would be to perform new periods of training as "booster doses" appropriate to the developmental stage of the child.

The third question that may rise is: "Which behaviors should be targeted as top intervention priorities in order to accomplish a successful preventive program?"

Since childhood obesity is a multifaceted problem, the behaviors that need to be changed are not the same in different countries in different areas of the same country and in different families as well as at different ages of the subject. Instead of using the very same structured program for everybody, it could be more convenient evaluating the negative behaviors in the target population or family. After noting these negative behaviors, one could then evaluate their importance and their changeability, and try to act on the incentives that promote those behaviors. But "How can these behaviors be changed?" Incentives play a fundamental role in human behavior, so we must try to change the established negative incentives in favour of new healthier incentives. The social cognitive theory underlines that new, weak, or inappropriate-for-age incentives, can make the efforts to change the negative old behaviors useless. These must be kept in mind while working with children whose thinking is quite concrete and present oriented. Adolescents, even if they are more abstract and flexible in thinking, perceive themselves as independent and invulnerable and so are not oriented in changing their own behavior. In other words, speaking of good health and risk of morbidity in adulthood may have some effect on the parents of obese children, but it is almost totally ineffective when working with children and adolescents. So we should emphasize more proximal outcomes that are important for the young subjects, i.e. personal appearance for teenage-girls, good sport performance for teenage-boys, tangible rewards like toys for younger children. Once that the incentives have been decided, the child or adolescent must be helped in managing his behavior through learning and practicing self-regulatory skills.

The first skill is self-monitoring to allow the child or adolescent to gain self-diagnostic and self-motivational functions; in addition self-monitoring is useful for evaluating changes in behavior. The second skill is setting a goal which provides direction and reasons for behavior change. However, in childhood and adolescence, goals must be quite proximal, explicit, quite challenging, but not too difficult to achieve.

Since a positive judgment of self-efficacy is modified, by performance accomplishments, vicarious experience, emotional states, and verbal persuasion, the creation of a series of subgoals of increasing difficulty and their successive attainments may influence positively the child's or adolescent's self-efficacy and as a consequence, the feeling of power to change behavior.

The last question is: "Who should stimulate the obese family to change behaviors?" Behaviors are modeled by incentives and by leaders. The pediatrician can have a leading role in providing good incentives to the parents in order to achieve a positive health-related behavior. Since the family trusts the pediatrician from the very early age of the child, he can interact with the family, in order to change the behaviors of the child. At school age, the environment becomes more complex; there the help of teachers, psychologists and mass media is also an asset. The answer to the original question "Can childhood obesity be prevented?", is "Yes". We have the basic knowledge to start preventing childhood obesity by performing structured individual preventive programs for high risk subjects and at the same time starting a general preventive approach through mass media in order to improve the health-related behavior of the whole population. In conclusion, we pediatricians must always remember our outstanding role in prevention and in order to get positive results, all of us must strongly believe in the necessity and the possibility of preventing obesity.

ABSTRACTS

WORKSHOP 1: WHAT ARE THE ESSENTIAL (NONANTHROPOMETRIC) MEDICAL INVESTIGATIONS IN THE ASSESSMENT OF THE OBESE CHILD?

INSULIN RESISTANCE, PLASMA SOMATOMEDIN-C (IGF-I) AND SERUM SEX HORMONE BINDING GLOBULIN (SHBG) IN CHILDHOOD OBESITY

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Childhood obesity may be characterised by basal and reactive hyperinsulinemia, insulin resistance, reduced growth hormone response to various provocative stimuli and normal or elevated plasma somatomedin-C (IGF-I) concentration. Obesity is commonly associated with low serum sex hormone binding globulin (SHBG) concentration in childhood, too.

For this reason the relationship between the degree of obesity (body mass index - BMI) serum immunoreactive insulin (IRI), plasma IGF-I and serum SHBG were investigated in children with obesity.

1. Insulin binding to erythrocytes (IB) and serum IRI were measured and relationship between these parameters and BMI wasinvestigated in obese children and age matched controls with normal body weight. IRI was increased and IB was decreased significantly in obese children compared to the data of the controls. The decreased IB was due to a decrease in the number of insulin receptors since it was not accompanied by alteration of half maximal inhibition dose (ID_{50}). Strong negative correlations were found between BMI and IB and between BMI and IRI.

2. Serum IRI and plasma IGF-I were measured in children with obesity. Significant positive correlations were found between BMI and IRI, between BMI and IGF-I, and between IRI and IGF-I.

3. Serum IRI and serum SHBG were measured in children with obesity. Significant positive correlation was found between BMI and IRI, and significant negative correlations were found between BMI and SHBG and between IRI and SHBG.

These results suggest that /1/ there is an interrelationship between weight excess, hyperinsulinemia and insulin resistance in childhood obesity; /2/ IGF-I production in obesity is regulated by IRI depending on BMI and this regulating effect of insulin may be important in obesity since HGH production to provocative stimuli is reduced; /3/ insulin hypersecretion has an important role in determining the reduction of SHBG production in obesity.

IS SCREENING FOR HYPERLIPIDEMIA IN OBESE CHILDREN WORTHWHILE?

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Given the tracking of lipid levels in childhood, obese children with an increased risk for cardiovascular disease might be identified very early by a screening for abnormalities in lipid metabolism.

In 80 obese children (27 boys, 53 girls) with an age between 5.0 and 15.9 years and a procentual overweight between 120 and 211%, a determination in fasting condition of cholesterol, trigliceride and HDL-cholesterol concentration was performed before treatment instauration.

The influence of age, sex, onset (before or after the age of 6 years) and degree of overweight (% overweight 120-140; 140-160; > 160%), body fat distribution (subscapular/triceps skinfold > or ≤ 0.8) and activity level (involvement in sport activities or not) on lipid levels was studied.

For the total group mean (±SD) concentration of cholesterol was 178 ± 34 mg/dl, or trigliceride 92 ± 43 mg/dl, of LDL cholesterol 118 ± 30 mg/dl. Eleven patients presented a cholesterol concentration above 200 mg/dl, 7 patients a trigliceride level above 150 mg/dl and fifteen patients an LDL concentration above 135 mg/dl. Girls had significantly higher cholesterol (183 ± 38 versus 167 ± 21 mg/dl ($p < 0.05$)) and trigliceride levels (99 ± 46 versus 77 ± 33 mg/dl ($p < 0.005$)). Age, onset and degree of overweight, type of fat distribution and activity level were without influence on the circulating lipid levels.

In conclusion, circulating lipid levels above normal adult values were found in 8 to 18% of obese children. Given this relatively high frequency and the negative finding of a specific hyperlipidemia associated clinical status, screening for hyperlipidemia in all obese children seems justified.

CONNECTION BETWEEN CHILDHOOD OBESITY AND LIPOPROTEIN PARAMETERS

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Cardiovascular diseases stand on the first place of Hungarian morbidity and mortality statistics. Obesity is one of the main risk factors of cardiovascular illnesses. In order to determine body fat we did not use invasive method. To determine body surface fat we use ultrasound (soft tissue) method and the determination of visceral fat is possible with CT.

We examined the relationship of the visceral, body fat and the lipid and lipoprotein parameters (cholesterol, triglyceride, HDL cholesterol). We found a strong connection between the body surface fat and triglyceride level and the cholesterol and HDL-cholesterol level correllated with the visceral fat.

We found a relationship between the visceral (intraabdominal) fat quantity and the impaired glucose metabolism at the same time.

CARBOHYDRATE METABOLISM IN CHILDHOOD OBESITY

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Oral glucose tolerance test (OGTT) was performed in 91 obese (O) children from 8 to 14 years of age being either in the stationary (S) or in the dynamic (D) phase of obesity. Capillary glucose (G), serum C-peptide (C-P) and immunoreactive insulin (IRI) were determined every 30 minutes for 180 minutes. The integrated values (Σ) of curves and ΣC-P/ΣIRI ratio were calculated. The results were compared with data of 15 nonobese children (relative weight < 120%) (C) of the same age. Specific insulin binding % of erythrocytes (SIB%) was determined in 9 S and 7 C children.

	Weight (kg)	ΣG (mmol/l)	ΣC-P (nmol/l)	ΣIRI (nmol/l)	ΣC-P/ΣIRI	SIB (%)
C (n=15)	28.3	31.8	5.66	1.00	6.11	6.5
DO(n=21)	72.6*	34.4*	16.47*	3.36^{o}	4.77^{o}	-
SO(n=91)	77.8^{o}	41.0*	17.01^{o}	6.75*	2.77*	3.9*

^{o}ns; *p<0.02

Relationship between ΣC-P/ΣIRI and SIB% is 0.702*.

Conclusions: 1. ΣC-P/ΣIRI ratio provides an indirect information about the insulin receptor function. 2. In obesity the C-P (beta-cell) response during OGTT is definitely increased and independent of the phase of obesity. 3. In DO, beside insulin hypersecretion, the normal ΣC-P/ΣIRI ratio indicates insulin resistance resulting decreased glucose utilization. 4. Metabolic changes of obesity during childhood are in S phase a predictive factor of multimetabolic syndrome (Syndrome X).

OBESITY IN CHILDREN WITH ACCUMULATED ATHEROSCLEROTIC FAMILY RISK

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Children whose parents had premature coronary heart disease were investigated. BMI, blood pressure (included 24 h monitoring) and serum lipid profile of 1087 (3 - 18 yr.) children were measured. Thirty-seven of the 61 obese children with a BMI above 25 had serum lipid abnormalities (together with high normal blood pressure in 22 cases). High normal blood pressure as measured by ambulatory blood pressure monitor was detected without any lipid abnormalities in 20 cases. These results suggest the importance of the measurement of both parameters: the serum lipid profile and the 24 h blood pressure in obese children especially in cases with high risk atherosclerotic family history.

MULTIMETABOLIC SYNDROME IN OBESE CHILDREN

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The occurrence of multimetabolic syndrome was studied in 114 (63 boys, 51 girls) obese children. From the blood sample taken after an overnight fast, blood sugar, serum insulin, and lipid levels were determined. During oral glucose tolerance test blood sugar concentrations were followed. Body mass index, body fat (on the basis of skinfold measurements), lean body mass and waist/hip ratio were calculated and blood pressure was measured 6 times in all subjects. Multimetabolic syndrome was found in 16% of boys and 19.6% of girls. No significant sex difference in the frequency of multimetabolic syndrome was found. Patients with multimetabolic syndrome could not be characterized by high waist/hip ratio or any other antropometric parameter. The duration of obesity was significantly higher in subjects with multimetabolic syndrome than in those not suffering from the syndrome. This finding supports the hypothesis that the development of multimetabolic syndrome is a process. Authors emphasize the significance of this problem and the importance of early recognition and prevention.

WORKSHOP 2: PREVENTION OF CHILDHOOD OBESITY

OBESITY IN LONG-TERM SURVIVORS OF CHILDHOOD MALIGNANCY

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Improved survival from childhood malignancy has led to the prediction that by the year 2000 approximately of 1 in 1000 adults in their third decade will be a long-term survivor of childhood cancer. Numerous adverse sequelae associated with treatment are now recognised. We have retrospectively investigated a clinical impression that obesity is one of these adverse late effects in two groups of patients. **Group 1** (12 boys and 26 girls) were long-term survivors of acute lymphoblastic leukaemia (ALL) treated with prophylactic low dose cranial irradiation (18 Gy and (n=32) or 24 Gy (n=6)) and adjuvant cytototoxic chemotherapy. **Group 2** (17 boys and 21 girls) were long-term survivors of other childhood malignancies who received cytotoxic chemotherapy but no radiotherapy. Body mass index (BMI) was calculated at diagnosis and 2, 4, 6 and 8 years thereafter and expressed as standard deviation scores (SDS).

There was no statistically significant difference in age at diagnosis between the two groups (median 3.4, range 0.9-9.9 years for group 1 and median 3.0, range 0.4-13.4 years for group 2). Mean BMI SDS for all patients (SE of mean) at diagnosis and at 2, 4, 6 and 8 years thereafter are shown in the table.

	Diagnosis	2 years	4 years	6 years	8 years
Group 1	-0.27(0.18)	0.55(0.15)*	0.67(0.18)*	0.76(0.26)†	1.12(0.28)‡
Group 2	-0.13(0.21)	0.41(0.18)*	0.28(0.21)#	0.12(0.28)	-0.71(0.29)

(*$p<0.001$; † $p=0.004$; ‡ $p=0.003$; #$p=0.008$ compared to BMI SDS at diagnosis).

Both males and females had significant changes in BMI SDS within group 1 at all time periods compared to BMI SDS at diagnosis, but within group 2 only the females had significant positive changes at 2 and 4 years after diagnosis and not thereafter. BMI SDS between groups showed significant differences at 8 years ($p<0.001$) for all patients. Although there was no significant difference between males, females were significantly more obese in group 1 than group 2 ($p=0.03$ and $p=0.01$) 4 and 8 years after diagnosis.

We conclude that obesity is a late long-term effect of treatment for childhood ALL but only temporarily so for other childhood malignancies. This may be as a consequence of cranial radiotherapy, though the mechanism in unknown.

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IS OBESITY PREVENTABLE IN PRADER-WILLI SYNDROM (PWS)? THE POSSIBLE ROLE OF GH DEFICIENCY

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In the last few years relevant amount of evidence about GH deficiency in PWS syndrome has been acquired. So far, the efficacy of GH therapy has been reported to be successful in improving height velocity, life quality and weight control in few PWS children and adolescents. Although an impairment of GH response to different diagnostic tests may be due to obese state, the abnormality in GH secretion in PWS appears to be more complex and a neurohypothalamic defect is suspected in these patients.

We have therefore studied GH secretion in 19 PWS subjects (M/F 10/9; age 17.1 ± 5.3; BMI 29.7 ± 7.3 kg/square meter). The diagnosis of PWS was determined by chromosome 15 deletion in 48% of subjects, uniparenteral disomy (UPD) in 5% had an unbalanced translocation involving chromosome 15.42% of patients, without deletion, were included according to the score of Holm et al. (mean score: 9.4 ± 0.4). GH secretion has been studied by GH RIA assay after clonidine test and GRF+pyridostigmine test. IGF-1 has been measured by RIA. Mean GH peak after clonidine was 4±5.4 ng/ml; obese subjects showed mean GH peak values after clonidine significantly different from non obese (3 ± 4 vs 13 ± 9 ng/ml, $p < 0.006$). After GRF-P, mean GH peak value was 12.3 ± 10.5 ng/ml; obese subjects showed mean GH peak values significantly different from non obese (10 ± 7 vs 34 ± 12, $p < 0.0005$). 100% of obese patients showed GH levels less than cut off value after clonidine and all but one patient did not normalize GH response after GRF-P. Mean IGF-1 values were 128 ± 47, with no differences between obese and non-obese subjects. An inverse relationship between BMII and GH response (clonidine: r -0.55, $p < 0.01$; GRF-P: r -0.74; $p < 0.0005$) was found. A similar relationship was seen between age and GH secretion (clonidine: r -0.45, ns; GRF-P: r -0.67, $p < 0.002$). Intractable obesity in PWS children seems to develop together with the onset of GH deficiency. Moreover, mean GH peak values in PWS appear markedly reduced with respect to normal population even after pyridostigmine, suggesting an underlying cause for GH deficiency other then obese state. GH

deficiency could be a characteristic feature of PWS and a necessary premise for obesity development; in this case an adequate follow up programme of GH secretion should be able to detect early derangements in order to start substitutive therapy to prevent severe obesity.

SECULAR TRENDS IN BODY MASS INDEX (W/H^2) DISTRIBUTIONS AT AGES 7-14 YEARS IN A POPULATION OF 142,000 DANISH BOYS BORN 1930 THROUGH 1965

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Previous studies of Danish young men examined at the draft boards have shown that the prevalence of extreme overweight (BMI > 31.0 kg/m^2) was almost stable at about 1 per 1000 from 1943 until 1960. Thereafter a steep increase began, which continued until mid-1970s when it levelled off at a several fold higher level. The central part of the body mass index distribution, reflected for example in the median body mass index, remained unchanged throughout this period, although moderate overweight showed a slight increase in the early 1960s. The increase began with the birth cohort 1942 and continued until the birth cohorts of the mid-1950s. The observation indicates a striking increase during this period in exposure to an environmental cause of obesity during childhood or adolescence. To identify the cause, it would be helpful to know at what age and in which years the change began.

All schools (public and private, general or specialized) in the Copenhagen municipality have carried out annual measurements of height and weight of the pupils born 1930 and later. The school health records are available until birth year 1965. We have computerized the measurements for all the boys from this period, in total app. 142,000 subjects. For each measurement the body mass index was computed, and interpolations were performed to estimate BMI at exact ages if measurements were available before and after the particular age with less than 2 years interval between them. The 1, 2.5, 5, 10, 25, 50, 75, 80, 85, 90, 95, 97.5, 99, 99.5 percentiles were estimated for each of the ages 7 through 14 years within each birth cohort. In order to assess the changes in prevalence of extreme overweight during childhood, the age-specific 99.9 percentiles were defined for the birth cohorts 1930-34, and these percentiles were then used as definition of extreme overweight throughout.

The lower percentiles including the median of the body mass index distribution (50 percentile) was remakably stable at all ages throughout this 35-year period. The 75, 80, and 85 percentiles showed a steady increase from birth year 1930 until a peak at birth year 1944, wherafter it levelled off, most pronounced for the higher percentiles

and for the older ages and barely detectable at age 7. For the 90, 95, 97.5, 99 and 99.5 percentiles the same pattern was observed, but peaking later and later.

The prevalence of extreme overweight showed in all age groups a low stable level at about 1 per 1000 until the birth cohorts in the early 1940s, whereafter a steep increase began, which was most pronounced and most similar to that seen among the draftees at age 10.

Thus, there was a complex secular trend in the central part of the BMI distributions, which was not directly compatible with the trends in extreme overweight among the draftees.

However, the prevalence of extreme overweight in childhood showed virtually the same secular trend pattern as it did for the draftees suggesting that the environmental exposure leading to extreme overweight began afflicting the birth cohorts 1942 and onwards before age 7. The nature of this environmental exposure remains unknown.

FAMILY FACTORS IN CHILDHOOD AND RISK OF OBESITY IN YOUNG ADULTHOOD

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The purpose of the study was to analyze the effect of various family factors in childhood on risk of obesity in young adulthood.

In 1974, a simple random selection of children aged 9-10 years from the third grade in Copenhagen schools was performed. Ten years later the population was followed up and 86 percent of the persons eligible for follow-up participated /1/. Degree of fatness was assessed using the body mass index. The effect of the family factors was analyzed by logistic regression analysis with overweight (90th percentile) and obesity (95th percentile) as dependent variables.

The results showed that among four social factors quality of dwellings in residential area was the most important factor. Being reared in areas with poor quality of dwellings increased the risk of becoming overweight more than three times while controlling for the effect of body mass index in childhood and sex. Neither parental school education nor householder's occupational status had similar effect /2/.

A child whose mother was not aware of her offspring's sweet eating habits had a more than fourfold increased risk of overweight compared to children who's mother was aware of these habits. Furthermore, having a mother who expressed acceptance of eating of sweets or having received much money for sweets during childhood doubled the risk of overweight /3/.

Family structure (biological or other parents and siblings) did not significantly affect the risk of adult obesity. Parental neglect increased the risk in comparison with harmonious support seven folds. Dirty and neglected children had a ten fold increased risk of adult obesity compared to averagely groomed children. However, being only child receiving overprotective parental support, or being well-groomed had no effect /4/.

In conclusion, it seems as if family factors in childhood, especially being neglected, greatly influence the risk of being obese in young adulthood. For preventive purposes it might be important to identify children suffering from parental neglect.

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NUTRIENT INTAKE AND FATNESS DEVELOPMENT

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Nutrition has a strong influence on growth. Obese children show some acceleration in height and maturation. This is generally attributed to energy excess, but less is known about the role of the composition of the diet on fatness development. On the basis of a French longitudinal study of nutrition and growth started in 1985, we compared the BMI pattern from birth up to the age of 8 years in 126 children according to high, medium and low energy and nutrient intakes at the age of 2 years /11/. Fatness development assessed by the BMI or skinfolds display several phases: an increase during the first year, followed by a decrease. The subsequent increase (named adiposity rebound) occurring at the age of 6 years in average, is associated with adult fatness, and bone age. Correlation coefficients between intake (energy and nutrients) at the age of two years and age at adiposity rebound show a negative and significant association only for the protein content (%) of the diet, i.e., the higher the protein content of the diet at the age of two years, the earlier the rebound.

The early rebound reflecting accelerated growth is a precocious characteristic of obesity development. It is concluded that protein excess should be avoided early in life.

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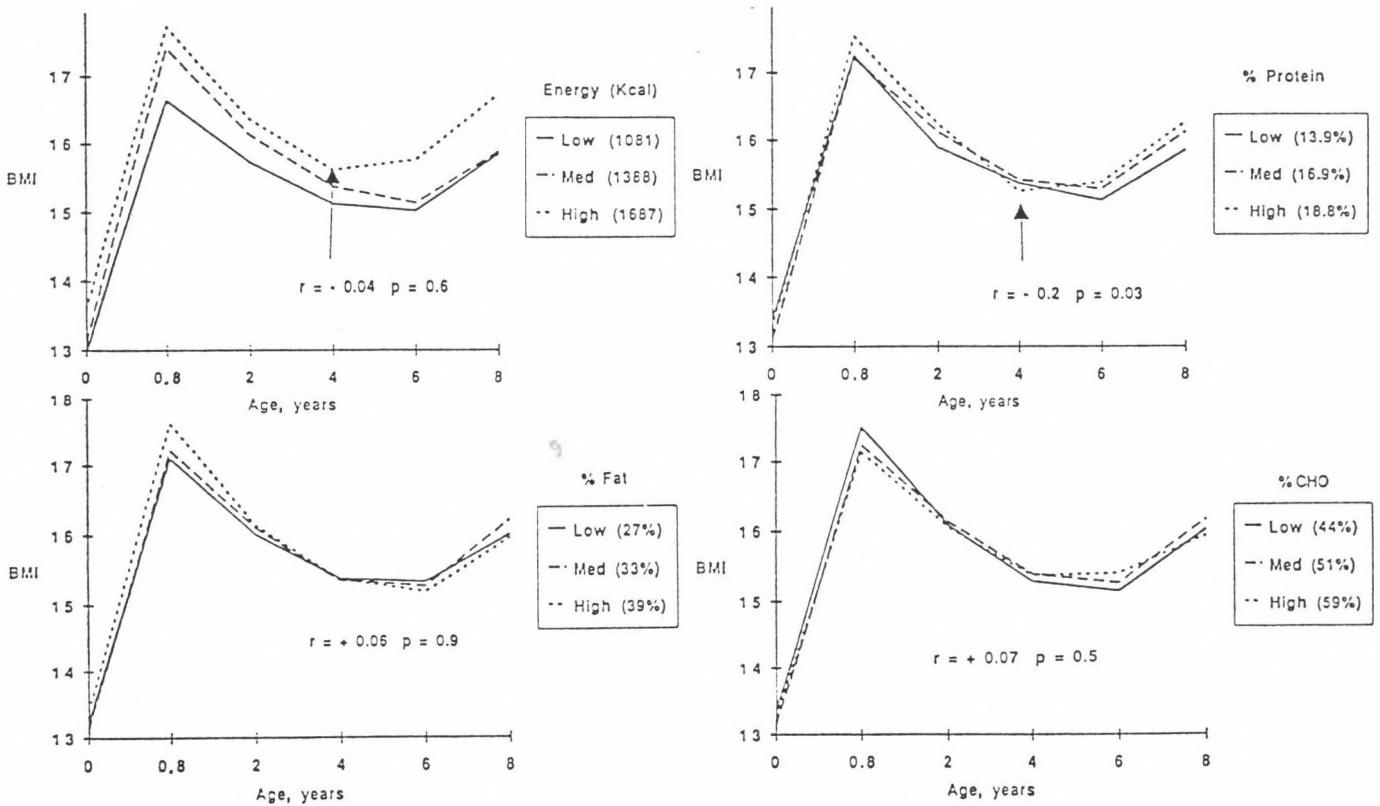

Fig. BMI patterns up to the age of 8 years

POSTERS

EFFECT OF CHANGES IN BODY COMPOSITION DURING WEIGHT LOSS ON REGAIN OF WEIGHT IN OBESE CHILDREN

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Changes in lean body mass associated with changes in metabolic rate during rapid weight loss in obese adults have been shown to predispose for later regain of weight /1/. Lean body mass and metabolic rate are also closely correlated in children /2/. The present study aimed to investigate, whether changes in body composition of obese children during rapid weight-loss might predict the medium term outcome.

Body composition was measured before and after a three weeks weight reduction program using a non-invasive method (Bioelectrical impedance analysis [BIA]). Percentage weight for height was more than 120% in all 41 subjects (19 M, 22 F, age 8.5 - 14.8 [median 11.8] years).

Mean percentage weight for height at baseline was 151% (SD20) and decreased significantly during the three weeks (139% SD18), P = 0.005). Also the mean percentage body fat significantly decreased during the three weeks (from 34.0 SD 5.0 to 31.3 SD 5.1, P = 0.02). Percentage body fat was lower in boys compared with girls at baseline (32.3 SD 5.8 vs. 35.1 SD 3.9 %, P = 0.08), this difference reaching statistical significance at the end of the three weeks (29.6 SD 5.7 vs 33.3 SD 3.9%, P = 0.02). The individual change in body-fat was inversely correlated with the change in lean body mass (R= -0.64, P = 0.0001). After 4 months, 18 out of the 41 children could be reevaluated for height and weight. The regain in body weight during these 4 months was positively correlated with the decrease in lean body mass and body cell mass during the weight reduction program (R = 0.66, P = 0.003, and R = 0.67, P = 0.003, respectively).

It is concluded that a reduction in lean body mass and body cell mass during rapid weight loss predisposes to later regain of weight due to a reduction in resting metabolic rate in obese children. This confirms studies in obese adults. Weight reduction programs for children should therefore not only focus on caloric restriction but also on maintenance of metabolic active tissue. Measuring body composition by an easy to perform, non-invasive method (BIA) during a weight reduction program might help to improve the longterm outcome by optimising the strategies.

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BIOELECTRICAL IMPEDANCE AS AN EASY METHOD TO STUDY CHANGES OF BODY COMPOSITION DURING WEIGHT LOSS IN CHILDREN: VALIDATION BY DEUTERIUM DILUTION

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Aims: Many different programmes for weight reduction in children are known. The success of such programmes depends also on the changes in body composition during weight loss. The best success would be a loss of body fat with no changes in lean body mass. Aim of the present study was 1) to establish a relation between total body water (TBW) and bioelectrical impedance (BIA) in obese children and 2) to investigate the degree of loss of lean body mass during our presently used weight reduction programme.

Methods: 67 obese children (23 boys, 44 girls), mean age 13.9 ± 17.2 kg participated in a 6 week weight reduction programme with a mean daily energy intake of 1000 kcal and a 2 hour sport programme every day. At the beginning (day 2) and at the end (day 38) of the weight reduction programme the following measurements were performed: skinfold thickness at 4 sites (ST), BIA using an AKERN 101, and TBW (oral load of 0.4 mL 99.8% D20/kg BW, pre-dose and post-dose urine and post-dose serum sample, analysis of 2H enrichment as described by Fusch 1993).

	BW(kg)	ST (mm)	H2/l(cm2/omega)	TBW(L)	TBW(BW(%))
Day 2	84.3±17.2	101.7±24.6	54.6±12.6	35.3±6.9	41.6±4.2
Day 38	75.7±14.9	81.9±20.7	53.7±12.8	35.6±6.8	46.2±5.4

Results: see table; linear regression revealed a significant correlation between TBW and BIA before (r = 0.906) and after (r =0. 013) weight loss.

Discussion: 1) TBW was constant during weight loss suggesting no changes in lean body mass. Weight loss seems to be merely due to loss of fat mass. 2) A close relationship between BIA and TBW was found which was stable during weight loss. Equation formulas for the calculation of TBW from BIA are going to be presented.

BODY COMPOSITION OF CHILDREN BY SKINFOLD AND BIA METHODS

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The exact assessment of body composition in children is a difficult task. A great variety of techniques for assessing human body composition have been developed and used.

The aim of the present study was to evaluate the reliability and reproducibility of body composition assessed by bioelectrical impedance analyzer (BIA) and to compare it with conventional skinfold methods. The subjects in this study were Hungarian children (40 males, 60 females ; age: 6-19.3 years; 32 obese children, 68 non-obese children). Skinfold thicknesses were measured by Holtain caliper, and impedance was determined using the BIA 101, RJL systems, Detroit MI, USA equipment. The measurements were done by two observers, twice in a week to determine the intra- and inter-observer variability. Data were elaborated by SOLO Statistical Programme (BMDP Statistical Software, Los Angeles, California).

The amount of lean body mass (LBM) was determined by different equations (for skinfold: Parizkova, Brook-Durnn-Rahaman, Deurenberg; for impedance: Deurenberg, Newman, Schaefer, Weight Manager Programme). LBM values of normal children estimated by different impedance and skinfold equations were similar, except that calculated by the Schaefer equation, which grossly underestimated the LBM. Whereas in obese children the calculated LBM values were much more equation dependent. The inter-observer error was markedly lower in impedance measurements compared to skinfold measurements.

Advantage of BIA technique is, that it can be used throughout childhood, it is painless, rapid, and independent of inter-observer variability. Disadvantage of the method is, that recently no age, sex and population specific equations are yet available.

INCREASED POSTABSORPTIVE FAT OXIDATION IN OBESE CHILDREN: A METABOLIC DEFENCE TO FURTHER WEIGHT GAIN?

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This study was performed to measure the postabsorptive fat oxidation at rest and to assess the association between fat mass and fat oxidation in a group of 72 prepubertal children. Children were divided into two groups: 35 obese (weight: 44.5 ± 9.7 kg, FM: 31.7 ± 5.4%) and 37 non obese (weight: 30.8 ± 6.8 kg, FM: 17.5 ± 6.7%). Postabsorptive metabolic rate was measured by means of indirect calorimetry (Deltatrac, Datex Inc., Finland) and fat mass by anthropometry.

Postabsorptive fat oxidation expressed in absolute value was significantly higher in obese than in nonobese children (31.4 ± 9.7 vs 21.9 ± 10.2 mg/min, $P < 0.001$) but not when adjusted for fat-free mass by ANCOVA, using FFM as the covariate (28.2 ± 10.6 vs 24.9 ± 10.5 mg/min). In the obese children, as well as in the total group, fat mass and fat oxidation were significantly correlated ($r = 0.651$, $P < 0.001$). The slope of the relationship indicated that for each 10 kg additional fat mass in these children, fat oxidation increased by 18 g/day.

In conclusion, obese prepubertal children have a higher postabsorptive rate of fat oxidation than nonobese children. This metabolic process may favour the achievement of a new equilibrium in fat balance, opposing adipose tissue gain.

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LIPOPROTEIN LIPASE AND HEPATIC LIPOPROTEIN LIPASE ACTIVITY IN OBESE CHILDREN DURING WEIGHT REDUCTION

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The objective of this study was to investigate the changes on plasma lipoprotein lipase activity (LPL) and hepatic lipoprotein lipase activity (HLPL) and their relationship to the amount of weight loss and changes in plasma lipids in obese children during weight reduction.

Thirty obese children (20 girls and 10 boys) in the mean age of 14 ± 2 years, with the mean weight excess of 75 ± 16% and body mass index (BMI) 29 ± 4 were treated with 900 Kcal diet for three weeks. Dietary treatment resulted in a significant weight reduction of 14 ± 6%, and a significant decrease in LPL and HLPL activity (from 37.5 ± 12.0 to 25.9 ± 13.3 μmol FFA/min/ ml; $p < 0.001$, and from 35.9 ± 10.1 to 28.2 ± 9.8 μmol FFA/min/ml; $p < 0.001$, respectively).

The amount of weight loss correlated weakly but significantly with the decrease in LPL activity ($R = 0.42$, $p = 0.02$), but showed no correlation with the HLPL activity.

Weight reduction resulted in a significant decrease in total cholesterol level (from 4.3 ± 1.1 to 3.6 ± 1.1 mmol/l; $p < 0.001$) and HDL_3 cholesterol level (from 1.04 ± 0.3 to 0.71 ± 0.2 mmol/l; $p < 0.001$). HDL_2 cholesterol and triglycerides remained almost constant. LPL and HLPL activities showed no significant correlation with the lipid levels.

These findings suggest that the amount of weight loss may be related to the suppression of LPL activity during the period of weight reduction. Our data do not confirm the suggestion that HLPL activity is closely related to the HDL_2 cholesterol levels.

INHIBITED PLASMA DELTA 6 DESATURASE ACTIVITY AND ABNORMAL MEMBRANE ESSENTIAL FATTY ACID (efa) PATTERN IN OBESE CHILDREN. IMPACT OF WEIGHT LOSS

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Weight gain leads to the accumulation and further release of the fat cell content which is poorly known. Adequate amounts of EFA are required in order to promote growth and development. The aim of this study is 1) to determine if obesity induces changes in desaturase activity and membrane and plasma EFA pattern in obese children, 2) to evaluate the impact of weight loss. Plasma delta 6 desaturase activity was measured by mean of the 18:3 n-6/18:2 n-6 ratio. The molecular species, principally those containing linoleic, arachidonic and docosahexaneoic acids of phosphadidylethanolamine (PE) and phosphatidylicholine (PC) of erythrocyte membranes were measured by high performance liquid chromatography (HPLC), plasma EFA pattern by gas liquid chromatography, non-esterified fatty acids (NEFA) by enzymatic assay. HPLC results are expressed as a percentage of PE or PC molecular species.

20 obese children were studied before and after weight loss (weight/size^2 = 32.1 ± 3.8 vs 26.6 ± 2.5kg/m^2, p = .001) and compared to 5 controls. Weight loss leads to a decrease in NEFA (0.84 ± 0.25 vs 0.46 ± 0.19 mmol/l, p = .001), and increased delta 6 desaturase activity (.024 ± .011 vs .038 ±. 014, p = .0001), and plasma long chain FA content (20 : 3 n-6, 20 : 4 n-6, 20 : 5 n-3, p = .001). Membrane PE 16 : 0/20 : 4 n-6 is low in cases vs control before weight loss (14.83 ± 1.67% vs 37.09 ± 6.54%, p = 0.0001) and does not turn to normal with weight loss. PC 16 : 0/20 : 4 n-6 raises above control values after weight loss (19.27 ± 2.09 vs 15.42 ± 3.62%, p = .006). Delta 6 desaturase activity is negatively correlated with 18 : 2 n-6 PC (r= -.48, p < .05) and positively with 22 : 6 n-6 PC (r = +.8, p < .01) content before weight loss. Obesity significantly afters EFA metabolism in children. Weight loss leads to a significant but limited improvement.

PLASMA RETINOL AND TOCOPHEROL VALUES IN OBESE CHILDREN

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The metabolic and endocrinological disturbances of obesity may influence vitamin status. Subnormal vitamin A (retinol, RET) and E (tocopherol, TOCO) values were reported for obese adults (Eur J Clin Nutr 46: 803, 1993; J Int Med 234: 53, 1993). We are unaware of data on vitamin A and E values in obese children (OB).

Subjects and methods: Plasma RET and TOCO concentrations were measured with high performance liquid chromatography in 17 OB (10 boys and 7 girls, age: 13.9 ± 1.4 years, mean ± SD) and related to anthropometric parameters and plasma cholesterol (CHOL), triglyceride (TG) and basal immunoreactive insulin (IRI) concentrations.

Results: Mean body weights (BW) were 88.9 ± 21.7 kg, body heights (BH) 165 ± 10 cm, relative body weights (RBW) 165 ± 24%, body fat contents (BF) 39 ± 5% and lean body masses (LBM) 54.3 ± 13.5 kg. Plasma concentrations of CHOL, TG and IRI were 4.31 ± 0.62 mmol/l, 1.43 ± 0.45 mmol/l, and 17.2 ± 6.5 µU/ml, respectively. Plasma RET concentrations were 0.58 ± 0.19 µg/ml. Plasma alpha-TOCO, beta+gamma-TOCO and delta-TOCO concentrations were 7.98 ± 2,84, 0.68 ± 0.28 and 0.02 ± 0.01 µg/ml, respectively. Mean RET, alpha-TOCO and alpha-TOCO/CHOL (1.83 ± 0.61 µg/µmol) values were close to those reported for healthy children aged 12-13 years (RET: 0.42 [0.24 - 0.66] and alpha-TOCO: 8.80 [4.8 - 13.1] µg/ml, alpha-TOCO/CHOL:2.06 [1.42 - 2.60] µg/µmol, median [range], n = 77, (Int J Epidemiol 22: 237, 1993). Neither plasma RET, nor TOCO concentrations were related to the age of OB. Plasma RET concentrations were positively related to BW, BH and LBM, whereas significant inverse correlations were seen between plasma alpha-TOCO concentrations and BF and IRI (Table). Alpha-TOCO referred to CHOL or CHOL CHOL + TG (1.39 ± 0.49 µg/µmol) were also inversely related to IRI ($r = -0.59$, $P < 0.05$ and $r=-0.57$, $P<0.05$).

TABLE

Linear correlation coefficients (r) (*P<0.05, **P<0.01).

	BW	BH	BF	LBM	IRI
Retinol	0.60*	0.65**	-0.22	0.68**	-0.08
alpha-TOCO	-0.18	0.08	-0.49*	-0.03	-0.53*

Conclusions: 1. Mean retinol and alpha-tocopherol concentrations in obese children were comparable with those in healthy children. 2. Plasma retinol concentrations were positively related to body size, particularly LBM, but not to body fat. In contrast, plasma alpha-tocopherol concentrations were not related to body size, but were inversely related to body fat. 3. Plasma alpha-tocopherol concentrations were inversely related to IRI (a parameter indicative of glucose intolerance), even after correction for lipidaemia. 4. Since oxidation of low-density-lipoproteins is causally involved in atherogenesis (Lancet 339: 1183, 1992) and preceeded by the loss of endogenous antioxidants (Am J Clin Nutr 53: 314, 1991), obese children with pronounced obesity (high BF) andor/or advanced glucose intolerance (high IRI) may be at risk of subnormal antioxidant protection by tocopherols.

ROLE OF THE CRITERION USED TO DEFINE FETAL HYPERTROPHY IN RELATION WITH THE RISK OF OBESITY AT AGE 6

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Fetal hypertrophy is a recognized factor of childhood obesity. We have examined how the definition of fetal hypertrophy influences this relation. The weight and size of French children are routinely recorded from birth in a so-called health book. The data of 9261 children in the Lyon area have been collected and studied in 1989 as they entered primary school. 6.2% of these children had a weight two standard deviations above the size-related average of the reference French population. This limit has been chosen as the criterion for obesity at age 6. Fetal hypertrophy was associated with a higher risk of later obesity, which varied according to the definition chosen. In act, the relative risk ranged from 1.70 to 2.14, according to whether the criterion of fetal hypertrophy was a single weight limit (gestational age and sex taken into account)(common attitude) or additional constitutional features were also considered. The definition that also takes the mother's size and weight and the birth order into account had a stronger predictive power for obesity, than the "common attitude".

Conclusion: 1. among the definitions tested, the new definition is associated with the highest risk of obesity; 2. children who were regarded as hypertrophic on the basis of the common attitude and who were not selected according to this new definition do not present with a significantly increased risk of obesity.

CHANGE IN THE INCIDENCE OF CHILDHOOD OBESITY DURING THE LAST DECADE

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The aim of the present study was 1. to determine the prevalence of obesity in the town of Pécs, in 1993; 2. to relate these results to the incidence of obesity measured 10 years earlier, in 1983. Methods: anthropometric survey was carried out to determine the prevalence of obesity in a representative sample of 3529, 6-18 years old schoolchildren. Triceps skinfold above the 90th percentiles on a local standard was the criterion of obesity. To evaluate the change in the incidence of obesity between 1983 and 1993 the two results were compared.

Conclusion: the incidence of obesity among schoolchildren in the town of Pécs has increased during the last ten years.

REPORT ABOUT A TRAINING-EDUCATING-NURSING CENTRE OF OBESE CHILDREN IN THE FACULTY OF HEALTH SCIENCES IN BUDAPEST

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The Department of Medical Sciences was instituted on 1 July, 1994 in our Faculty. The Faculty of Health Sciences in multilateral, preparing programmes for a wide range of the paramedical professions (health visitors, physiotherapists, dieteticians, etc.). One of the planned programmes is a consultation for obese children. This consultation - as a complex health preserving, illness-preventing training-educating-nursing activity - is based on the speciality of the Faculty and serves this pedagogical purpose.

The consultation has a very good and fruitful relationship with the Hungarian Foundation for the Study of Obesity. Our poster demonstrates the program of the project and the expected favourable consequences. The incorporation of obesitology into the graduate and postgraduate education, as well as the edition of a textbook about obesitology are important future plans.

EXPERIENCES ON DIETARY TREATMENT OF CHILDREN WITH OVERWEIGHT (FATTY CAMPS)

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Nowadays obesity give us much trouble. The frequency of obesity is increasing, due to inadequate feeding and physical inactivity. In childhood nutritional habits can be influenced easier than in adults. Children do not suffer from the diseases that are considered to be the consequences of obesity such as coronary diseases, hypertension, type II diabetes, some types of cancer etc. Therefore, early weight reduction programs can prevent the late consequences.

Three camps were held in summer-time between 1987 and 1989. The conception was that the low calorie diet alone cannot result in lasting weight loss, but physical training, manual occupations, psychological treatment and education all together conduce to acquire a healthy lifestyle. The different specialists (dietetician, psychologist, gymnast, educationalist) worked in a team, and their group occupations were held like revolving stage. The diets contained 1200 calories, 12-18% proteins, 20-25% fat and 58-60% carbohydrates with no sugar added. The main meals consisted of vegetables, fruits and other high dietary fibre containing foodstuffs completed with meat, cold plates, milk products, fish, poultry and some soya products. Great emphasis was given to teach the children how to continue the diet at home, and show them as wide assortment of low calorie meals as it was possible during the two weeks of the camps. Children were given 5 meals a day in the same time every day. Courses were held on nutritional physiology, on different slimming diets, on cookery, on the main components of light meals for the children as well as for the parents during the family weekend.

One hundred and seven children from 9 to 16 years of age took part in our 3 camps. They had 2 to 31 kilograms overweight as calculated with the modified Broca index. During the two weeks 96% of them lost 0.5 to 8.5 kg. None of them gained weight. Analysing the nutritional habits of these children we found that the main causes of childhood obesity were the abundant feeding, the incorrect rhythm of meals, the physical inactivity, and some familial and psychological effects.

The success of the slimming program can be measured not only by the kilograms lost during the two-week camp, but by the effectiveness of the education which may result in decreasing obesity in the families of the children attending the Fatty Camps.

SELECTED PHYSICAL PARAMETERS OF CZECH OBESE CHILDREN AND CHANGES WHICH OCCURRED DURING THE REDUCTION PROGRAM

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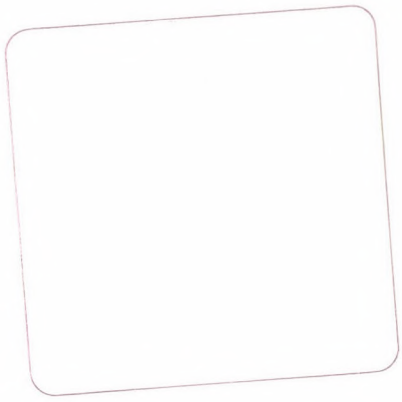
The development of body built and its changes in ontogenetic development of obese children differs from the normal population. To cover its development and the objective evaluation of obese children therapy primarily directed to body mass decrease the processing of data on body height and body mass of 3865 Czech obese boys and girls in age from 6 up to 16 years was conducted by the standard anthropometric technique of Martin and Saller. Body composition was determined by Matiegka's equations. The pair T-test was used as a criterion for the evaluation of the significance of a given measurement with respect to successfulness where a decrease of body mass was the main aim. On the basis of the pair T-test results we settled the order of importance of selected circumferential diameters and thickness' of skinfolds. Matiegka's equations for the Czech population are recommended to determine the components of body composition. For a more objective use the BMI index should be differentiated into body fat component and the lean body mass component.



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