ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

VOLUMEN XIX * 1978 * NO. 1

AKADÉMIAI KIADÓ. BUDAPEST

Acta paediat. Acad. Sci. hung.

ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

A MAGYAR TUDOMÁNYOS AKADÉMIA
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FŐSZERKESZTŐ

VÉGHELYI PÉTER

Az *Acta paediatrica Academiae Scientiarum hungaricae* angol, francia, német, és orosz nyelven közöl értekezéseket a gyermekgyógyászat és határterületei köréből. Megjelenik negyedévenként; 4 füzet képez egy kötetet.

Kéziratok az alábbi címre küldendők:

Acta paediatrica Academiae Scientiarum hungaricae
1083 Budapest, Bókay János u. 53.

A szerzők közleményük honoráriumán felül költségmentesen 100 db különlenyomatot kapnak.

Megrendelés belföldre: *Akadémiai Kiadó* (1363 Budapest Pf. 24. Bankszámla: 215 11 448), a külföld számára *Kultura* (1389 Budapest 62, P.O.B. 149, Bankszámla: 218 10990).

Editorial office	Rédaction	Редакция	Redaktion

H-1083 Budapest, Bókay J. u. 53.

Annual subscription (one volume)	Abonnement par an (un volume)	Подписная цена за год (один том)	Jahresabonnement (ein Band)

$ 36.00

H-1389 Budapest 62, P.O.B. 149, KULTURA

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1978

ACTA PAEDIATRICA

VOLUME XIX

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 1–7 (1978)

Mucocutaneous lymph node syndrome: Three cases observed in Hungary

By

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Received 21st October, 1976

Three patients are reported whose symptoms were very similar to those described in mucocutaneous lymph node syndrome, a disease prevalent in Japan. In one case the disease was complicated by otomastoiditis which prolonged the course and reactivated the symptoms. In the other two cases recovery was uneventful. No epidemiological relation could be demonstrated among the cases. Prednisolone was administered to two patients with immediate antifebrile effect.

The mucocutaneous lymph node syndrome (MLNS) is a disease with fever and rash common in Japan. The disease was first reported by Kawasaki in 1967 [8] and a few years later Kawasaki et al. [9] published a detailed study of more than 6000 cases and summarized the clinical and epidemiological features. Since then some cases have been observed in the USA and Canada [2, 4, 7, 11, 12, 13, 14, 15] and in Europe [1, 16].

The main symptoms are: fever lasting 1 to 2 weeks not responding to antibiotics; conjunctivitis; dryness, reddening and fissuring of lips; reddening and prominence of tongue papillae ("strawberry tongue"); reddening of palms and soles with indurative oedema of hands and feet, followed by membranaceous desquamation from the fingertips; polymorphous exanthem on the trunk and non-suppurative cervical lymphadenitis. Other symptoms are arthralgia or arthritis, diarrhoea, albuminuria, pyuria, aseptic meningitis and mild jaundice. The most severe change is coronary thrombarteritis leading to aneurysms and thrombotic occlusion with myocardial infarction or ischaemia [1, 17].

The most consistent laboratory abnormalities found in MLNS are elevated ESR, leukocytosis with a shift to the left, slight anaemia, positive C-reactive protein, negative antistreptolysin-O titre, increased alpha$_2$-globulin level.

The aetiology of MLNS is unknown. Rickettsia-like bodies have been found in biopsy and autopsy specimens from patients with MLNS [3, 5, 6].

We present three cases from Hungary, the symptoms of which were very similar to those described for MLNS.

Case Reports

Case 1. S. P., a one-year-old girl, was admitted on February 17, 1976, with symptoms suggesting measles. Formerly, apart from a mild facial eczema, she had been healthy and developed well. She had been vaccinated with BCG, DPT and live polio vaccine types 1 and 3 without any inconvenience. Six days before admission she had developed fever up to 39°C and a rash. The rash was maculopapular; it was first seen on the trunk and by next day it had spread all over the body. The baby then developed coryza with sanguino-purulent discharge, her lips became swollen, dry and fissured. The doctor diagnosed measles and gave her penicillin and antipyretics. On the third day the exanthem faded but the fever persisted. On the 4th day the exanthem reappeared on the face and the eyelids, the hands and feet became swollen.

On admission the baby had a toxic appearance. Her eyelids were red and swollen, there was a maculopapular rash on the face. The lips were red, swollen and fissured. Some slightly swollen cervical lymph nodes were palpable. The hands and feet were also swollen with erythema on the palms and soles. A fusiform swelling of the fingers with a lilac-red coloured skin over the joints could be observed (Fig. 1). There was a dry eczema on the legs. Oral and pharyngeal mucosa were reddened, the papillae of the tongue were red and prominent.

Physical examination revealed no abnormality over the chest. The abdomen was moderately swollen, the liver was palpable 1 cm below the right costal margin. No neurological sign could be observed. Rectal temperature was 38.7°C, the chest X-ray was normal. ESR on admission was 8 mm/hr, WBC 5800 with 6% band forms, 36% polynuclears and 56% lymphocytes. Haemoglobin, 9.8 g/dl; haematocrit, 30%. The urine was negative. A throat swab culture revealed no pathogenic bacteria, the blood culture was sterile.

In view of the fever and the sanguino-purulent discharge from the nose, erythromycin therapy was started. The rash, swelling of hands, feet and digits were thought to be of allergic nature and though penicillin was suspected as allergen, penicillin skin tests gave negative results.

During the next two weeks the child had fever persisting between 38 and 39°C. At the end of the first week of hospitalization the ESR increased to 110 mm/hr, and the child developed leukocytosis and anaemia (WBC 17,200, with 21% immature and 58% mature polynuclears, 3% eosinophils, 13% lymphocytes and 5% monocytes; haemoglobin, 8.0 g/dl). The abdominal swelling increased and she had diarrhoea for a few days. Otherwise no pain or mass could be found in the abdomen and the abdominal X-rays were normal.

The fever, leukocytosis and increased ESR suggested a septicaemia of unknown origin and ampicillin, cephalosporin and gentamycin therapy was introduced. The symptoms persisted unchanged for another week and even a swelling of the left shoulder appeared. Repeated urine examinations, X-rays of chest and bones, examination of paranasal sinuses, ears, and pyelography revealed no septic focus and the repeated blood culture was also sterile. Other laboratory findings were, serum protein, 6.0 g/dl; albumin, 3.24 g/dl; alpha$_1$-globulin, 0.36 g/dl; alpha$_2$-globulin, 1.2 g/dl; beta-globulin, 0.84 g/dl; gamma-globulin, 0.36 g/dl; IgG, 579 mg/dl; IgM, 108 mg/dl; IgA, 40 mg/dl. Serum electrolytes, urea nitrogen, alkaline phosphatase, transaminases, aldolase, bilirubin were normal, the latex test was negative. LE phenomenon was also negative. Measles and rubella HAI-titre was repeatedly negative. Adenovirus C'BR: 1 : 4, later 1 : 128; antistreptolysin-O titre repeatedly 86 Todd units. C-reactive protein, 1 : 70, later 1 : 400. Repeated throat swabs, urine, stool and blood cultures were negative. The ECG showed no abnormality.

By the end of the second week of hospitalization the symptoms decreased, the general condition improved, and a membranaceous desquamation from the fingertips started. The ESR decreased to 70 mm/hr. In the third week the fever rose again, the mucous membrane, skin and joint symptoms reappeared. At that time otoscopy revealed a purulent otitis media and repeated ear X-rays pointed to mastoiditis. On the 23rd day of hospitalization, mastoidectomy was performed; it revealed a purulent process but no pathogenic bacteria could be isolated from the pus. In spite of the mastoidectomy the fever and the symptoms persisted for another week and the ESR increased again to 100 mm/hr. The fever ceased in the 5th week, and the other symptoms gradually disappeared by the end of the 7th week. By that time the baby's appetite improved, she gained weight, ESR and blood counts became normal. She was discharged after two months hospitalization.

When the child was seen two months later, she was asymptomatic and the laboratory findings were normal.

Case 2. R. M., a previously healthy 16-month-old girl, was admitted with the diagnosis of scarlet fever on January 14, 1977. She had developed fever and rash two days before admission and had been given penicillin.

On admission the child had a scarlatiniform exanthem and sore throat, therefore penicillin therapy was continued. The fever persisted and a maculopapular rash appeared on the arms and legs; the palms and soles were reddened. An allergy to penicillin was supposed and penicillin therapy was discontinued. During the following days the child became distressed. Dryness, reddening and fissuring of the lips, diffuse reddening of oral and pharyngeal mucosa, a "strawberry tongue", conjunctivitis, mild coryza and moderate enlargement of the cervical lymph nodes developed. She had loose stools. No other organic changes could be demonstrated by physical, X-ray or ECG examination.

Laboratory findings were, ESR, 88 mm/hr; RBC, 3,400,000; haemoglobin, 9.2 g/dl; WBC, 10,200, with 8% band forms, 68% polynuclears, 22% lymphocytes and 2% monocytes. Antistreptolysin-O, 143 Todd units; C-reactive protein, 1 : 1120; serum protein, 6.8 g/dl; albumin, 3.2 g/dl; alpha$_1$-globulin, 0.4 g/dl; alpha$_2$-globulin, 1.08 g/dl; beta-globulin, 0.68 g/dl; gamma-globulin, 1.42 g/dl. Serum electrolytes, urea nitrogen, bilirubin, alkaline phosphatase, transaminases, aldolase were normal. A mild proteinuria and leukocytes in the urinary sediment were found. No pathogenic bacteria were isolated from the throat, stools and urine. Blood culture was negative. Attempts to isolate respiratory or enteroviruses remained unsuccessful. No antibodies to measles, rubella and adenoviruses were found in repeated serum samples.

In spite of antibiotics (gentamycin, tetracycline, erythromycin) an intermittent fever persisted for 17 days while the rash and the mucous membrane signs gradually disappeared and a membranaceous desquamation from the fingertips was noticed. From the 15th day of hospitalization prednisolone therapy was introduced whereupon the child became afebrile within two days. ESR and blood counts became normal within ten days. After six weeks of hospitalization the child was discharged symptom-free. A month later she was healthy and well.

Case 3. K. T., a previously healthy 6-year-old girl, was admitted with the diagnosis of scarlet fever on May 16, 1977. She had a four-day history of fever, sore throat, bilateral painful enlargement of cervical lymph nodes, conjunctivitis and polymorphous exanthems all over the body. She had been treated with penicillin.

On admission she had fever, but her general condition was good. On the arms and legs a polymorphous while on the trunk a scarlatiniform exanthem was seen. The bulbar conjunctivae were congested; the lips were swollen, dry, red and fissured (Fig. 2). The oropharyngeal mucosa was

also congested with some small ulcerations. The tongue papillae were red and swollen. A few moderately enlarged cervical lymph nodes were palpable. Oedema of hands and feet with diffuse erythema of the palms and soles was observed.

An innocent systolic murmur was heard in the II—III costal space along the left sternal border. No abnormality was found over the lungs by physical examination. The liver and the spleen were palpable 1 cm below the costal margins. X-rays of chest and ECG showed normal conditions.

Laboratory findings were, ESR, 120 mm/hr; RBC, 3,500,000; haemoglobin, 10.8 g/dl; WBC, 10,000 with 14% band forms, 60% polynuclears, 22% lymphocytes, 2% monocytes and 2% eosinophils. Antistreptolysin-O titre, 84 Todd units. On admission C-reactive protein, 1 : 200, one week later, 1 : 400. Serum protein, 6.3 g/dl; albumin, 3.4 g/dl; alpha$_1$-globulin, 0.44 g/dl; alpha$_2$-globulin, 1.02g/dl; beta-globulin, 0.38 g/dl; gamma-globulin, 1.02 g/dl; IgG, 1731 mg/dl; IgM, 216 mg/dl; IgA, 223 mg/dl. Urine was negative. Serum electrolytes, urea nitrogen, bilirubin, alkaline phosphatase, transaminases, aldolase were normal. No pathogenic bacteria were found in the throat-swab, stool and urine cultures. From repeated blood cultures *Streptococcus viridans* was isolated on one occasion. No respiratory or enteroviruses could be isolated. On admission the measles HAI titre was 1 : 80, rubella HAI titre 1 : 256; adenovirus C'BR, 1 : 16. These titres were unchanged when examined three weeks later.

After admission, penicillin therapy was continued, but the fever persisted. During the second week of hospitalization a mild diarrhoea developed. Since the clinical picture and the laboratory findings showed all the characteristics of MLNS, the patient was given prednisolone from the 6th to 12th days of hospitalization. On the second day of prednisolone therapy the child became afebrile and remained so until discharge. The mucocutaneous signs gradually disappeared and a membranaceous desquamation from the fingertips developed at the end of the second week (Fig. 3). The child was discharged symptom-free after one month of hospitalization.

Discussion

The MLNS has no definitive diagnostic criteria. The diagnosis is based on a special combination of symptoms which separately or in other combinations can be found in other diseases as well. The usual symptoms and their frequency given by Kawasaki et al. [9] are presented in Table I; it also shows which of the symptoms were present in our cases. In Case 1 only two of the principal symptoms were lacking. These two were conjunctivitis and polymorphous exanthems on the trunk, but both had been noticed by the doctor at home, who diagnosed the symptoms as measles. The rash in some MLNS cases has in fact been described as a morbilliform one [13]. The repeatedly negative measles HAI-tests, however, excluded the diagnosis of measles. In Case 2 only the indurative oedema of hands and feet was lacking, while in Case 3 all the principal symptoms were present.

In addition to the principal symptoms arthritis was present in one, leukocyturia and proteinuria in one and diarrhoea in all the three cases.

All the characteristic laboratory abnormalities could be found in the cases presented, thus increased ESR, leukocytosis, slight anaemia, negative antistreptolysin-O titre,

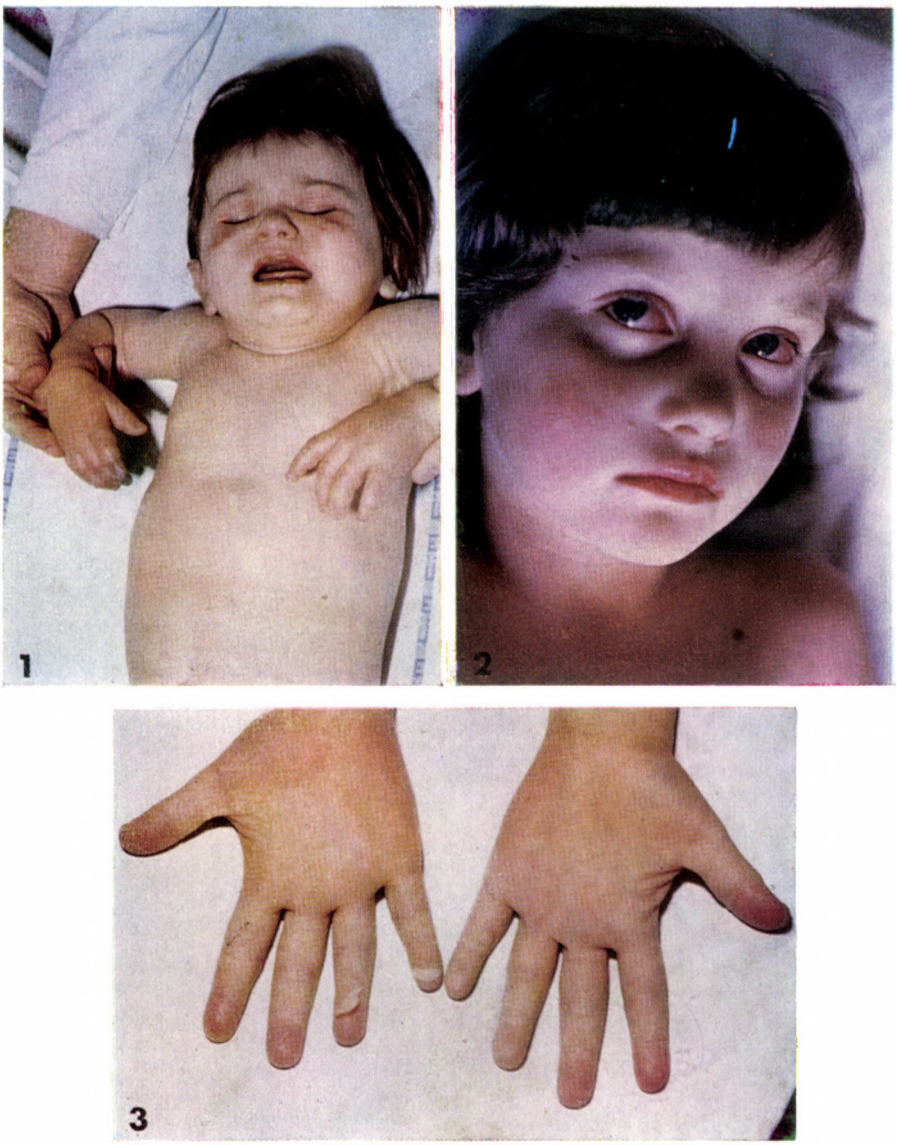

FIG. 1. Case 1. Red and swollen eyelids; maculopapular rash on face; swollen and fissured lips; oedema of hands; fusiform swelling of fingers with lilac-red coloured skin over the joints

FIG. 2. Case 3. Congested conjunctivae; diffuse erythema on face; swollen and fissured lips

FIG. 3. Case 3. Membranaceous desquamation from the fingertips

TABLE I

Symptoms of MLNS according to Kawasaki [9] and their presence in our cases

Symptoms	Frequency, per cent	Presence in case		
		1	2	3
Principal symptoms				
Fever lasting from one to two weeks and not responding to antibiotics	95	+	+	+
Bilateral congestion of ocular conjunctivae	88	±	+	+
Changes in lips and oral cavity				
Dryness, redness and fissuring of lips	90	+	+	+
Protuberance of tongue papillae	77	+	+	+
Diffuse reddening of oral and pharyngeal mucosa	90	+	+	+
Changes in peripheral extremities				
Reddening of palms and soles	88	+	+	+
Indurative oedema	76	+	−	+
Membranaceous desquamation from fingertips	94	+	+	+
Polymorphous exanthem on trunk without vesicles or crusts	92	±	+	+
Acute nonpurulent swelling of cervical lymph nodes 1.5 cm or more in diameter	75	+	+	+
Other significant symptoms or findings				
Carditis, especially myocarditis and pericarditis		−	−	−
Diarrhoea		+	+	+
Arthralgia or arthritis		+	−	−
Proteinuria and increase of leukocytes in urine sediment		−	+	−
Changes in blood tests				
Leukocytosis with shift to the left		+	+	+
Slight decrease in erythrocyte and haemoglobin levels		+	+	+
Increased ESR		+	+	+
Increased $alpha_2$-globulin		+	+	+
Positive CRP		+	+	+
Negative ASLO		+	+	+
Changes observed occasionally				
Aseptic meningitis		−	−	−
Mild jaundice or slight increase of serum transaminase		−	−	-

positive C-reactive protein, increased $alpha_2$-globulin level; though in Case 1 some of them (increased ESR, leukocytosis) developed only during the second week of the disease.

We believe that in our cases the combination of symptoms and signs closely resembled those described in MLNS. Other diseases with similar symptoms such as scarlet fever, sepsis, juvenile rheumatoid arthritis, Stevens—Johnson syndrome, periarteritis nodosa could be excluded on the basis of the absence of special symptoms and the differing clinical course [9, 13].

In Case 1, the course of the illness differed somewhat from that outlined

in the literature. In the cases reported from Japan the disease lasted 2 to 3 weeks, but our patient became symptom-free only by the end of the 7th week. The other difference in this case was the otomastoiditis which has not been mentioned among the symptoms of MLNS. The protracted course may have depended on the otomastoiditis that developed in the third week and in fact we observed that the symptoms which by the end of the second week had improved reappeared when the fever again became higher. The question arises whether the disease observed was a sepsis associated with an initially latent mastoiditis. Though many symptoms of MLNS occur in sepsis, the observed combination is not characteristic of sepsis. Looking at the course of the disease, otomastoiditis seemed rather a complication of MLNS.

Two of our aetiological tests gave a positive result. In Case 1 the adenovirus complement-binding titre increased from 1 : 4 to 1 : 128 during the disease. Though this points to an adenoviral infection, we do not believe in its aetiological role. On the one hand, there is no similar observation in the literature, and on the other, if an adenoviral infection had an aetiological role in MLNS, it is highly improbable that MLNS would be so rare considering the frequency of adenoviral infections. In all probability it was a concomitant infection in our Case. In case 3, *Streptococcus viridans* was isolated from one of the blood cultures. Since no similar symptoms caused by *Streptococcus viridans* had been reported, we believe that it was an accidental finding without any aetiological importance.

There had been no contact among our cases. Cases 1 and 2 originated from two villages far from each other and from Budapest. Case 3 came from Budapest. There was a one-year interval between admission of the first and the second case and a three-month interval between the second and the third case. No similar disease in the patients' families was reported.

As to the therapy, prednisolone was administered to two of our patients. In accordance with the literary data [9] it had an immediate antifebrile effect. Though the aetiology of MLNS is unknown, the beneficial effect of prednisolone and the observation that the serum IgE level increases during the disease [10] suggest that allergy may have an important role in the pathogenesis of MLNS.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 9–16 (1978)

D-penicillamine treatment of hyperbilirubinaemia in preterm infants

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Received 5th April, 1977

In 41 hyperbilirubinaemic infants born before the 38th gestational week intravenous D-penicillamine treatment was applied in doses of 300 mg/kg body weight/day. As compared to 41 infants of identical gestational age and treated under identical circumstances, penicillamine ensured favourable results, especially in babies born after the 33rd gestational week. Some undesirable side-effects have to be taken into account, but they are infrequent if the indication is correct.

Elevation of the conjugated bilirubin level is a frequent occurrence in preterm infants. Both its incidence and level are the higher the shorter was the gestational time [10, 11]. The histotoxicity of bilirubin depends, however, also on the degree of simultaneous hypoxia and acidosis [3]. These factors should, therefore, be taken into account when indicating an exchange transfusion.

In order to state its optimum time, we have prepared a new chart (Fig. 1). In contrast to the well-known in-

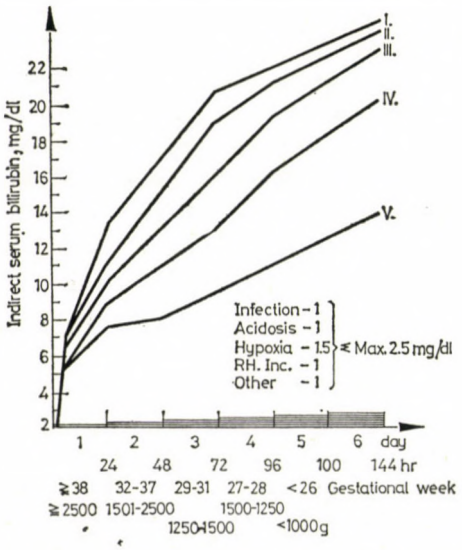

Fig. 1. Indication of exchange transfusion in preterm infants according to gestational age and pathologic conditions

dication charts [1, 9] we have taken into consideration in our chart the baby's gestational age in the first place and only secondarily its body weight. Then, in addition to hypoxia and acidosis, also infection, hypoglycaemia, hypocalcaemia, apnoea and the history of pregnancy were accepted as factors contributing to the severeness of jaundice and promoting central nervous system damage. Finally, with non-immunized infants delivered after the 36th week or of large body weight, the indication of exchange transfusion was put at a higher serum bilirubin level than in the other tables.

In addition to exchange transfusion, during the last two decades numerous procedures have been applied in the treatment of neonatal hyperbilirubinaemia. Among these, polyvinylpyrrolidone, agar-agar and corticosteroids failed to fulfil expectations. In term newborns barbiturate treatment is applied with satisfactory results but due to its depressive effect, it is contraindicated in somnolent, hypoxic premature infants [3]. Albumin infusions have been given extensively but by themselves they are satisfactory only exceptionally. The most widely used method today is phototherapy and its effect is unanimously considered excellent. In the treatment of preterm infants and chiefly those of very low body weight and short gestational age this therapy too meets with a number of problems [4, 8]. These experiences have justified the introduction of new methods. One of them is D-penicillamine treatment.

D-penicillamine (PA) or dimethylcysteine is a metabolite of penicillin excreted in urine. Similarly as numerous compounds containing a sulphhydryl group, the compound possesses a specific biological activity; this manifests itself chelate-formation, inhibition of collagen synthesis and a cytostatic effect [12]. As it binds metals, it ensured excellent results in Wilson's disease [14].

In the treatment of hyperbilirubinaemia of the newborn, Lakatos et al. [5, 6, 7, 13] were the first to apply PA orally and/or intravenously in a dose of 300 to 400 mg/kg body weight/day. According to their hypothesis, newborn infants have a low serum copper and coeruloplasmin level, whereas large copper reserves are stored in the liver. These are mobilized by PA and bilirubin is transformed into some non-toxic biliverdin-like compound, probably copper [5].

A pharmacological effect can be expected only from D-penicillamine, the L- and racemic modifications are ineffective. Among the three, D-PA is the least toxic. As the toxicity is dose- and time-dependent, in the course of the short neonatal treatment severe side-effects are exceptional [5, 6, 7]. If, however, PA is administered for a prolonged time, urticaria, albuminuria, leuko- and thrombocytopenia, even pemphigus foliaceus may occur [12].

Based on these considerations we have studied the effect of PA in the treatment of hyperbilirubinaemia in preterm infants.

Materials and Methods

The material included 82 preterm infants. Patients below 1000 g birth weight were excluded from the series. From April 1, 1975 to March 31, 1976, the hyperbilirubinaemic preterm infants were randomized: those born on even days received phototherapy and 5% glucose solution, with electrolytes when necessary. Those born on uneven days received PA in addition. Otherwise, the two groups were identical concerning body weight, gestational age and feeding methods as well as occurrence of infections, hypoxia or acidosis. Gestational age was estimated according to Dubowitz et al. [2].

PA (Metalcaptase®, Knoll, Ludwigshafen, FRG) was applied intravenously in doses of 300 mg/kg body weight, t. i. d., injected with a glass syringe very slowly. Of the 41 treated infants, PA treatment was started on the first day in 2, on the second in 4, on the third in 15, on the fourth in 13, on the fifth in 7, and on the ninth day in 1. For statistical evaluation of results, the chi square test was used.

Results

The efficiency of the methods applied in the treatment of hyperbilirubinaemia is indicated by the decrease in the number of exchange transfusions and of the serum bilirubin level.

Among the 41 children not treated with PA an exchange transfusion had to be performed in 19; among

Table I

Exchange transfusions performed in patients treated or not treated with D-penicillamine, according to birth weight

Birth weight, g	Not treated		Treated	
	number of patients	number of exchange transfusions	number of patients	number of exchange transfusions
1001—1250	5	4 (in 1 case 2×)	4	2
1251—1500	3	1	1	—
1501—1750	7	5 (in 1 case 2×)	6	2
1751—2000	6	1	8	3 (in 2 cases 2×)
2001—2250	12	4	13	4
2251—2500	7	4	6	2
2501—	1	—	3	—
Total	41	19	41	13

those treated with PA, in 13 babies. The indication was set on the basis of our chart (Fig. 1) in every case. From the aspect of exchange transfusions, statistical evaluation revealed no significant global difference between the two groups. Thus, the efficiency of PA in all the treated babies cannot be accepted.

Subsequently, we examined which are the factors that influence the effect of the drug and which among

TABLE II

Exchange transfusions performed in patients treated or not treated with D-penicillamine, according to gestational age

Gestational age (weeks)	Not treated		Treated	
	number of patients	number of exchange transfusions	number of patients	number of exchange transfusions
28	2	1	—	—
29	1	—	2	—
30	2	1	6	3
31	4	2*	3	2*
32	4	2	6	5*
28—32 Total	13	6	17	10
33	4	1	4	1
34	9	6*	5	—
35	9	5	5	—
36	5	1	6	1
37	1	—	2	—
38	—	—	2	1
33—38 Total	28	13	24	3
28—38 Total	41	19	41	13

* in 1 case 2×

them could be considered important. The results demonstrated that taking the body weight groups into consideration, no positive conclusions could be drawn from the number of the necessary exchange transfusions (Table I). On the other hand, if the efficiency of PA was examined as a function of gestational age, the favourable clinical experience was supported by statistical evaluation (Table II). Its result proved with 99% probability ($p < 0.01$) the efficiency of the drug in children born in the 33rd gestational week or later.

The distribution of the patients according to blood groups and Rh incompatibility is demonstrated in Table III.

To study by a similar method the connection between gestational age and the frequency of exchange transfusions in the PA treated infants, three age groups were formed: from

TABLE III

Exchange transfusions performed in patients treated or not treated with D-penicillamine, according to blood group incompatibility

Blood group incompatibility	Not treated		Treated	
	number of patients	number of exchange transfusions	number of patients	number of exchange transfusions
None	35	15	33	11*
ABO	2	1*	2	1
Rh	4	3*	3	1*
ABO + Rh	—	—	3	—
Total	41	19	41	13

* in 1 case 2×

TABLE IV

Exchange transfusions performed in the period 1974 to 1975, according to birth weight

Birth weight (g)	1974	1975
>2500	25	20
<2500	84	77
Total	109	97

28 to 32 weeks, from 33 to 35 weeks, and beyond 36 weeks. In this case the positive connection has again been proven.

Case Reports

Case 1. J. V., the fourth child from the 6th pregnancy (after 3 healthy children and 2 artificial abortions) was born at 36 gestational weeks with 2700 g body weight. No isoimmunization was present. The child was admitted on the 4th day of life, when the serum bilirubin level was 17.8 mg/dl. PA was prescribed. On the 5th day the bilirubin level was 21 mg/dl, a border value for exchange transfusion. Taking into consideration the satisfactory general condition of the newborn, the slow elevation of the bilirubin level and the gestational age, no blood exchange was performed. On the 6th day the level was 16.0, on the 7th day, 14.2 mg/dl, and on the following days the decrease remained even. The infant was discharged on the 12th day. Thus, in this case the exchange transfusion could be avoided by PA administration and recovery was undisturbed.

Case 2. T. H., the second child from 3 pregnancies (1 healthy child, 1 artificial abortion), was born at 38 gestational weeks with 2800 g body weight. He was admitted with Rh incompatibility and cardiorespiratory insufficiency. The direct Coombs test was negative. On due treatment the circulation had normalized, but on the 4th day of life the serum bilirubin level was 18 mg/dl. Then PA administration was introduced. On the 5th day, the bilirubin level was 20.3 mg/dl, on the 6th day, 15.8 mg/dl, then after a gradual decrease it became normal and the infant could be discharged at the age of 16 days.

In this seriously ill patient an exchange transfusion would have involved more risk than PA treatment, which was effective despite the additional pathological conditions. This case illustrates that after the 34th gestational week the efficiency of PA treatment is not affected by associated diseases.

Case 3. J. W., the first living child from 3 pregnancies (2 artificial abortions) was born at 36 gestational weeks with 2400 g body weight. On admission A-O incompatibility and respiratory distress were observed; the latter condition responded well to treatment. On the 3rd day the serum bilirubin level was 19.3 mg/dl, on the 6th day, 23.8 mg/dl, when an exchange transfusion had to be performed. This decreased the bilirubin level to 9.2 mg/dl. Then PA was given, but despite this therapy the bilirubin level was 17.1 mg/dl on the 8th day and decreased only on the 14th day to 9.5 mg/dl.

In this case it seems difficult to evaluate how far PA was effective, but it probably prevented the necessity of a second exchange transfusion.

Case 4. A. B., the first living child from the 6th pregnancy (3 spontaneous abortions, 2 stillborn babies) was delivered in the 31st gestational week with 2000 g body weight. No blood group incompatibility was present. Jaundice manifested itself on the first day of life, therefore PA, phototherapy and albumin infusion were applied. Despite this treatment the bilirubinaemia increased to 26.6 mg/dl by the 5th day when an exchange transfusion was performed. This resulted in a decrease of serum bilirubin to 11.0 mg/dl, but on the next day the level rose to 14.6 mg/dl. Despite continuous PA administration serum bilirubin on the 7th day reached the critical level of 19.2 mg/dl, the baby was faint and could not be fed and a second exchange transfusion had to be performed. The further course was uneventful.

In this infant of low gestational age, PA treatment started in the first 24 hours was ineffective.

Case 5. C. S., the first living child from 7 pregnancies (3 artificial, 2 spontaneous abortions, 1 dead preterm infant) was born at 32 weeks with 2200 g weight. No blood-

group incompatibility was present. The immediate postnatal period was undisturbed. PA treatment was started on the 4th day of life, when the bilirubin level was 19.0 mg/dl. On the 6th day it was 21.6, on the 7th 15.8 mg/dl, on the 8th day, 8.6 mg/dl. From the second day of PA administration anorexia, occasional vomiting, loss of weight were noted. These symptoms persisted even 4 days after discontinuing PA treatment and the baby's body weight decreased to 2000 g. He started to gain weight in the 4th week, and regained its birth weight only at 5 weeks. After 35 days hospitalization the infant was discharged.

The protracted course of the disease may have been connected with the PA treatment and the question seems justified whether an exchange transfusion performed on the 5th or 6th day of hospitalization would not have considerably shortened the course.

Discussion

The favourable effect of PA on hyperbilirubinaemia of term newborns was shown by Lakatos et al. [5, 6, 7]. In our preterm babies the results were not so uniformly satisfactory, due perhaps to the peculiarities of such patients. In our experience, the efficiency of PA depends on the gestational age rather than on birth weight and good results can only be expected from PA after the 33rd gestational week. The borderline seems to be between the 33rd and 34th weeks, when the baby's organism is sufficiently mature for utilizing PA.

Another aspect is the undesirable side-effects of PA. They are transitory during the usually short course of treatment which seldom lasts more than 5 to 6 days. Among our 41 cases, in 4 low-weight newborns, during and sometimes after PA treatment anorexia, vomiting, loss of weight and lagging development were observed. The severity of side-effects was directly proportional to the duration of treatment and inversely to the gestational age. Under the effect of PA, the serum bilirubin level may display a dramatic decrease in a number of cases, but at the same time recovery may considerably be prolonged owing to the side-effects.

Taking all these into consideration, PA represents an efficient drug in the therapy of hyperbilirubinaemia of newborns and especially in babies born after the 33rd week of gestation. Its combination with phototherapy is recommended and such treatment will often help to avoid exchange transfusions. Estimation of the serum bilirubin level is of course a precondition of successful treatment.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 17—26 (1978)

Perinatal asphyxia and jaundice in newborn infants*

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Received 27th May, 1977

The serum bilirubin concentration was studied in 114 full term and 199 preterm babies suffering from either perinatal asphyxia or idiopathic indirect hyperbilirubinaemia, in order to establish the effect of asphyxia on the serum bilirubin level. Infants with any other disease causing non-physiologic jaundice were excluded. It was found that perinatal asphyxia *per se* does not exaggerate hyperbilirubinaemia either in full term or in preterm babies. Weight loss correlated significantly with the peak bilirubin concentration in all groups of patients. This would suggest the possible role of feeding and hydration in the genesis of hyperbilirubinaemia.

The role of perinatal asphyxia (hypoxaemia, hypercarbia and acidosis) has well been established in increasing the liability to bilirubin encephalopathy via various mechanisms [1, 2, 4, 5, 10]. This means that newborn infants suffering from asphyctic insults are at greater risk of kernicterus at similar or even lower serum bilirubin concentrations than those with no asphyxia [3, 9, 12]. The situation is worse and more complicated if neonatal diseases due to, or associated with, perinatal asphyxia *per se* increase the hyperbilirubinaemia. This has been stressed on clinical grounds [9, 11] but some theoretical considerations also seem to provide a basis for the assumption. Destruction of erythrocytes in haematomas, the effect of delayed oral feeding and partial starvation [13], disturbances of hepatic circulation due to asphyxia and the prolonged persistence of fetal circulation can all be causative factors in hyperbilirubinaemia of newborn babies with perinatal asphyxia [6, 7, 8].

In the present paper changes of serum bilirubin concentration in full term and preterm infants suffering from disorders of cardiorespiratory adaptation due to asphyxia were compared with that of babies with idiopathic indirect hyperbilirubinaemia without asphyxia. The purpose of the comparison was to study the effect of asphyxia on the time course of bilirubin concentration. In principle, jaundice of infants with perinatal asphyxia should have been compared with that of infants without asphyxia. As perinatal asphyxia is not necessarily associated with

*Supported by the Scientific Research Council, Hungarian Ministry of Health, (3—23—0502—04—1/M)

non-physiological jaundice, it seemed reasonable to use as a control newborn infants with non-physiologic icterus but without asphyxia.

Patients and Methods

The clinical course in newborn infants with "non-physiologic" jaundice was studied retrospectively, over a period of three years (1972—1974). Jaundice was considered physiologic if serum bilirubin concentration did not exceed 12 mg/dl in full term and 15 mg/dl in preterm infants, furthermore if it dropped below 7 mg/dl by the postnatal age of one week in full term and two weeks in preterm babies. A further selection was made according to whether they had had perinatal asphyxia or had only developed jaundice the cause of which could not be detected. Patients with haemolytic disease due to blood group incompatibility, perinatal infection, cephalhaematoma and/or multiplex skin bruises, and congenital malformations were excluded. Perinatal asphyxia was assumed to have occurred if hyaline membrane disease, type II respiratory distress syndrome or postasphyctic syndrome could be diagnosed on admission on the basis of physical examination, X-rays, and blood pH status.

A total of 199 preterm and 114 full term babies were selected; 22 full term and 89 preterm infants had perinatal asphyxia, the rest in both groups had jaundice of unknown origin. Sex distribution of the patients and their relevant clinical data are shown in Tables I and II.

Serum bilirubin estimations were done by the Jendrassik—Grof method when it was needed on clinical grounds. The first estimation was usually performed at the appearance of jaundice and subsequent determinations were then decided upon depending on the bilirubin concentration measured and the clinical course and signs. If two or more estimations were performed on a day, the higher value was taken into

Table I

Number, sex distribution, data of obstetric history of newborn infants and number of exchange transfusions performed

	Perinatal asphyxia		Idiopathic neonatal hyperbilirubinaemia	
	Full term	Preterm	Full term	Preterm
Number of infants	22	89	92	110
males	12	62	52	51
females	10	27	40	59
Pregnancy				
normal	11	40	67	84
pathological	11	49	25	26
Delivery				
spontaneous	16	71	77	98
Caesarean section	3	7	8	3
breech presentation	3	11	7	9
Exchange transfusion	4	30	19	25

TABLE II

Clinical data of the infants studied

	No.	Mean	SD	SE	Range
Maternal age (year)					
FT–PA	22	24.8	5.5	1.1	18–36
FT–INIH	88	24.7	6.0	0.6	17–43
PR–PA	89	26.1	5.5	0.5	17–44
PR–INIH	101	24.0	4.9	0.4	17–40
Pregnancy					
FT–PA	22	2.2	1.9	0.4	1– 8
FT–INIH	92	2.6	1.6	0.1	1– 7
PR–PA	89	3.6	2.7	0.2	1–14
PR–INIH	106	3.0	2.8	0.2	1–17
Delivery					
FT–PA	22	1.5	0.8	0.1	1– 3
FT–INIH	92	1.9	1.2	0.1	1– 7
PR–PA	89	2.1	1.3	0.1	1– 7
PR–INIH	106	2.0	1.6	0.1	1– 9
Birth weight (g)					
FT–PA	22	2846	459	97	1850–3700
FT–INIH	92	2972	460	62	1700–4250
PR–PA	89	1830	543	57	810–3100
PR–INIH	110	1977	512	49	1000–3050
Gestational age (week)					
FT–PA	22	38.5	1.5	0.3	37–42
FT–INIH	92	39.1	1.7	0.1	37–44
PR–PA	89	32.2	2.4	0.2	27–36
PR–INIH	110	33.2	1.9	0.1	27–36

Abbreviations: FT = full term infants; PR = preterm infants; PA = perinatal asphyxia; INIH = idiopathic neonatal indirect hyperbilirubinaemia.

account. The total number of patients and of bilirubin estimations performed in each group are shown in Table III. Averaged bilirubin curves were then plotted and compared. Correlation analysis was done between the following parameter-pairs within each group of infants: (1) gestational age—maximum serum bilirubin concentration; (2) gestational age—postnatal age at the time of peak bilirubin concentration; (3) gestational age—rate of increase in bilirubin level; (4) birth weight—maximum serum bilirubin concentration; (5) birth weight—postnatal age at the time of maximum bilirubin concentration; (6) birth weight—rate of increase in bilirubin level; (7) maximum bilirubin concentration—weight deficit in percentage of birth weight; (8) maximum bilirubin concentration—rate of increase in bilirubin concentration. In addition, in 24 preterm infants with perinatal as-

TABLE III

Plasma bilirubin concentration (mg/dl) of full term and preterm infants with perinatal asphyxia or idiopathic indirect hyperbilirubnaemia

Postnatal age	No.	Mean	SD	SE	Range
0—2 days					
FT–PA	18	8.2	2.3	0.5	3.8—12.9
FT–INIH	40	9.3	3.8	0.6	2.4—15.3
PR–PA	79	9.1	3.1	0.3	2.5—17.1
PR–INIH	48	8.5	2.8	0.4	2.3—13.8
3 days					
FT–PA	18	12.2	2.9	0.6	5.8—17.5
FT–INIH	43	14.4	4.3	0.6	5.8—24.6
PR–PA	74	14.3	3.5	0.4	8.6—24.5
PR–INIH	64	13.0	3.7	0.4	6.4—26.9
4 days					
FT–PA	17	15.7	4.7	1.1	8.5—28.0
FT–INIH	52	16.5	4.0	0.5	7.6—25.0
PR–PA	71	15.8	3.6	0.4	9.9—26.0
PR–INIH	84	15.2	3.5	0.3	6.4—25.2
5 days					
FT–PA	17	14.7	4.5	1.1	4.8—24.0
FT–INIH	52	16.7	4.7	0.6	7.3—28.5
PR–PA	45	16.2	2.6	0.3	11.4—23.9
PR–INIH	81	16.8	3.5	0.3	10.0—26.0
6 days					
FT–PA	14	13.1	5.8	1.5	7.5—25.0
FT–INIH	47	16.2	4.9	0.7	5.7—27.9
PR–PA	33	15.0	3.9	0.6	5.4—22.1
PR–INIH	67	15.5	3.1	0.3	10.0—24.7
7—8 days					
FT–PA	19	14.1	4.1	0.9	8.6—21.3
FT–INIH	39	13.8	4.4	0.7	2.4—20.8
PR–PA	47	15.6	3.8	0.5	9.9—26.2
PR–INIH	57	14.8	3.9	0.5	5.9—20.6
9—10 days					
FT–PA	12	7.1	3.3	0.9	1.3—10.5
FT–INIH	23	10.0	4.2	0.8	2.2—17.8
PR–PA	20	10.5	4.1	0.9	2.9—18.2
PR–INIH	17	13.5	3.9	0.9	5.1—18.5

TABLE III (cont.)

Postnatal age	No.	Mean	SD	SE	Range
11—14 days					
FT–PA	9	4.9	3.1	1.0	1.6— 9.4
FT–INIH	34	7.7	3.4	0.5	1.0—12.2
PR–PA	38	6.4	2.9	0.4	1.5—12.5
PR–INIH	42	7.0	3.6	0.5	1.2—16.7
15—21 days					
FT–PA	10	1.8	0.8	0.2	0.9— 3.4
FT–INIH	22	5.2	3.2	0.7	0.8—11.4
PR–PA	22	4.5	2.3	0.5	1.7— 8.9
PR–INIH	26	4.3	2.9	0.5	0.9—12.7

Abbreviations: FT = full term infants; PR = preterm infants; PA = perinatal asphyxia; INIH = idiopathic neonatal indirect hyperbilirubinaemia.

phyxia correlation analysis could be done between arterial pH, base excess and pCO_2 measured within two hours after birth and maximum serum bilirubin concentration observed later.

In all babies, prevention and treatment of jaundice were done according to generally accepted principles. Newborn infants who needed exchange transfusion were excluded from further study after the procedure. Full term infants received formula feeding while preterm babies were fed human milk. Oral or tube feeding was initiated as soon as possible. Patients with perinatal asphyxia could be fed orally considerably later than those with no asphyxia. No reliable data on prepartal and *sub partu* drug treatment of mothers could be obtained in most of the cases. Many patiens were admitted at various postnatal ages from various district hospitals.

Of the 89 preterm infants with perinatal asphyxia, 25 died. Necropsy revealed hyaline membrane disease in 13, and primary atelectasis in 7 cases. Pulmonary changes were associated with intraventricular haemorrhage in 10 patients. In 5 infants the only postmortem finding was intracerebral haemorrhage without pulmonary disorders. All full term infants survived and so did the preterm babies with idiopathic jaundice.

RESULTS

The changes in serum bilirubin concentration were closely similar in full term infants either with perinatal asphyxia or idiopathic indirect hyperbilirubinaemia during the first postnatal week (Fig. 1, Table III). After that time in babies with perinatal asphyxia a more precipitated fall in bilirubin concentration could be observed and the level remained significantly lower ($p < 0.05—0.01$) later on, too. No statistically significant difference was found in the peak bilirubin concentration between full term infants suffering from perinatal asphyxia and those with idiopathic jaundice. In both groups the bilirubin peak occurred on the fifth

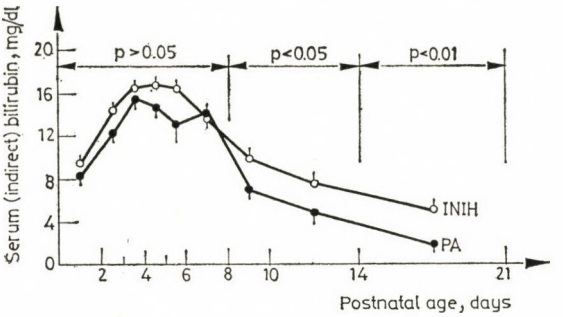

FIG. 1. Serum bilirubin concentration in full term infants suffering from perinatal asphyxia (●—●) or idiopathic indirect hyperbilirubinaemia (○—○)

TABLE IV

Maximum serum bilirubin concentration, postnatal age, weight loss and rate of bilirubin concentration in the infants studied

	No.	Mean	SD	SE	Range
Maximal serum bilirubin concentration (mg/dl)					
FT–PA	22	17.5	4.3	0.9	13.3 – 28.0
FT–INIH	92	18.0	4.2	0.4	12.7 – 28.5
PR–PA	89	17.9	3.0	0.3	12.2 – 26.6
PR–INIH	110	18.1	3.4	0.3	11.7 – 26.0
Postnatal age (days)					
FT–PA	22	4.9	1.4	0.3	3 – 7
FT–INIH	92	4.5	1.3	0.1	2 – 9
PR–PA	89	4.3	1.2	0.1	3 – 7
PR–INIH	110	5.1	1.3	0.1	3 – 10
Weight loss (in percentage of birth weight)					
FT–PA	22	4.5	2.6	0.5	0.0 – 10.9
FT–INIH	92	3.7	2.5	0.2	0.0 – 12.1
PR–PA	89	4.1	2.7	0.2	0.0 – 10.2
PR–INIH	110	4.5	2.3	0.2	0.0 – 10.6
Rate of increase (mg/dl 24 hours)					
FT–PA	13	2.1	1.6	0.4	0.5 – 6.5
FT–INIH	39	2.4	1.6	0.2	0.5 – 6.2
PR–PA	60	2.2	2.1	0.2	0.9 – 9.3
PR–INIH	59	2.4	1.3	0.1	0.5 – 5.1

Abbreviations: FT = full term infants; PR = preterm infants; PA = perinatal asphyxia; INIH = idiopathic neonatal indirect hyperbilirubinaemia.

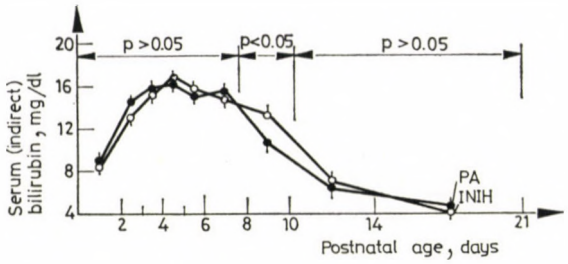

FIG. 2. Serum bilirubin concentration in preterm infants suffering from perinatal asphyxia (●—●) or idiopathic indirect hyperbilirubinaemia (○—○)

postnatal day, when the weight deficit was similar and no difference was observed in the rate of increase in bilirubin concentration either (Table IV).

Averaged bilirubin curves of preterm infants with perinatal asphyxia or idiopathic icterus are shown in Fig. 2. The only difference between the two groups was that in babies with perinatal asphyxia bilirubin concentration was significantly ($p < 0.05$) lower on the 9th and 10th postnatal days but not before or after that time. Maximum serum bilirubin concentration, postnatal age and weight loss at the time of highest bilirubin level, furthermore the rate of increase in bilirubin level were all practically the same in the preterm infants with perinatal asphyxia and those with idiopathic hyperbilirubinaemia (Table IV). To find out if asphyxia was more serious when associated with more pronounced hyperbilirubinaemia, we compared the peak bilirubin concentrations observed in preterm infants who had died, with that of the survivors (Table V). Despite the fact that gestational age and birth weight of those who died were considerably lower than of the survivors (30.6 *vs* 32.8 weeks and 1405 *vs* 1995 g) no difference in peak bilirubin concentration was detected. Postnatal age at the time of the peak bilirubin level was, however, similar in the two groups, and death occurred on the sixth (5.4 ± 0.5) day of life on the average. The assumption that no relationship exists between the severity of asphyxia and hyperbilirubinaemia was further supported by the finding that no significant correlation could be found between peak bilirubin concentration and arterial pH, base excess and pCO_2 measured within two hours after birth in 24 preterm infants. On the other hand, a significantly positive correlation was found between the peak serum bilirubin concentration and weight loss in both groups of full term (perinatal asphyxia: $r = 0.682$, $p < 0.001$; idiopathic jaundice: $r = 0.227$, $p < 0.05$) and preterm infants (perinatal asphyxia: $r = 0.3600$, $p < 0.01$; idiopathic jaundice: $r = 0.293$, $p < 0.01$). In full term and preterm infants with idiopathic hyperbilirubinaemia a significantly positive correlation

TABLE V

Gestational age, birth weight, maximum serum bilirubin concentration, postnatal age at time of bilirubin peak and weight loss (in percentage of birth weight) of preterm infants who died and of survivors

	No.	Mean	SD	SE	Range
Gestational age, week					
died	25	30.6	2.5	0.5	27—35
survived	64	32.8	2.1	0.2	27—36
all	89	32.2	2.4	0.2	27—36
Birth weight, g					
died	25	1405	489	97	780—2900
survived	64	1995	535	66	810—3100
all	89	1830	543	57	780—3100
Maximum serum bilirubin, mg/dl					
died	25	17.2	3.1	0.6	12.5—26.0
survived	64	18.2	2.9	0.3	13.3—26.6
all	89	17.9	3.0	0.3	12.5—26.6
Postnatal age, days					
died	25	4.1	1.2	0.2	2—7
survived	64	4.4	1.2	0.1	2—7
all	89	4.3	1.2	0.1	3—7
Weight loss, per cent					
died	25	4.2	2.7	0.5	0.0—11.0
survived	64	4.1	2.6	0.3	0.0—11.8
all	89	4.1	2.7	0.2	0.0—11.8

was found between the peak bilirubin concentration and the rate of increase in bilirubin level ($r = 0.428$, $p < 0.01$ and $r = 0.458$, $p < 0.001$, respectively). Gestational age and birth weight correlated significantly with the peak bilirubin concentration in preterm babies with perinatal asphyxia ($r = 0.214$, $p < 0.05$ and $r = = 0.335$, $p < 0.01$). No statistically significant correlations were found in any of the other parameter-pairs tested.

DISCUSSION

Kernicterus is known to threaten hypoxaemic and acidotic newborn infants at a considerably lower bilirubin concentration than babies of similar gestational age, birth weight, postnatal age and bilirubin concentration but with normal blood gas and pH status. As an additional risk factor, an exaggerated increase of bilirubinaemia has also been suggested [6, 7, 8, 9, 11, 13].

The present results, however, contradict that assumption. Figs 1 and 2 show that the time course of jaundice was remarkably similar in full term babies with perinatal asphyxia or idiopathic hyperbilirubinaemia just like in preterm infants with perinatal asphyxia or idiopathic icterus at least during the first postnatal week. After that time the bilirubin level fell more rapidly in full term babies with perinatal asphyxia than in the controls and remained at a significantly lower level. Changes in bilirubin concentration differed much less in preterm infants of the two groups. The only difference was that in babies with perinatal asphyxia the bilirubin level was significantly lower at the age of 9—10 days, but not before or after that time.

The natural course of the bilirubin concentration could not be observed and followed in the patients studied. Since many of the therapeutic measures applied may have influenced the bilirubin concentration, conclusions should be drawn with extreme caution. All what can be said is that the hyperbilirubinaemia of full term and preterm infants with perinatal asphyxia was not more severe as regards both its peak and duration than that of control babies.

It is known that like "physiologic" jaundice, hyperbilirubinaemia of newborn infants with perinatal asphyxia develops unpredictably. Data in Table III show that the severity of jaundice varies widely in asphyctic newborn infants. Furthermore, no correlation was found between peak bilirubin concentration and arterial pH, base excess and pCO_2 measured within two hours after birth in 24 preterm infants. For all these reasons infants with indirect hyperbilirubinaemia of unknown aetiology but without asphyxia have been selected for control instead of babies with perinatal asphyxia but without jaundice.

The cause of hyperbilirubinaemia of newborn infants either with perinatal asphyxia or idiopathic indirect hyperbilirubinaemia is still an enigma. The role of numerous factors has been assumed, some of which may well be common. The finding that weight loss correlated significantly with peak bilirubin concentration in both groups of full term and preterm infants suggests the possible role of nutrition, feeding and hydration. A mass of evidence has accumulated in the relevant literature proving the partial role of these factors in the genesis of neonatal hyperbilirubinaemia, but some more explanations are needed to settle the problem. The positive correlation between gestational age, birth weight and peak bilirubin concentration in preterm infants with asphyxia reflects very likely the therapeutic principle that the tolerance of a high bilirubin concentration increases with the advance of maturity.

In conclusion, it is suggested that hyperbilirubinaemia of newborn infants with perinatal asphyxia varies widely once it has developed. The similar time course of hyperbilirubinaemia in asphyctic babies and in those without asphyxia but with jaundice

of unknown aetiology suggests at least in part a common mechanism independent of the pathophysiological changes due to asphyxia. In consequence, if hyperbilirubinaemia develops, all efforts should be made to clarify its aetiology just like in any other case of non-physiologic jaundice. Since weight loss and dehydration seem to contribute to the increased bilirubin level, they should be prevented by any means.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 27–30 (1978)

Serum non-esterified fatty acid in undernourished children during recovery

By

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Received 27th May, 1977

Seventy-one children from five to sixty months of age with protein-energy malnutrition were classified into compensated and incompensated groups. Serum non-esterified fatty acid concentration was determined in every child at admission and in a control group of thirty-one well-nourished children. Analysis of variance revealed significant differences between the three groups. Twenty of the undernourished patients were subjected to follow-up study at weekly intervals. Ten out of the twenty recovered immediately, showing significantly decreasing serum non-esterified fatty acid concentrations in the weekly intervals. The other ten did not present any definite pattern of behaviour.

The metabolic aspects of protein-energy malnutrition (PEM) have been studied widely, mainly those related to protein metabolism [2, 12, 13], while studies of lipid metabolism are few and contradictory [5, 7].

The purpose of this study was to investigate the serum non-esterified fatty acid (NEFA) concentration in undernourished children before and during recovery.

Patients and Methods

Seventy-one children with PEM have been studied. The diagnostic criterion of undernutrition was based on Waterlow's classification [11], and the values obtained for height and weight were referred to the Harvard Standards [10]. At admission the stage of malnutrition was determined and the patients were grouped into two categories: incompensated and compensated, according to the presence or absence of hydroelectrolytic disturbances [1, 4], hypothermia and hypoglycaemia.

A venous blood sample was taken from each child and after centrifugation serum NEFA was determined according to Dole and Meinertz [3].

The children were fed a diet of 460 KJ per kg of expected body weight for actual height, composed of 20% protein, 55% carbohydrate and 25% fats. Routine treatment included intravenous hydration and antibiotics whenever necessary.

The same investigation was carried out in a control group of the same age.

Analysis of variance (ANPVA) for a completely randomized design and superposition of intervals was the statistical method employed [6].

Twenty of the undernourished children were subjected to a study of the behaviour of their serum NEFA concentration. Venous blood samples were taken from these

children on admission and subsequently on the 8th, 15th and 22nd days. Ten of them showed signs of recovery immediately after hospitalization and therefore were grouped as undernourished in recovery. Another ten patients failed to show clinical improvement and were classified as undernourished without recovery. Recovery was considered if the signs and symptoms of incompensation disappeared and weight gain took place.

The statistical design employed for the follow-up studies was an ANOVA for randomized blocks to each group of ten children. Processing of data was carried out with a CID 201-B computer from the Department of Applied Mathematics and Computation, CNIC, University of Havana.

Results

Figure 1 shows the serum NEFA values for the two groups of undernourished children and for the matched control group.

The ANOVA for group comparison among compensated and uncompensated undernourished children and the control group gave a value of $F = 67{,}893$ which was significant statistically ($p < 0.001$).

The follow-up of NEFA concentrations performed in ten undernourished children during recovery (Fig. 2) showed a tendency to decrease and the ANOVA for randomized blocks gave $F = 18{,}288$ which revealed that there were significant differences in the mean NEFA values obtained at admission and on the 15th and 22nd days, respectively, as well as those obtained on days 8 and 22. All the significant differences were $p < 0.01$.

In the unrecovered group, NEFA concentrations did not exhibit any definite pattern of behaviour because in most of them intercurrent episodes of infection have affected the lipolytic activity.

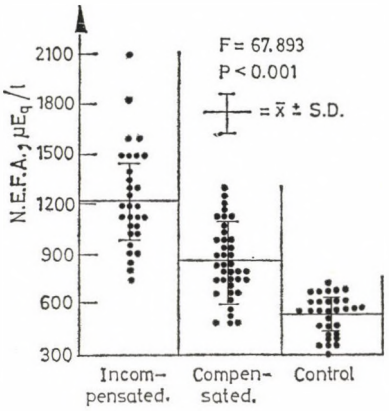

Fig. 1. NEFA concentrations in incompensated and compensated undernourished children and in a control group

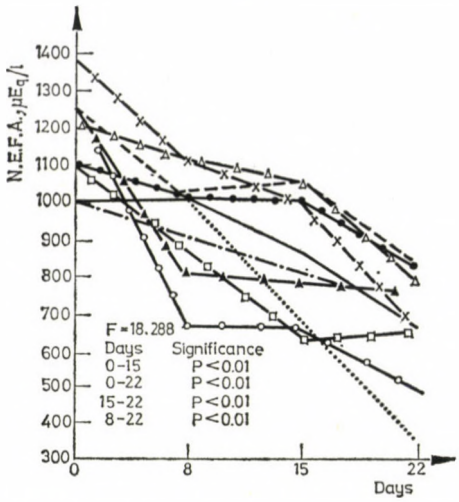

FIG. 2. Changes in NEFA concentrations during recovery in undernourished children

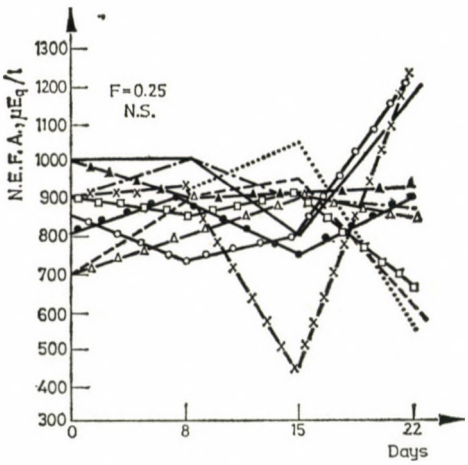

FIG. 3. Changes in NEFA concentrations during treatment in non-recovered undernourished children

DISCUSSION

Taylor [8], in follow-up studies of eight kwashiorkor children showed that the total fatty acid level rose considerably during the first 20 days of treatment and fell to control levels only by the 30th day. We considered the high figures for NEFA concentrations detected in the sera of undernourished children as evidence of an increased lipolytic activity conditioned by two main situations: the general stress of PEM [9] and the necessity of energy reserve mobilization.

The decreasing tendency of NEFA concentrations found in the follow-up studies of the undernourished children

during recovery pointed to the progressive adaptation taking place during this period. On the other hand, children who did not recover immediately, showed no uniformity in NEFA concentrations and the results obtained did not reveal any differences during the period of study.

Taking into account these findings, estimation of serum NEFA seems to be a useful index of the degree of metabolic inadaptation in protein energy malnutrition as its values are high during the incompensated stage and are modified precociously when a complication occurs, e. g. in the case of an infection. Finally, the rate of decrease of serum NEFA level will help to assess the patient's recovery.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 31—34 (1978)

Dermatoglyphic features in diabetes mellitus

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Received 1st June, 1977,

Dermatoglyphic features of 290 children and 180 adults with diabetes mellitus were investigated. W_D occurred significantly more frequently on the fingers, and pattern intensity was low in certain interdigital areas in these patients. A high TRC value was more frequent in both girls and boys with diabetes mellitus than in the controls.

The hereditary character of diabetes mellitus has been proven but opinions differ as to its mode of inheritance. Both dominant and recessive heredity have been suspected but the multifactorial origin seems to have the greatest probability. Since the clinical picture of juvenile and adult type diabetes mellitus shows differences, the dermatoglyphic features have been investigated in both types.

Methods

Examinations were carried out in 290 diabetic children and 180 adults. The disease had manifested itself between 1—15 and 20—75 years of age. The control group consisted of 1000 children 8—18 years of age. Evaluation was carried out according to Cummins and Midlo [2] as well as Penrose and Loesch [11].

Results

Fingers

The mean TRC value did not significantly differ in juvenile diabetes from that found in adult type diabetes (Table I).

The distribution of TRC in both sexes was different from the control.

Table I

Mean TRC value found in juvenile and adult type diabetes

	Control	Type	
		Juvenile	Adult
Female	124.3±44.1	129.8±47.4	124.1±45.5
Male	137.5±44.0	144.2±48.6	137.4±47.2

High values for TRC (>190 in girls and >200 in boys) were significantly more frequent than in the controls. Such differences were not found in the adult diabetics (Figs 1, 2) in agreement with our previous observations [1]. The frequency of W_D was higher on the fingers of diabetic patients than of the controls. Significant differences were found on the first finger on the left side in girls ($p < 0.01$) and the first finger on the right side in boys ($p < 0.001$), and on the first, third and fifth fingers ($p < 0.05$) of the right hand of adult males. Adult females did not show any differences in respect to the frequency of the finger-pattern (Tables II, III).

Palm

Exit of the main lines and position of the axial triradius did not display any significant difference between the diabetic and control groups. The pattern intensity was significantly lower in the 3rd interdigital

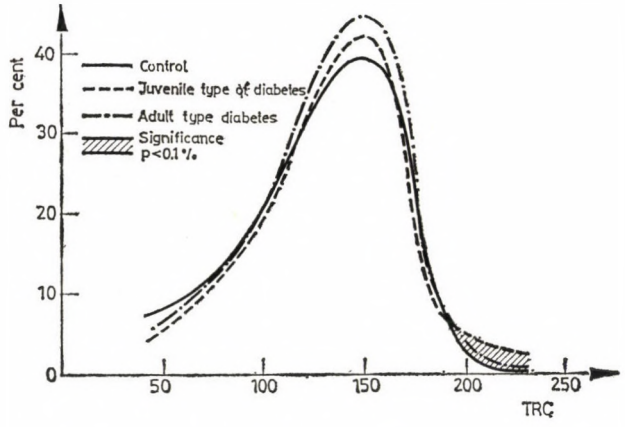

FIG. 1

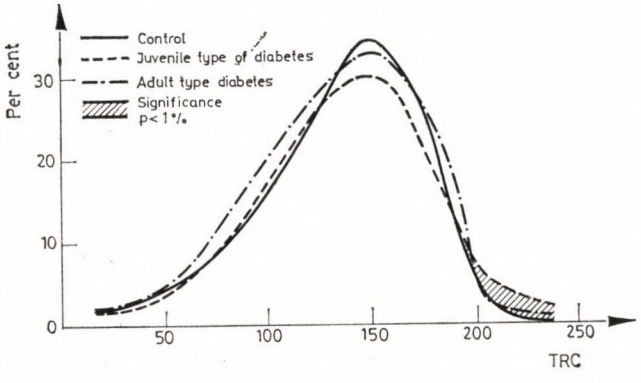

FIG. 2

TABLE II

Double loop on fingers

	Right hand					Left hand				
	1	2	3	4	5	1	2	3	4	5
Girls	−	−	−	−	−	++	−	−	−	−
Boys	+++	−	−	−	−	−	−	−	−	−
Adult females	−	−	−	−	−	−	−	−	−	−
Adult males	+	−	+++	−	+++	−	−	−	−	−

+ $p < 5\%$; ++ $p < 1\%$; +++ $p < 0.1\%$

TABLE III

Palm patterns

	Right hand					Left hand				
	th	II	III	IV	hyth RH	th	II	III	IV	hyth RH
Girls	−	−	−	−	−	−	−	++	−	−
Boys	−	−	−	−	−	−	−	++	−	−
Adult females	−	−	−	−	−	−	−	−	−	+
Adult males	−	−	+++	−	−	−	−	−	−	+

+ $p < 5\%$; ++ $p < 1\%$; +++ $p < 0.1\%$

area on the left side in both sexes with juvenile diabetes and on the right side in males with diabetes of adult type. Females and males with adult type diabetes showed less L_R in the hypothenar region on the left side.

DISCUSSION

Characteristic dermatoglyphic patterns are well-known to occur in chromosome aberrations [9]. The extreme breadth of hands of patients with 21-trisomy involves many special features. Fetal oedema in XO chromosome aberration is associated with a high total ridge count whereas a low TRC value is found in X-polysomy [7].

Dermatoglyphics were investigated in diabetes mellitus by Verbov [13] and Knusmann [8]. In contrast to our results, Verbov did not find any differences in TRC, while the frequency of whorls was lower in his diabetic material than in the control population of Holt [5]. In Knusmann's patients the value for TRC did not differ from the control [8]. Whorls and arches were more frequent on the fingers, while the pattern was significantly less frequent in the 3rd interdigital area and on

the thenar of females than in the control groups; such differences did not appear in the males. Verbov examined the dermatoglyphic features of patients whose diabetes had manifested between 20—40 years of age. In Knusmann's material juvenile type and adult type diabetics were not differentiated. In view of these differences our results could not be compared to those of the above quoted authors.

The dermatoglyphic features, especially TRC, are inherited multifactorially. Beside the genetical determination it must be taken into consideration that the hydrodynamic conditions of the amniotic fluid and teratogenic damages may affect the formation of finger and palm ridges.

Also, in subjects with Turner, Klinefelter or Down syndrome, carbohydrate metabolism often tends toward the diabetic form [3, 6, 10] while fetopathies have a high frequency in diabetics.

From the above observations we may conclude that there are differences in dermatoglyphic features not only between diabetic children and adults, but also between female and male diabetics. The heredity of diabetes is not sex-linked, but its heredity is certainly influenced by sex, diabetes being more frequent among females than males [7]. On the other hand, there is no sex difference in juvenile type diabetes.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 35—40 (1978)

Familiäres Asplenie-Syndrom

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Eingegangen am 29. Mai 1977

Es wird über ein asplenisches Geschwisterpaar mit IVEMARK-Syndrom berichtet. Verwandtschaftsehen, Entwicklungsanomalien kamen in der Familie nicht vor. Beide neugeborene Mädchen hatten Dextrokardie, Cor biloculare, Truncus arteriosus communis, bilaterale dreilappige Lunge, symmetrische Leber und Asplenie, in einem der Kinder ließ sich außerdem ein partieller abdominaler Situs inversus feststellen. Die Heredität des Syndroms ist ungeklärt.

Bei Polysplenie findet man häufig, bei Asplenie dagegen fast immer irgendeine schwere Entwicklungsanomalie der übrigen Organe. Die Symptomatologie ist unter der Bezeichnung Asplenie-Polysplenie bzw. IVEMARK-Syndrom bekannt. Die charakteristische Symmetrieneigung der Eingeweiden kann für eine Persistenz des weniger differenzierten embryonellen Zustands aufgefaßt werden [1, 4, 13].

Das Leitsymptom des Krankheitsbildes, welches gleichzeitig auch die Prognose bestimmt, ist der angeborene Herzfehler. Die Entwicklungsanomalie betrifft meistens das Vorhof- und Kammerseptum, den atrioventrikulären Kanal und die Kono-Trunkus-Region. Das Herz befindet sich in etwa der Hälfte der Fälle auf der rechten Seite. Meistens findet man eine gemeinsame Kammer und häufig einen gemeinsamen Vorhof; nicht selten sieht man die Transposition der Großvenen oder den anomalen Verlauf der Zentralvenen. Die Leber ist mitunter symmetrisch, da der linke Lappen hypertrophisch ist. Der Magen befindet sich entweder auf der linken, oder auf der rechten Seite oder in der Mitte. Mesenterium commune sowie andere Darmanomalien gehören nicht unter die seltenen Erscheinungen [1, 2, 3, 4, 7, 8, 9, 13, 14, 15].

Das familiäre Vorkommen des Asplenie-Syndroms gilt als eine Seltenheit. In der einschlägigen Literatur fanden wir die Beschreibung von 6 Fällen: In 5 Familien litten je 2 Geschwister und in einer Familie 3 Geschwister an dieser Entwicklungsanomalie [6, 8, 9, 12].

FALLDARSTELLUNGEN

Fall Nr. 1. Ein aus erster Schwangerschaft stammendes 1974 geborenes

Mädchen. Bei der Mutter wurde im Laufe des ersten Schwangerschaftsmonats eine Magen-Röntgenuntersuchung durchgeführt (sie wußte nicht, daß sie schwanger ist). Ungestörte Gravidität und Entbindung. Das 3300 g wiegende Mädchen wurde am 2. Lebenstag wegen Zyanose auf unsere Abteilung aufgenommen. Aufnahmebefund: Symmetrische Leber, Dextrokardie; kein Geräusch über dem Herz. Thoraxröntgenuntersuchung: In der rechten Thoraxhälfte liegendes Herz, mit der Spitze nach rechts gerichtet; symmetrische Leber. Links lokalisierte Magenluftblase. EKG-Befund: Breiter QRS-Komplex, in den thorakalen Ableitungen rechts hohe, links niedrige positive R-Wellen. Nach paartägiger stationärer Behandlung starb das Neugeborene.

Sektionsbefund: Beiderseits aus 3 Lappen bestehende Lunge. Das Herz liegt größtenteils in der rechten Thoraxhälfte, seine Spitze ist nach rechts gerichtet. Der gemeinsame Vorhof besitzt zwei Aurikel, anstelle des Vorhofseptums befindet sich ein muskulärer Bündel, in dem gemeinsamen atrioventrikulären Kanal ist eine Bikuspidalklappe ersichtlich. Aus dem aus der stark trabekulierten, gemeinsamen Kammer ausgehenden Truncus arteriosus entstammt die A. pulmonalis, die sich verzweigt und die Lungen versorgt (Abb. 1). Regelmäßige Einmündung der Großvenen in den Vorhof. Wegen der Ver-

Abb. 1. Fall Nr. 1. Aus der gemeinsamen Kammer geht ein Truncus arteriosus aus. An der mit Pfeil markierten Stelle entspringt die A. pulmonalis

größerung des linken Lappens symmetrische Leber. Asplenie. Magen-Darmsystem: keine pathologische Abweichung.

Fall Nr. 2. Das zweite Kind des Ehepaars, wieder ein Mädchen, kam 2 Jahre später zur Welt. Diesmal erfuhr die Mutter während der Schwangerschaft keine schädigende Einwirkung, die Schwangerschaft und termingerechte Entbindung waren normal. Beim 3800 g wiegenden Neugeborenen waren Zyanose, Dextrokardie und symmetrische Leber zu beobachten. Thorax- und Bauchröntgenuntersuchung: In die rechte Thoraxhälfte gelagertes, mit der Spitze nach rechts gerichtetes Herz, symmetrische Leber und auf der rechten Seite liegender Magen (Abb. 2). EKG-Befund: dem Alter entsprechende Kurve. Ergebnis der aus dem peripheren Blut durchgeführten Chromosomenuntersuchung: 46 XX.

Sektionsbefund: Beiderseits dreilappige Lungen, in der rechten Thoraxhälfte liegendes Herz, mit der Spitze rechts. Auf dem rechten Vorhof zwei Aurikula, anstelle des Vorhofseptums ein bandartiges Bündel. Der Vorhof wird von der gemeinsamen Kammer durch eine Bikuspidalklappe abgetrennt. Die beiden Aa. pulmonales entspringen aus dem aus der Kammer ausgehenden Truncus arteriosus communis. Der Magen liegt rechts, das Duodenum links, der Pankreasschwanz ist nach rechts gezogen. Symmetrische Leber, Asplenie. Normallage von Dickdarm, Kolon und Zökum.

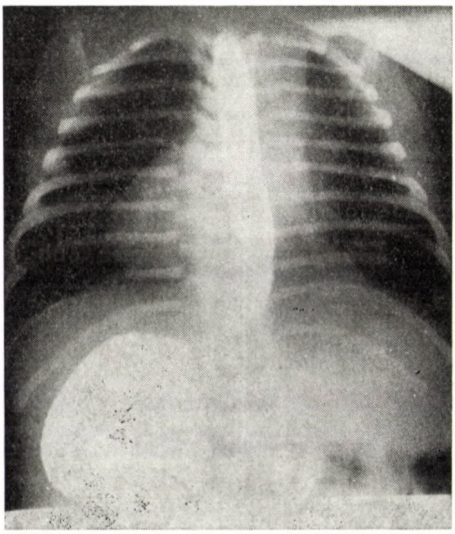

Abb. 2. Fall Nr. 2. Das Herz befindet sich in der rechten Thoraxhälfte, seine Spitze nach rechts gerichtet. Symmetrische Leber, rechts lokalisierter Magen

Die Eltern der beiden Patienten haben 13 gesunde Geschwister und diese 7 gesunde Kinder. Die 22 Ge-

schwisterkinder und ihre 15 Kinder sind ebenfalls gesund (Abb. 3). Verwandtschaftsehen bzw. Entwicklungsanomalien in der Familie kamen nur bei unseren beiden Patienten vor.

Besprechung

In der einschlägigen Literatur wurde über 6 Familien berichtet, dieselben Herzfehler — Cor biloculare, Truncus arteriosus communis und Dextrokardie — vorlagen; unterschiedlich war nur der abdominale Situs.

Der Hereditätsgang der Anomalie ist ungeklärt. Laut Rose und Mitarb. [8] beträgt die Inzidenz des Syndroms mindestens 1 : 40 000. Die dementsprechend gerechnete Geschwisterhäufigkeit würde im Falle polygener Vererbung 0,49% aus-

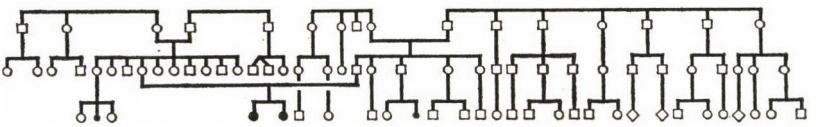

Abb. 3. Stammbaum der beiden Patientinnen. □ Mann; ○ Frau ◇; Geschlecht unbekannt; ● kranke Frau; • Spontanabort

in denen das Ivemark-Syndrom gehäuft vorkam [6, 8, 9, 12]. Außerdem wurden 3 Familien beschrieben, in denen die Geschwister, nebst dem Ivemark-Syndrom auch an einer anderen Entwicklungsanomalie des Herzens litten [5, 10, 11]. Asplenie und Polysplenie bzw. Asplenie und Milzhypoplasie kamen auch innerhalb einer Familie vor [12]. Da die Ätiologie der verschiedenen mit Milzveränderung einhergehenden Anomalien wahrscheinlich gemeinsam ist, wäre es berechtigt, letztere für die Varianten ein und desselben Syndroms zu betrachten. Das Geschlecht der Geschwister und die Herzlokalisation können identisch oder auch unterschiedlich sein [8, 9].

In unseren dargestellten Fällen handelte es sich um zwei Mädchen, bei denen gleichfalls Asplenie und machen, diese Prozentzahl macht dagegen im Material der Autoren 4,65% aus. Auf die in der Weltliteratur veröffentlichten rund 3—400 Fälle fallen 6 Geschwisterpaare (1,7—2,3%) und auch diese Zahl repräsentiert eine wesentlich höhere Inzidenz, als das im Falle einer polygenen Vererbung zu erwarten wäre. Unter den behandelten Fällen gab es nur einen, in dem die Eltern blutverwandte waren [10]: Das Ehepaar hatte fünf Kinder, das eine litt an Ivemark-Syndrom, bei einem anderen kam Situs inversus totalis mit offenem Ductus Botalli und Kammer-Septumdefekt vor, während bei zwei weiteren Geschwistern schwere extrakardiale Entwicklungsanomalien zu beobachten waren.

Das durchschnittliche Lebensalter der Mütter der an Ivemark-Syndrom

leidenden Kinder ist laut Literaturangaben nachweisbar höher als durchschnittlich [8]. Die Mutter unserer beiden Patienten war bei der Geburt ihres ersten Kindes 21 Jahre alt. Das Karyogramm des zweiten Mädchens fiel normal aus. Das Vorkommen entspricht nicht einmal der rezessiven Heredität. Soviel steht allerdings fest, daß das Syndrom durch eine zwischen dem 31. und 40. Schwangerschaftstag einwirkende fötale Noxe verursacht wird [8, 9]. Gerade in dieser Zeit erfolgte bei der Mutter unserer Patienten während ihrer ersten Schwangerschaft eine diagnostische Röntgenuntersuchung des Magen-Darmtrakts. Da jedoch in solchen Fällen die Strahlenbelastung wesentlich unter der schädigenden Dosis liegt, ist der Röntgenuntersuchung in der Entstehung der Entwicklungsanomalie keine Bedeutung beizumessen. In der Literatur fanden wir ebenfalls keine Angaben, aus denen auf die Rolle der ionisierenden Strahlung in der Entwicklung des IVEMARK-Syndroms zu folgern wäre.

ROSE und Mitarb. [8] veröffentlichten den Stammbaum von drei an IVEMARK-Syndrom leidenden Geschwisterpaaren. In allen drei Familien hatten die kranken Kinder mehrere gesunde Geschwister, in einer dieser Familien kamen nach zwei kranken drei gesunde Kinder auf die Welt.

Aufgrund der Literaturangaben empfahlen wir den Eltern unserer Patienten, sich zu einer neuen Schwangerschaft zu entschließen.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 41—44 (1978)

HLA B8 and BW15 antigens in diabetic children

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Received 10th July, 1977

The simultaneous occurrence of HLA B8 and BW15 and B8 antigens is significantly more frequent in diabetic children than in the general population. BW15 alone shows no significant difference but may be considered as a potentiating factor. The relative risk of the manifestation of diabetes is the highest when HLA B8 and BW15 occur simultaneously. In the nearest diabetic relatives of diabetic children the occurrence of B8 and B8 and/or BW15 antigens is significantly more frequent than in the diabetic child population.

It has been observed [1] that HLA B8 antigen is significantly more frequent in diabetic children than in the general population, while HLA BW15 antigen shows no significant difference. A study was therefore made on the frequency of simultaneous occurrence of HLA B8 and BW15 antigens in insulin dependent diabetic children and in the different age groups. Further examinations were carried out to clarify the incidence of these antigens in diabetics and their nearest insulin dependent relatives (parents, brothers and sisters) as according to data in the literature a close relation might exist between the onset of diabetes and the appearance of the HLA B8 and BW15 antigens [2, 3, 5].

Material and Method

A total of 254 diabetic patients whose diabetes was diagnosed before 15 years of age and 14 diabetic children and their nearest relatives were examined. HLA antigens were typified in 8 siblings, further in 6 children and their insulin dependent diabetic parents. HLA antigen determination was carried out by the lymphocyte cytotoxicity microtest [7]. The findings were grouped according to the age at the manifestation of diabetes. Data obtained from the National Blood Service, Budapest, were used as controls. Statistical analysis was carried out according to Woolf [8].

Results

B8 antigen, and B8 + BW15 jointly differed highly significantly from those found in the healthy population (Table I). In accordance with our previous findings, in the case of BW15 antigen there was no significant difference. Compared with the controls, the frequency of B8 + BW15 antigens differed significantly in all age groups (Table II). In age groups under 5—10 years the

TABLE I

Occurrence of HLA B8 and BW15 antigens in diabetic and control children

HLA antigens	Diabetic children		P	Controls		Relative risk
	No.	per cent		No.	per cent	
B8+	78	30.70	< 0.001	57	16.19	1.89
BW15+	23	9.05	< 0.5	28	7.95	1.13
B8 + BW15	29	11.41	< 0.001	3	0.85	13.39
n	254			352		

+The number of the B8+BW15 cases has been subtracted from the number of B8 and BW15 cases

TABLE II

Presence of HLA B8 and BW15 antigens and the onset of diabetes in children

HLA antigens	Age, years						Controls	
	1—5		6—10		11—15			
	No.	per cent	No.	per cent	No.	per cent	No.	per cent
B8+	28	31.11*	31	28.9*	19	33.3*	57	16.19
BW15+	9	10.0	8	7.4	6	10.5	28	7.9
B8 + BW15	11	12.2**	14	13.0**	4	7.0**	3	0.8
n	90		107		57		352	

+The number of the B8+BW15 cases has been subtracted from the number of B8 and BW15 cases

* $P < 0.01$
** $P < 0.001$

simultaneous occurrence of B8 and BW15 antigens was higher than in the age groups over 10 years, but the difference failed to reach significance. Table III shows the data for HLA antigens in the nearest relatives in families with diabetes accumulation where the simultaneous occurrence of B8 and B8 + BW15 antigens was significantly more frequent than in the diabetic child population. (14 pairs of relatives were examined; the case number was 26, because in the case of a brother and a father the examination was unsuccessful).

TABLE III

Occurrence of HLA antigens among nearest diabetic relatives

HLA antigens	Nearest diabetic relatives	Diabetic child population	P
B8 + B8 and BW15	19	107	< 0.01
B8 and/or BW15	22	130	< 0.01
n	26	254	

DISCUSSION

The HLA antigens B8 and BW15 which are frequent in the Caucasian population, might play a role in the manifestation of juvenile diabetes by lowering the resistance of the organism. In their presence the susceptibility to viral infections increases and thus the beta-cells will be damaged with increased frequency. On the other hand, an inclination to autoimmune diseases may also induce the damage of beta-cells [6]. The significantly higher incidence of HLA B8 antigen in insulin dependent diabetes is well-known. BW15 antigen is also frequently present in juvenile diabetes but according to our own observations and those of Ludwigsson et al. [4] it shows no significant difference in diabetic children. The simultaneous presence of HLA B8 and BW15 is the greatest risk factor of the manifestation of diabetes. At the same time BW15 is also a potentiating factor. The importance of B8 antigen in the manifestation of diabetes has been supported by our finding, i.e. it is present with a statistically higher frequency in diabetic children and their insulin dependent nearest relatives even in comparison with our diabetic child population.

Diabetes mellitus being a multifactorial disease, HLA antigen positivity is only one of the factors which may influence the manifestation of diabetes. This however occurs in the majority of cases without the presence of these antigens. Their role is only to increase the risk of manifestation. This was clearly shown in our material by two cases of diabetic siblings. One each of these siblings was positive, while the other negative, for B8 antigen.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 45—50 (1978)

Amöben-Meningoencephalitis: Heilung durch Pyrimethamin

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Eingegangen am 1. Juni 1977

Bei einem zweijährigen Mädchen, das mit Pneumonie aufgenommen wurde, entwickelte sich eine schwere Meningoencephalitis. Als Erreger wurden im Liquor freilebende Amöben gefunden. In der Therapie war Amphotericin B erfolglos, mit Pyrimethamin wurde jedoch vollkommene Heilung erzielt.

Die Pathogenität der verschiedenen freilebenden Amöben ist seit Jahrzehnten bekannt, und es wurde gezeigt, daß diese Protozoen in Tieren schwere, durch Meningoencephalitis charakterisierte Krankheitsbilder verursachen können [12]. Die ersten Berichte über ähnliche Erkrankungen bei Menschen wurden anläßlich von Sektionen festgestellt [4, 5, 6]. In den letzten zehn Jahren wurden aus den Vereinigten Staaten [5, 7, 11, 13, 14, 15, 16, 17], Australien, usw. etwa 60 Fälle von durch freilebende Amöben verursachte Meningoencephalitis beschrieben, und in Usti (Tschechoslowakei) wurde eine epidemieartige Häufung von solchen Fällen beobachtet [18]. In den Jahren 1962—63 wurden insgesamt 16 ähnliche Erkrankungen, alle mit tödlichem Ausgang, registriert. Bei allen diesen Kranken war das klinische Bild nach einer Inkubationszeit von 6 Tagen durch heftige Kopfschmerzen, Fieber und Bewußtseinsverlust gekennzeichnet. Bei der Sektion wurde stets eine purulente Meningoencephalitis mit polynuklearen Infiltrationen entlang den Kapillaren, kleine Granulome bis größere Gehirnabszesse gefunden. Als Erreger konnten aus dem Gehirn ausschließlich Amöben der Limax-Gruppe isoliert werden [8, 9, 10]. Der Infektionsort war ein mit Elbe-Wasser gespeistes Hallenbad, das täglich chloriert wurde.

Falldarstellung

T. E., ein Mädchen im Alter von 2 Jahren, wurde nach 4täglichem Fiebern und Husten am 11. 4. 1974 mit Bronchopneumonie aufgenommen. Die Diagnose wurde röntgenologisch bewiesen. Aufnahmebefund: Temperatur 39,8 °C, Blutsenkungsgeschwindigkeit 38 mm/St, Urin negativ. RBK 3,800,000, Hb 10,8 g/dl, WBK 9500. Blutbild: St 8, Se 42, Ly 46, Mo 2, Eo 2. Tuberculinprobe: BCG geimpft.

Die Pneumonie reagierte schnell auf Meticillin, am fünften Tag war das Kind fieberfrei. Zwei Tage später entwickelte sich eine Hyperpyrexie von 40 °C, mit Bewußtseinsverlust, tonisch-klonischen Krämpfen an allen Extremitäten und anderen meningealen Zeichen. Die Lumbalpunktion ergab einen trüben Liquor mit gesteigertem Druck; Eiweiß 154 mg/dl, Zucker 76 mg/dl, Zellzahl 2, Züchtung negativ. In den folgenden 3 Tagen war der Liquorbefund unverändert, doch erreichte die Zellzahl 200—500, und im Sediment waren viele sich lebhaft bewegende Amöben zu beobachten (S. Abb. 1, 2, 3). In dem Nasen- und Rachensekret waren die gleichen Amöben zu finden. Ihre nähere Differenzierung war aus technischen Gründen nicht durchführbar.

Als Therapie wurde zuerst Amphotericin B verabreicht, das sich aber als völlig wirkungslos erwies: der Zustand des Patienten verschlechterte sich von Tag zu Tag. Aufgrund seines ausgezeichneten antiplasmodischen Effektes wurde hiernach Pyrimethamin in einer täglichen Dosierung von $2 \times 12{,}5$ mg versucht. Der Erfolg war dramatisch: bereits am 3. Tag der Therapie war das Kind fieberfrei, bei völligem Bewußtsein und fast symptomfrei. Da im Liquor noch einige Amöben zu finden waren, wurde die Behandlung fortgesetzt. Am 10. Tag meldeten sich jedoch eine Leukopenie von 3000 und Zeichen der Agranulocytose, sodaß die Therapie abgebrochen wurde.

Zwei Tage nach der Einstellung der obigen Medikation kehrten die

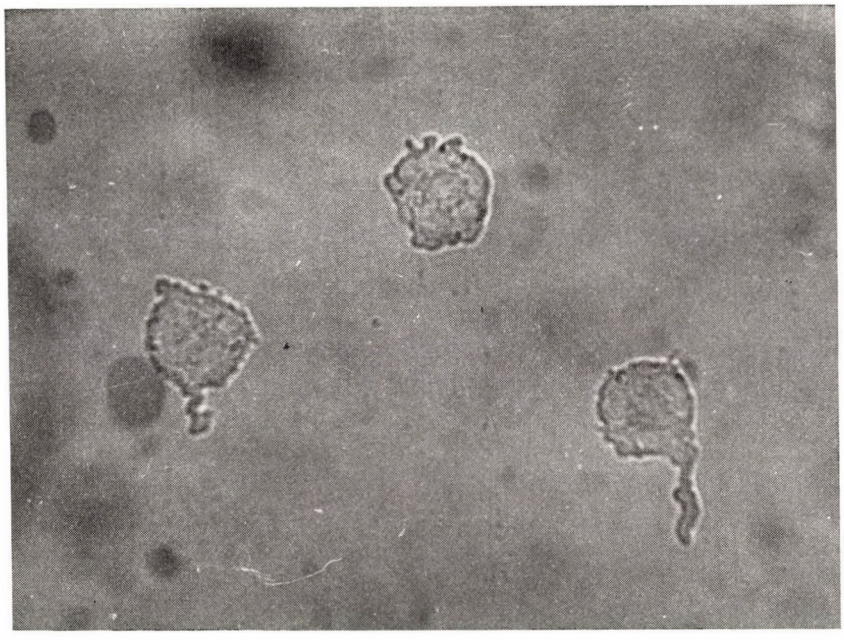
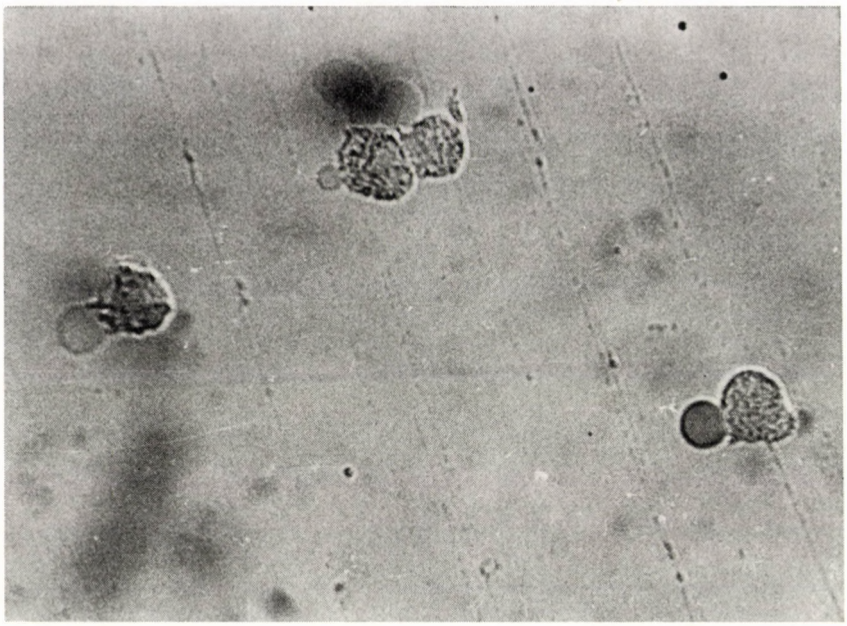


Abb. 1. Amöben im Liquor



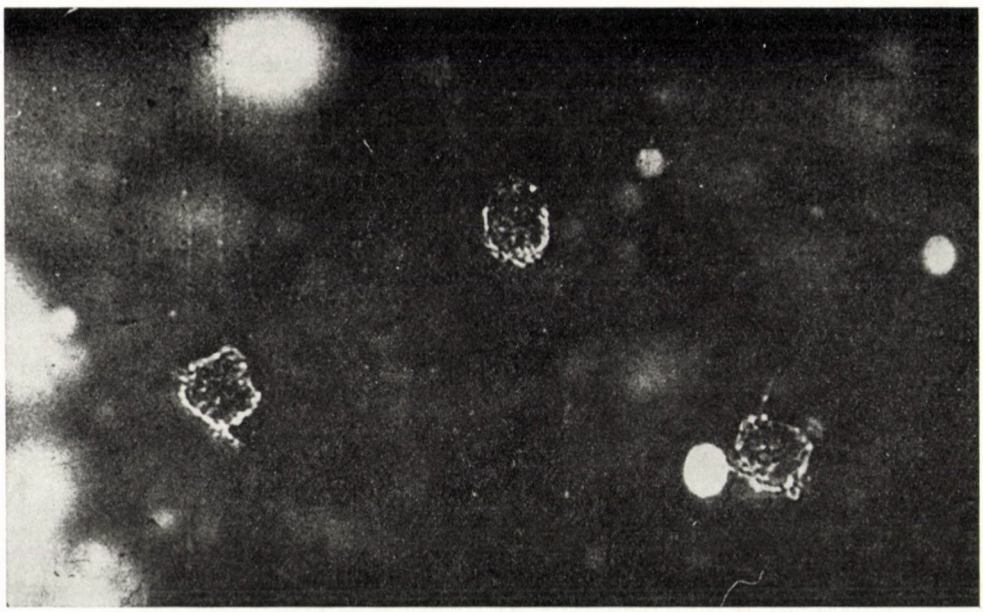


Abb. 2—3. Rote Blutkörperchen einverleibende Amöben im Rachensekret

Hyperpyrexie und Bewußtseinsstörung und am 3. Tag der ganze schwere Zustand zurück. Im Liquor wurden wieder massenhaft Amöben beobachtet, doch das Nasen- und Rachensekret blieb negativ. Nach weitere 2 Tagen wurde die Pyrimethaminbehandlung wieder eingeleitet, diesmal jedoch zusammen mit Bluttransfusionen, Prednisolon, Folsäure und Vitaminen. Der Erfolg war wiederum ausgezeichnet: in einigen Tagen verschwanden das Fieber und alle Symptome. Die Behandlung wurde noch 6 Wochen lang fortgesetzt. 2 Monate nach der Aufnahme konnte das Kind mit etwas schütteren Haaren und leichter Muskelschwäche, doch beschwerdefrei, mit normalen statischen und geistigen Funktionen und normalem Blutbild entlassen werden. Ein Monat später zeigten die physikalische und neurologische Nachuntersuchung und die Laborergebnisse völlig normale Verhältnisse.

Wiederholte Untersuchungen auf Amöben (Rachen- und Nasensekret) in der Familie und Umgebung des Kranken (Haustiere, Wasserbehälter, Laken) fielen alle negativ aus.

Besprechung

In die Gruppe der sog. freilebenden Amöben (free-living amoeba) gehören eine Reihe von Spezies: Hartmannella, Acanthamoeba, mehrere Arten der Limax- und Naegleria-Gruppe. Nach unseren heutigen Kenntnissen verursachen alle eine durch Meningoencephalitis charakterisierte Krankheit, die oft von Rhinitis und Epistaxis begleitet ist. Es wird allgemein angenommen, daß die Infektion durch Wasser vermittelt wird. In den meisten beschriebenen Fällen wird in der Ätiologie der Krankheit Baden im Freien oder Trinken von unbehandeltem Fluß- oder Seewasser erwähnt [16]. Aus solchen Gewässern konnten diese Protozoen mehrmals isoliert werden, besonders wenn die Temperatur des Wassers dauernd lauwarm war, da viele von diesen Amöben (in erster Reihe Naegleria) thermophil sind [3, 13]. Nur ein einziger Fall ist bekannt, wo freilebende Amöben aus dem Leitungswasser gezüchtet werden konnten [1, 2].

Die Pforte der Infektion ist die Schleimhaut der Nase. Diese in der Literatur mehrmals betonte Anschauung wurde auch durch Sektionsbefunde bekräftigt: die schwersten Infiltrationen mit Lymphocyten, Plasmocyten und manchmal Neutrophilen befinden sich selektiv um die Olfactoriuskerne und in den Stirnlappen. Die Anwesenheit von freilebenden Amöben im Rachen- und Nasensekret wurde wiederholt bestätigt. Im Rachensekret von 2289 Personen konnten mit Hilfe von Gewebekulturen in 33 Fällen (1,4%), meistens bei Kindern unter 5 Jahren, Hartmannellen isoliert werden [19]. In einer anderen Studie von 1000 Soldaten im Alter von 20—21 Jahren wurden Amöben der Limax-Gruppe in 5% isoliert [18].

Auch die Infektion des Liquors wurde eingehend untersucht, mit be-

sonderer Rücksicht auf die Pathogenität der dort eventuell anwesenden Amöben. Die Frage wurde eindeutig entschieden, als von 390 Proben nur 2 positiv ausfielen, beide bei an Meningoencephalitis leidenden Kranken [7].

In der Therapie wurde eine ganze Reihe von Mitteln angewandt, die meisten ohne jeglichen Erfolg. In vitro und im Mausexperiment erwiesen sich nur Quinuron, Acriflavin, Diminazen sowie das Antibiotikum Paramomycin als wirksam, doch in der Humantherapie konnten auch diese den tödlichen Ausgang nur ganz ausnahmsweise aufhalten. In einem australischen Fall [2] wird die Heilung der intensiven Behandlung mit Amphotericin B zugeschrieben, doch in anderen Fällen — wie auch in unserem — wird dieses Mittel ohne Erfolg angewandt. Aufgrund von Tierexperimenten wurde neuestens das Antimycoticum Clotrimazol empfohlen; unseres Wissens wurde es bisher bei Kranken mit Amöben-Meningoencephalitis nicht erprobt. Das Pyrimethamin, das sich in unseren Fall so gut bewährt hat, wurde im Schrifttum im Zusammenhang mit diesem Krankheitsbild nicht erwähnt.

*

Auch an dieser Stelle sei Frl. Dr. I. Litter und Herrn Dr. J. Berky (Staatliches Hygieneinstitut, Székesfehérvár) für ihre Hilfe bei der Labordiagnose bestens gedankt.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 51—54 (1978)

Point prevalence at birth of ventricular septal defect in Hungary

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Received 1st August, 1977

An attempt was made to estimate the occurrence of ventricular septal defect in Hungary. The study was based on data derived from three surveys. Point prevalence at birth of isolated ventricular septal defects amounted to $1.33 \pm 0.34‰$, $1.39 \pm 0.31‰$ and $1.77 \pm 1.12‰$, respectively. Considering the diagnostic difficulties and other distorting factors, the figure of 1.5‰ is assumed to represent the actual point prevalence rate. Ventricular septal defect cases constituting part of the complex congenital cardiovascular malformations and of multiple malformations may increase the above 1.5‰ estimate by another 1‰.

In Hungary, point prevalence at birth of congenital cardiovascular malformations (CCM) ranges between 7.0‰ and 10.0‰, thus they are the most common organ localization of congenital malformations [20]. The mortality rate of CCM surpasses that of all infectious diseases. Ventricular septal defect (VSD) is responsible for the most common group of CCMs (Table I). The present paper reports on surveys aimed at assessing the occurrence of VSD in Hungary.

The data were obtained from (a) an "intensive" survey of the births in Budapest for the period 1963 to 1965 [3]; (b) an "optimal" epidemiological model study of babies born in county Szolnok in 1963 [14]; (c) the patient material of the Paediatric Cardiology Care Unit of county Szolnok.

Material

Of the data sources only item (c) will be discussed in detail, since the others have already been treated elsewhere [3, 14]. About one-third of the territory of county Szolnok but one-half of the live-born babies come within the competence of the Cardiology Care Unit. The frequency of CCM and VSD was examined in 36,721 births registered in the period 1965—1974. The diagnoses were made by a paediatric cardiologist (M. M.) in co-operation with the Paediatric Ward of the National Institute of Cardiology. It is therefore assumed that the sample represents verified VSD cases.

Results and Discussion

(i) Of the 52,569 babies born in Budapest between 1963 and 1965, 129 suffered from VSD, a point prevalence of 2.45‰. Excluding the

TABLE I

Point prevalences for 1,000 livebirths of CCM and VSD in some surveys

Author (and place of survey)	Number of livebirths	CCM		VSD		Per cent
		No.	p.	No.	p.	
MacMahon et al., 1953 (Birmingham U. K.)	199,418	633 (372)	3.17 (1.87*)	86	0.43	23.1
Richards et al., 1955 (New York, USA)	5,530	33	5.97	15	2.71	45.5
Carlgren, 1959 (Gothenburg, Sweden)	58,105	365	6.28	99	1.70	27.1
Micheälsson, 1964 (Several places, Sweden)	about 26,000	363	13.96	82	3.15	22.6
Hoffman and Rudolph, 1965 (New York, USA)	22,957	—	—	31	1.35	—
Hay, 1966 (Liverpool, U. K.)	80,641	316**	3.91	128	1.59	40.5
Kerrebijn, 1966 (Leiden, Netherlands)	1,817	15	8.25	6	3.30	40.0
Carlgren, 1969 (Gothenburg, Sweden)	58,314	439	7.53	190	3.26	43.3
Mitchell et al., 1971 (Several places, USA)	56,109	459	8.18	133	2.37	29.0
Feldt et al., 1971 (Minnesota, USA)	32,393	186	5.74	62	1.91	33.3
Harvald and Hels, 1972 (Greenland, Denmark)	757	14	18.50	6	7.92	43.0
Czeizel et al., 1972 (Budapest, Hungary)	52,569	371	7.06	107	2.04	28.8
Levin and Kanarek, 1973 (Johannesburg, South Africa)	21,810	141	7.79	49	3.48	35.0
Kenna et al., 1975 (Liverpool, U. K.)	163,692	1081	6.60	325	1.99	30.0
Mészáros et al., 1976 (Szolnok, Hungary)	2,259	23	10.18	6	2.66	26.1
Mészáros and Czeizel, 1977*** (Szolnok, Hungary)	36,721	227	6.18	66	1.79	29.1

* in 261 cases the exact diagnosis has not been clarified
** 134 questionable cases have been excluded
*** present study
p = point prevalence per 1000 livebirths

cases with multiple malformations, the rate becomes 2.0‰. If the 22 tetralogy of Fallot cases and 10 complex VSD malformations associated with infundibular pulmonary stenosis are disregarded, point prevalence at birth of the 73 isolated VSDs amounts to 1.39 ± 0.31‰.

(ii) The "optimal" epidemiological survey conducted in county Szolnok comprised 2,259 cases. Of the verified 23 CCM cases, 6 had VSD: 4 the isolated and 2 the complex type. Thus, point prevalence at birth of isolated and of all VSD cases was 1.77 ± 1.12‰ and 2.67‰, respectively. It has to be mentioned that an accidental distortion of the values cannot be excluded because of the small number of patients.

(iii) Among the children born between 1965 and 1974 and belonging

to the territorial competence of the Cardiology Care Unit, 87 suffered from VSD (2.37‰). Disregarding the 11 multiple malformations, point prevalence for 36,721 births amounts to 1.79‰. Seventeen children (29.1%) had complex CCM, so the point prevalence at birth for the isolated VSDs is 1.33 ± 0.34‰.

The 1.33, 1.39 and 1.77‰ point prevalence rates of isolated VSDs should be regarded only as a minimum estimate for the following reasons.

(i) *Diagnostic difficulties.* Only part of the VSD patients display symptoms that induce the parents to seek medical advice. A loud ('harsh') holosystolic or pansystolic murmur is suggestive of VSD, but a physical examination in itself does not suffice to ascertain the malformation unequivocally and thus can be the source of misdiagnosis. To substantiate or exclude the presence of VSD requires up-to-date diagnostic procedures; these are, however, performed only in cases with severe clinical symptoms. In lethal cases necropsy will conform the diagnosis. The actual frequency can only be assessed by screening and cardiologic examination of every subject constituting the sample. In practice, this is rarely possible and mostly in small samples as has been the case in our "optimal" model study [14]. Since spontaneous closure is frequent, even the follow-up of a sample cannot reveal all affected persons.

(ii) *The age of the child at examination.* The 7th to 9th week of intrauterine life is regarded as the teratological termination time for the development of VSD [1, 19]. A number of reports indicate that the defect may close in utero and during infancy. It is estimated that spontaneous closure occurs in 25—50% of the cases [8, 5, 18]. Due to spontaneous closure on the one hand, and to the high lethality (at least 10%) of the disease on the other hand, point prevalence decreases parallel with age. Consequently, point prevalence at birth must be considerably higher than found later in life.

(iii) *The ascertainment of patients.* What has been said above, further the inaccuracy and heterogeneity of medical records contribute to the difficulties in assessing VSD cases.

(iv) *Prenatal selection* is also involved in the fact that point prevalence at birth does not reflect actual incidence.

(v) *Stillborn* infants who had not been necropsied, *babies dying of other diseases*, clinically undiagnosed cases, further VSDs which remain undetected post mortem will also distort the results.

Considering the above, we estimate the point prevalence at birth for isolated VSD at 1.5‰. On the other hand, it is certain that a considerable part of the complex CCMs consisting of VSD is nosologically related to isolated VSD.

Table I shows that VSD can be responsible for 22.6 to 45.5% of all CCMs representing a mathematical mean of approximately 30%. However, most of the surveys referred to

did not differentiate between isolated, complex and multiple cases. Because of the comparability, our estimates in Table I represent point prevalence at birth of the isolated and the complex types of VSD.

Allowing a generalization of the international data (Table I) and our values [2.45‰; 2.67‰; 2.37‰] we may reckon with a 2.5‰ overall occurrence of VSD, since in addition to the 1.5‰ point prevalence of isolated VSDs, the condition may constitute part of some complex CCM or multiple congenital malformations in a further 1‰ of births. Accordingly, isolated VSD would be responsible for about 15—25% of all CCM cases.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 55—62 (1978)

Sanduhrartiges Cor triatriatum mit Foramen ovale apertum in der akzessorischen linken Vorhofhöhle

Von

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Eingegangen am 12. März 1977

Es wird über einen 10wöchigen Säugling berichtet, bei dem sich im Zusammenhang mit Pneumonie die Symptome eines kongenitalen Vitiums meldeten; in Kürze erfolgten Herzinsuffizienz und Tod. Sektion: gemeinsamer Lungenvenenstamm, auf dem schwach entwickelten linken Vorhof über dem Herzohr eine zirkuläre, die Höhle des linken Vorhofs sanduhrförmig einengende Einschnürung. Das offene Foramen ovale öffnet sich in die akzessorische linke Vorhofhöhle. Durch die in den eingeengten Abschnitt des linken Vorhofs einragende Klappe des Foramen ovale wurde das Blut der V. pulmonalis communis größtenteils in den rechten Vorhof geleitet. Es ließen sich noch zweizipflige Aortenklappe, hypoplastische linke Kammer und Aorta sowie präduktale Aortenisthmus-Stenose registrieren.

Falldarstellung

Zehnwöchiger Säugling mit negativer familiärer Anamnese; ungestörte neonatale Periode, weder Herzgeräusche, noch Zyanose, normale Entwicklung. Vier Tage vor der stationären Aufnahme merkte die Mutter, daß sich die Haut des Säuglings gräulichblau verfärbte.

Aufnahmebefund: unruhiger Säugling mit Dyspnoe und Zyanose. Bei der Auskultation melden sich Zeichen eines Lungenödems; Atemfrequenz: 80—100/Min. Rhythmische Herzfunktion, leises, kurzes systolisches Geräusch. Palpierbarer Puls, Frequenz 180/Min. Systolischer Blutdruck sowohl auf der oberen, als auch auf der unteren Extremität 70 mm Hg (mit der Flush-Methode). Den Rippenbogen um 1 cm überragende Leber, palpierbare Milz.

Aus zwei Richtungen verfertigte Thoraxaufnahme: nach rechts mäßige, nach links bedeutende Herzvergrößerung, eingeengtes hinteres Mediastinum, ausgeprägtere Lungenvaskularisation, im rechten oberen Lappen auch bronchopneumonische Infiltration (Abb. 1). EKG: auf linke Vorhofbelastung und rechte Kammerhypertrophie weisende Zeichen (Abb. 2). Allmählich wurde das Herzgeräusch holosystolisch [Stärke 3/6], außerdem meldete sich in der Projektion der A. pulmonalis die Verdoppelung des 2. Tones. Parallel damit vergrößerten sich die Leber auf 3 cm und die Milz auf 2 cm und es entwickelte sich auch ein leises, kurzes diastolisches Geräusch.

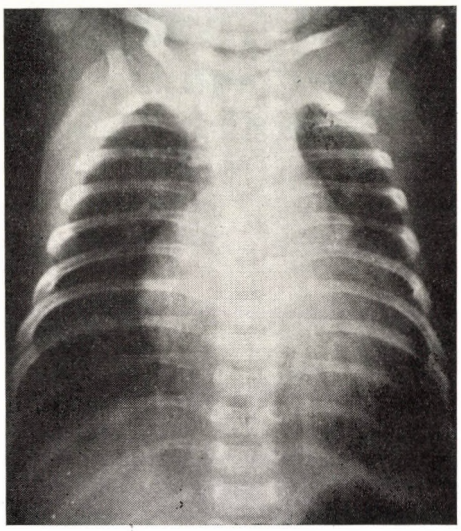

Abb. 1. Thorax-Röntgenaufnahme: Herzvergrößerung, deutlichere Lungenzeichnung. Bronchopneumonisches Infiltrat neben dem rechten oberen Hiluspol

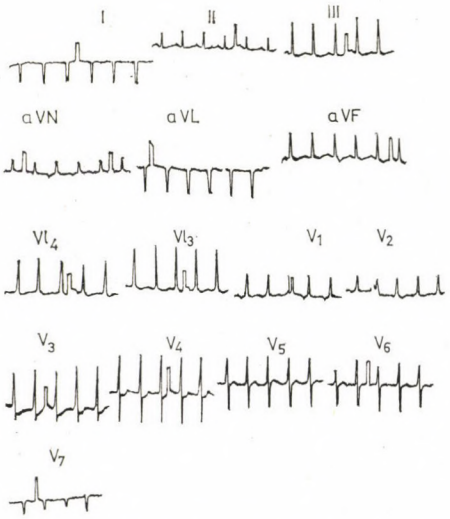

Abb. 2. EKG: auf linke Vorhofbelastung und rechte Kammerhypertrophie weisende Zeichen

Nach anfänglicher Besserung starb das Kind an Kreislaufinsuffizienz.

Sektionsbefund

Regelmäßige Lokalisation der thorakalen Organe. Herzgröße: 6,5 × 4,5 × 4 cm, die beträchtlich erweiterte rechte Kammer bildet die Herzspitze. Durch eine unter der V. cava inferior ausgehenden, über das Herzohr des linken Vorhofs zirkulär verlaufenden Einschnürung (Abb. 3) wird die Vorhofhöhle sanduhrartig eingeengt (Abb. 4). Linker Vorhof und Kammer sind hypoplastisch, rechter Vorhof und Kammer dilatiert, die Muskulatur der rechten Kammer hypertrophisiert, das Kammerseptum, die bi- und trikuspidalen Klappen intakt. Die etwas hypoplastische Aorta hat nur zwei Klappen, sie ist über der Einmündung des geschlossenen Ductus Botalli eingeengt. Das Blut der einen gemeinsamen Stamm bildenden Vv. pulmonales strömt in den schwach entwickelten linken Vorhof. Regelwidriger Aufbau des Vorhofseptums: Die lockere, erweiterte Valvula foraminis ovalis hängt der Einmündung des gemeinsamen Lungenvenenstammes gegenüber segelartig in die eingeengte Höhle des linken Vorhofs hinein (Abb. 5). Auf diese Weise führt neben der erweiterten Klappe des Foramen ovale auf der einen Seite ein schmaler Kanal zur im substenotischen Teil des linken Vorhofs befindlichen Mitralöffnung,

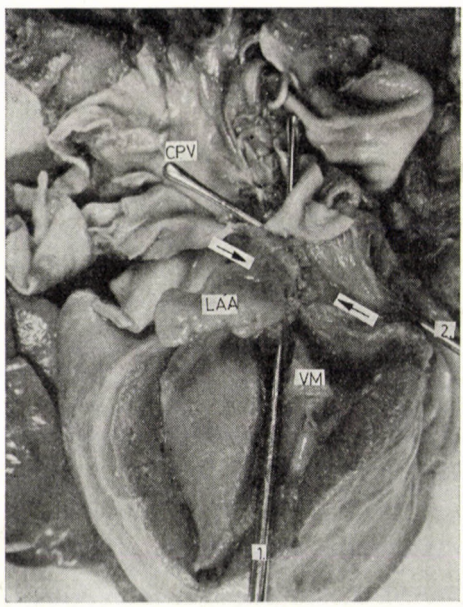

Abb. 3. Der Weg der Sonde Nr. 1 führt aus der linken Kammer durch das Mitralostium in den linken Vorhof und der Sonde Nr. 2 aus der V. cava inferior durch das Foramen ovale in die aufgeschnittene V. pulmonalis communis. Auf dem linken Vorhof verläuft zirkulär über dem Herzohr eine unterhalb der V. cava inferior ausgehende Einschnürung (Pfeile). LAA: linkes Herzohr, VM: Mitralklappe, CPV: V. pulmonalis communis

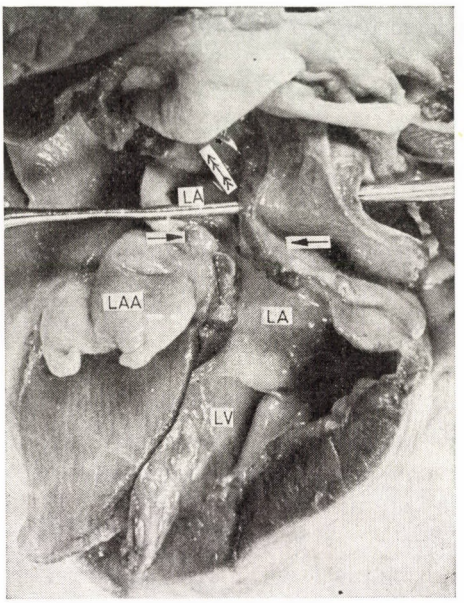

ABB. 4. Durch die den linken Vorhof zirkulär umgehende Einschnürung (Pfeile) wird die Vorhofhöhle sanduhrförmig eingeengt. Die Sonde führt aus der V. cava inferior durch das Foramen ovale in den linken Vorhof. Die V. pulmonalis communis mündet über der Sonde in den linken Vorhof ein. Das Doppelpfeil zeigt in Richtung der Lungenvene. Unter der Stenose erweitert sich der linke Vorhof in Richtung der Mitralklappe: hier befindet sich die Öffnung des linken Herzohrs. LAA: linker Vorhof, VM: Mitralklappe, LV: linke Kammer

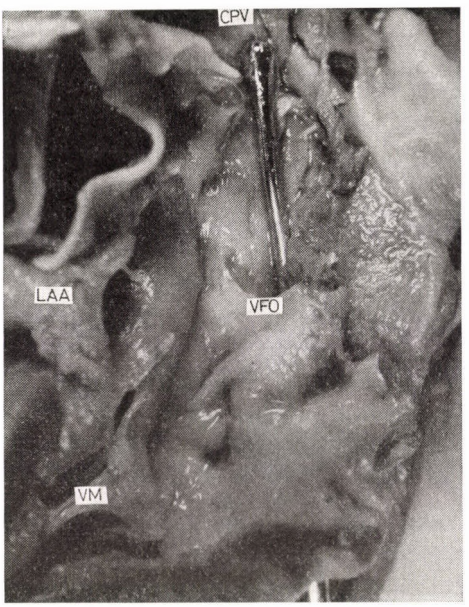

ABB. 5. Vorhofseptum vom linken Vorhof her. Die Sonde verläuft aus der V. cava inferior, durch das Foramen ovale in die V. pulmonalis communis. VM: Mitralklappe, VFO: Klappe des Foramen ovale, CPV: V. pulmonalis communis

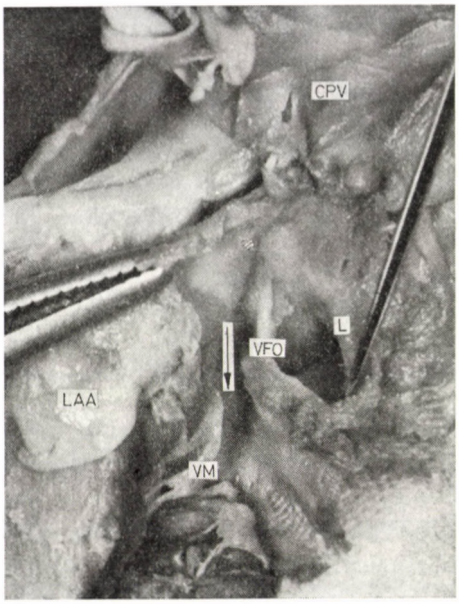

Abb. 6. Die erweiterte Klappe des Foramen ovale liegt der V. pulmonalis communis gegenüber, und ragt in die Höhle des linken Vorhofs ein, wodurch der zur Mitralklappe führende Weg verengt wird (Pfeil). LAA: linkes Herzohr, VFO: Klappe des Foramen ovale, VM: Mitralklappe, CPV: V. pulmonalis communis, L: Limbus des Foramen ovale

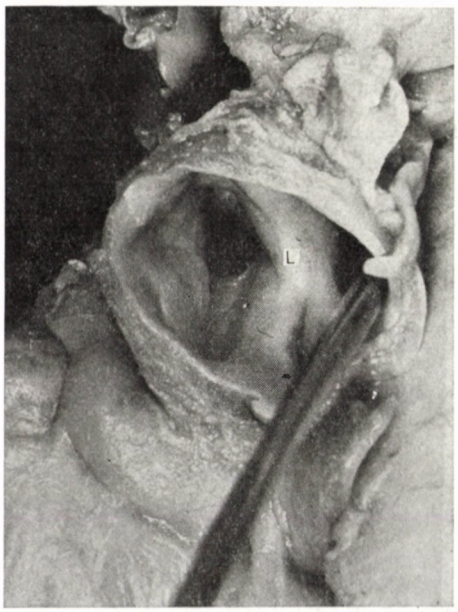

Abb. 7. Einmündung der V. cava inferior von hinten her. Die Sonde führt in den rechten Vorhof. Links verläuft ein erweiterter Kanal in den linken Vorhof. Gegenüber der sich im linken Vorhof befindlichen Öffnung des Kanals liegt die Einmündung der V. pulmonalis communis. L: Limbus des Foramen ovale

während auf der anderen Seite das breite, offene Foramen ovale in Erscheinung tritt (Abb. 6). Sinus coronarius, V. cava superior und inferior münden der Norm entsprechend in den rechten Vorhof ein. Durch den Limbus des Foramen ovale wird das Ostium der V. cava inferior in zwei Teile geteilt. Auf der linken Seite führt ein weiter Kanal in den linken Vorhof; die Wand des Kanals bildet die Klappe des Foramen ovale und das Septum secundum, der Öffnung des linken Vorhofs gegenüber befindet sich die Einmündung der V. pulmonalis communis, durch die rechtsseitige Öffnung gelangt man in den rechten Vorhof (Abb. 7).

Die übrigen Organe zeigten außer Hyperämie und Bronchopneumonie keine pathologischen Abweichungen.

Besprechung

Im dargestellten Fall handelte es sich um das gleichzeitige Vorkommen mehrerer Entwicklungsanomalien, unter denen die hämodynamischen Verhältnisse vor allem durch die weite, sich im eingeengten Teil der Höhle des linken Vorhofs befindlichen Klappe des Foramen ovale beeinträchtigt wurden; wegen dieser anomalen Lokalisation wurde die Klappe durch das ihr entgegenströmende Blut der ihr gegenüber einmündenden V. pulmonalis communis segelartig ausgespannt, so daß sie anstatt ihrer ursprünglichen Bestimmung gerade entgegengesetzt funktionierte, indem sie den zur Mitralklappe führenden Weg einengte und das Blut durch das Foramen ovale zum rechten Vorhof leitete (Abb. 8). Dem hochgradigen Links–Rechts-Shunt zufolge entwickelte sich eine der totalen Transposition der Lungenvenen ähnliche hämodynamische Situation.

Wir hatten die Gelegenheit, den Säugling auch als Neugeborenen zu untersuchen, ohne daß irgendwelche auf eine Herzkrankheit weisende Zeichen zu beobachten gewesen wären. Die ersten Symptome des Vitiums meldeten sich im 10wöchigen Alter, wonach die Krankheit bereits einen rapiden Verlauf nahm.

Es ist eine häufige Entwicklungsanomalie, daß sich die Lungenvenen in einen gemeinsamen Stamm zusammentun, welcher dann in den linken Vorhof einmündet. In der Frühphase des embryonalen Lebens ist das ein Normalzustand, später schmilzt die V. pulmonalis communis in die Wand des linken Vorhofs ein, während sich die vier Vv. pulmonales voneinander entfernen und einzeln in den linken Vorhof einmünden.

Im Falle eines klassischen Cor triatriatum schmilzt die V. pulmonalis communis nicht in den linken Vorhof ein; die Lage wird dadurch erschwert, daß das Gefäß durch eine anomale Membran vom linken Vorhof getrennt wird, sich erweitert und einen akzessorischen Vorhof bildet. Die Membran besteht einerseits aus der Wand der V. pulmonalis communis, anderseits aus der Wand des linken Vorhofs bzw. dem Septum primum [2, 4, 7]. Das häufig offene

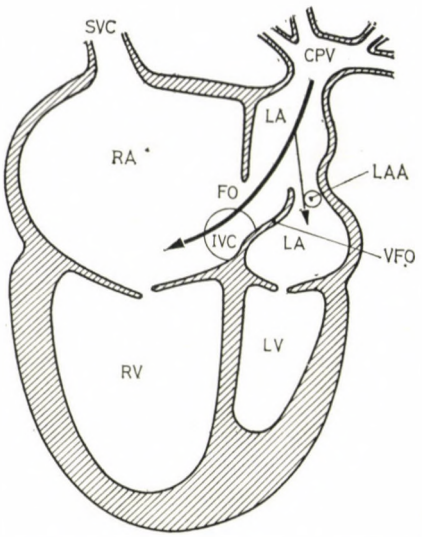

ABB. 8. Schematische Zeichnung des anomalen Herzens. Der größte Teil des Blutes gelangt aus der V. pulmonalis in den linken Vorhof und stößt an die Klappe des Foramen ovale. Durch die sich vorgewölbte Klappe des Foramen ovale wird der zur Mitralklappe führende Weg eingeengt und das Blut größtenteils durch das Foramen ovale in den rechten Vorhof geleitet. CPV: V. pulmonalis communis, LA: linker Vorhof, LAA: linkes Herzohr, VFO: Klappe des Foramen ovale, LV: linke Kammer, FO: Foramen ovale, IVC: V. cava inferior, SVC: V. cava superior, RA: rechter Vorhof, RV: rechte Kammer

Foramen ovale befindet sich meistens unter dem anomalen Septum, während das sich aus dem echten linken Vorhof öffnende linke Herzohr stets unter dem Septum liegt [5, 6].

Marin-Garcia und Mitarb. [3] breiteten den Begriff des Cor triatriatum auch auf jene Fälle aus, in denen sich der Lungenvenenstamm — ohne daß er von der Höhle des linken Vorhofs durch eine Membran getrennt wäre — durch einen Kanal mit gleichmäßiger Weite oder durch eine sanduhrförmige Einengung der Höhle des echten linken Vorhofs anschließt. Die Autoren beschrieben drei Typen des Cor triatriatum: den diaphragmatischen, tubulären und den sanduhrförmigen. Der Unterschied zwischen den von den erwähnten Verfassern veröffentlichten drei sanduhrförmigen Cor triatriatum-Fällen und unserem Fall manifestierte sich darin, daß in letzterem die Einengung tiefer lag und das Foramen ovale sich aus der distalen, akzessorischen Höhle öffnete.

Unser Fall unterscheidet sich auch von der supravulvären Mitralstenose: Bei diesem Krankheitsbild befindet sich nämlich die Einengung unmittelbar über der Mitralklappe, während das Herzohr stets über der Stenose in den Vorhof einmündet [1].

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Recensiones

G. MATHÉ: *Cancer active immunotherapy.* XV + 405 pages with 123 figures and 87 tables. Springer-Verlag, Berlin—Heidelberg—New York 1976. Price DM 72.—.

In the field of experimental tumour immunology, a great deal of new information is published every year and many of the results are almost simultaneously applied in the treatment of oncologic patients. The aim of this book was to summarize and comment this rapidly increasing amount of data.

The first part of the book deals with the tumour antigens and the immune response of the organism. From this point of view the spontaneous leukaemia of the AKR strain of mice, Burkitt lymphoma, human acute leukaemia and carcinoma of the bladder are discussed in detail. Of the immune responses, cell mediated immunity is described: T-cells, B-cells, macrophage functions, K-cells and the problem of immune unresponsiveness. In the next part of the book systemic active immunotherapy and local active immunotherapy are introduced. Both chapters have an experimental and a clinical part dealing with leukaemia as well as with solid tumours. The chapter on the immunoprophylaxis of tumours contains besides experimental data the observations with BCG vaccination, the question of its prophylactic value and the trials of immunoprophylaxis of the blastic crisis in chronic myeloid leukaemia. The next chapter deals with immune deficiency in malignant diseases, the increased risk of malignancies in congenital immune deficiency syndromes and the methods of immunorestoration. An important part of the book discusses the theoretical and practical aspects of systemic, specific active immunotherapy, immunoprophylaxis and systemic unspecific active immunotherapy, their methods and evaluation of their effect. The effects and side effects of the different types of immunotherapy are sometimes of no benefit for the patient, or can even result in an enhancement of tumour growth, which is also described in this book. In the last chapter the procedures of examination of the immunological status of the patients are found, along with the recommendations of the author concerning the best time and the best way of the application and evaluation of immunotherapy.

The reader can find the most important data concerning the problems discussed at the end, and to each chapter a list of references published up to 1976 is attached. The subject index is short but the detailed table of contents ensures easy handling of the book.

The book will be most useful for the scientist and clinician working in tumour immunology, as well as for those who want an orientation in this topic of experimental and clinical science.

D. SCHULER

J. SEIFERTH: *Das Spina-bifida-Kind.* IX + 140 Seiten mit 35 Abbildungen und 27 Tabellen. F. K. Schattauer Verlag, Stuttgart 1976. DM 22,—.

Die Behandlung des Spina-bifida-Kindes wird heute von einem interdisziplinären Team — Pädiater, Kinderneurologe, Urologe, Orthopäde — durchgeführt, und diese Arbeitsgruppe muß gelegentlich mit Institutionen zusammenarbeiten, die sich mit körperlich, mental oder verhaltensbehinderten Kindern befassen.

Bei den Spina-bifida-Kindern sind neben den verschiedenen Wirbelsäulenanomalien (Myelocele, Meningomyelocele, Meningocele) auch andere Entwicklungsmißbildungen zu beobachten. Oft sind Hydrocephalus, Arnold-Chiari Syndrom, Mißbildungen des urogenitalen Traktes und etwas seltener jene des Verdauungstraktes oder anderer Organe (Auge, Herz usw.) vorzufinden. Neben den Mißbildungen der Nieren und der ableitenden Harnwege kommt der durch eine Wirbelsäulenanomalie bedingten Innervationsstörung der Blase eine besondere Bedeutung zu, da diese zu Reflux, Pyelonephritis und später zum Tode führen kann.

Die vom bekannten Kinderneurologen verfaßte Monographie gliedert sich in 3 Hauptteile. Im ersten Teil werden der Problemenkreis des Spina-bifida-Kindes, Lebenserwartungen, Pathologie, chirurgische und andere Behandlungsmöglichkeiten — den Hydrocephalus-shunt inbegriffen — erörtert. Der zweite Teil befaßt sich eingehend mit den urologischen Beziehungen der Spina bifida, der dritte faßt jene urologischen Erfahrungen sehr gründlich doch maßhaltend zusammen, die der Verfasser im Laufe der Behandlung von 125 solcher Kranken gewonnen hat.

Angenommen, daß ein interdisziplinäres Team zur Verfügung steht, werden folgende Gesichtspunkte hervorgehoben:

Eine Myelocele oder ein Anencephalus kann anhand der Bestimmung des pathologisch vermehrten Alphafötoproteins aus dem Mutterblut und mittels Amniozentese aus dem Fruchtwasser bereits in der 15—18 Schwangerschaftswoche diagnostiziert werden.

Bei den mit Spina bifida geborenen Säuglingen muß aufgrund der klinischen Symptome gleich nach der Geburt beschlossen werden, ob eine konservative Behandlung oder der chirurgische Eingriff in Frage kommt (Selektion).

Bei etwa 85% der Spina-bifida-Kinder muß mit einer Entwicklungsanomalie des Urogenitaltraktes oder mit dessen pathologischer Funktion gerechnet werden, weshalb diese Kinder urologisch untersucht bzw. dauernd urologisch versorgt werden müssen. Die Methoden der medikamentösen und elektrischen Blasenstimulation und die operativen Verfahren, welche die Lösung der urogenitalen Probleme herbeiführen können, werden ausführlich geschildert.

Das Buch wird allen Ärzten, Pflegeschwestern und Heilgymnastikern usw. empfohlen, die in irgendeiner Beziehung mit den vielfaltigen und problematischen Fragen der Spina-bifida-Kinder zu tun haben.

J. SZÉNÁSY

W. PLENERT: *Praktische pädiatrische Therapie.* 494 Seiten mit 12 Abbildungen und 28 Tabellen. Georg Thieme Verlag, Leipzig 1976. DM 33,—.

Der Verfasser hatte sich zum Ziel gesetzt, dem praktisch tätigen Kinderarzt eine Monographie zur Verfügung zu stellen, mit deren Hilfe er sich ohne die zeitraubende Hinzuziehung verschiedener Fachpublikationen in allen Problemen der Therapie ausreichend orientieren kann. Dazu war natürlich eine starke Einschränkung des Stoffes erforderlich, so daß das Buch vor allem über entsprechende Fachkenntnisse verfügende Pädiatern und in den Grenzgebieten tätigen Ärzten von Nutzen sein wird.

Die Erkrankungen und deren Therapie werden aufgrund der Organsysteme in 15 Kapitel gegliedert erörtert: Respirationstrakt, kardiovaskuläres System, Gastrointestinaltrakt, Stoffwechselerkrankungen, Nervensystem, Neuromuskuläre und endokrine Erkrankungen, Urogenitaltrakt, Störungen immunologischer Funktionen, Infektionskrankheiten, ferner rheumatische neoplastische Erkrankungen und jene der Neugeborenenperiode und schließlich spezielle Probleme von Ernährung und Stoffwechsel.

Die Konzeption ist völlig zeitgemäß. Es werden die neuesten, in der Praxis bereits bewährten therapeutischen Maßnahmen angeführt, wobei bei der Wahl der besten und erfolgreichsten Möglichkeiten die persönliche Erfahrung und Meinung des Autors zum Ausdruck kommen. Durch die ganze Arbeit zieht sich das Leitprinzip »nil nocere«. Sie versetzt den Arzt in die Lage, die Grenze zu beurteilen, wo er noch selbst ausreichend behandeln kann oder wann er die Hilfe von Spezialisten anderer Gebiete in Anspruch nehmen soll.

Die Struktur des Buches ist klar und übersichtlich, die Orientierung wird auch durch ein gutes Inhalts- und Sachwortverzeichnis und ein eingehenderes Studium der Fragen durch ein ausführliches Literaturverzeichnis gefördert. Das Ziel des Verfassers ist weitgehend erreicht worden, da das Werk ein äußerst praktischer und nützlicher Wegweiser in den Problemen der Therapie in der Kinderheilkunde ist.

K. SCHMIDT

A. CLARYSSE, Y. KENIS, G. MATHÉ: *Cancer chemotherapy*. XX + 566 pages with 154 figures and 129 tables. Springer-Verlag, Berlin—Heidelberg—New York 1976. Price DM 96.—.

There is a rapidly expanding literature on chemotherapeutic drugs and their application in different combinations. The authors of this book collected and summarize a great amount of information, the survey of which is facilitated by many tables. A critical evaluation and objective comparison of the different treatment protocols was not, however, always possible because of the lack of uniform terminology, criteria and controlled clinical trials. The authors emphasize therefore the general statements and directives which can be used as guidelines in the planning of new treatment protocols. According to this concept the first part of the book deals with the structure of normal and tumour cells, their molecular biology, surface markers, biochemical characteristics and kinetics. It is followed by the description of antitumour drugs grouped by their clinicopharmacological effect. The application and significance of the cyclic or phase-specific effect of chemotherapeutic drugs is also discussed. There are general statements and conclusions concerning the single and combined application of the drugs, referring also to the problem of drug resistance. They describe the basic principles of human tumour chemotherapy, e.g. the tumour mitoses, and the rational combination of the different drugs. The next part of the book deals with the preclinical and clinical evaluation of the new cytostatic drugs: phase I + IV clinical trials. This is followed by a description of the methodology of tumour chemotherapy in medical practice: the sort of cases, drugs and actual application of tumour chemotherapy, and the evaluation of the therapeutic effect, the side effects and the recommended therapy of these.

In the second part the therapeutic protocols of the different kinds of tumours can be found in the following order: acute lymphoid leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, polycythaemia vera, myelosclerosis with myeloid metaplasia, chronic lymphoid leukaemia, multiplex myeloma, primary macroglobulinaemia, Hodgkin disease, non-Hodgkin lymphoma, Burkitt tumour, mycosis fungoides, histiocytosis-X, skin cancer, malignant melanoma, carcinoma of

the head and neck, lung cancer, gastrointestinal carcinoma, breast cancer, ovarial and uterine cancer, cancer of the bladder, prostate and testicles, renal carcinoma, endocrine tumours, cerebral tumours, osteogenic sarcoma, Ewing sarcoma, soft tissue carcinoma. A separate short chapter deals with some paediatric tumours: retinoblastoma, neuroblastoma and Wilms tumour. In spite of the good collection and interpretation of the published data in the therapy of each tumour type it is not easy for the reader to find the best one. At the end of each chapter a long list of references can be found.

The book is a useful collection of the most important theoretical and practical principles and protocols of tumour and leukaemia chemotherapy for all those involved in tumour or leukaemia therapy.

D. SCHULER

Pädiatrie. Ein Lehrbuch für Studenten. Herausgegeben von H. PATZER, P. GROSSMANN, W. BRAUN. 403 Seiten mit 73 teils farbigen Abbildungen und 23 Tabellen. Volk und Gesundheit, Berlin 1976. M 19,—.

Wie es bereits aus dem Titel hervorgeht, bietet das Buch für die Studenten einen allgemeinen Überblick über die grundlegenden pädiatrischen Fragen, vor allem aus deren praktischen Aspekt. Ein gesondertes Kapitel befaßt sich mit der Sozialpädiatrie (Beratung, Prophylaxe, Morbidität, Mortalität), dessen organisatorischer Teil natürlich die deutschen Verhältnisse widerspiegelt, doch nützliche Informationen liefert. Als allgemeiner Teil der Arbeit dürften jene Kapitel betrachtet werden, die die humangenetischen Grundbegriffe, die Probleme des normalen Wachstums und der Entwicklung enthalten. Ein Kapitel schildert die physiologischen Eigenheiten, Krankheiten und Wachstumsstörungen der Neugeborenen und Säuglinge. Die übrigen Krankheitsbilder werden nach Organen bzw. Organsystemen geordnet erörtert: Endokrinopathien, Stoffwechselkrankheiten, Enzymopathien (Diabetes mellitus), Störung des Wasser- und Elektrolythaushaltes, Infektionskrankheiten, Hämatologie, lymphoretikuläres System, Atemwege und Lunge, Herz und Kreislauf, Nieren und Harnwege, Verdauungssystem, Nervensystem, Haut, Knochen, Muskeln. Kürzere Kapitel sind der Immunologie, Onkologie und Traumatologie gewidmet.

Der Aufbau der Kapitel ist gut und klar, die Abbildungen sind didaktisch. Die Betonung ist stets auf die klinischen Symptome und den Ablauf gelegt. Der praktische Wert wird auch durch die Schilderung der wichtigsten Pflegemaßnahmen (Wickeln, Fieberbekämpfung usw.) gefördert. Die eingehendere Erläuterung von fachlichen Angaben wie Differentialdiagnose, Flüssigkeitstherapie oder Medikation wurde von den Autoren nicht als Aufgabe dieser Arbeit betrachtet.

D. SCHULER

H. EGGERS, K.-D. WAGNER und M. WIGGER: *Bedingungen und Störfaktoren der frühkindlichen Entwicklung.* 136 Seiten mit 9 Abbildungen und 44 Tabellen. Georg Thieme Verlag, Leipzig 1976. M 29,—.

Bei der Entwicklung des Menschen sind die ersten drei Lebensjahre von grundlegender Bedeutung. Positive oder negative soziale Bedingungen, Morbidität und organische Belastungsfaktoren sind in keiner Entwicklungsphase so wirksam wie beim Kleinkind, dessen somatopsychische Reaktionsbereitschaft besonders ausgeprägt ist.

Nach einem kritischen Überblick von 15 kleinkindlichen Entwicklungstests erörtern die Autoren in der vorliegenden Arbeit ein von ihnen entwickeltes Testverfahren (Rostocker Entwicklungstestverfahren für Kleinkinder), das Längsschnittbeurteilungen und die frühe Erfassung psychischer Retardation ermöglicht. Ei-

nerseits werden die Beziehungen zwischen körperlicher und psychischer Entwicklung, anderseits die Rolle der Einflüsse der sozialen Umwelt untersucht. Es wurde beobachtet, daß sich bei gesunden Krippenkindern Sprache und soziales Verhalten in einer guten Umgebung günstiger gestalten und daß der durchschnittliche Entwicklungsstand der Mädchen besser war, was der besseren Anpassungsfähigkeit des weiblichen Geschlechtes zuzuschreiben sein dürfte. Ein günstiges Milieu vermag organisch bedingte Entwicklungsstörungen zu kompensieren, während ungünstige Bedingungen diese verschlechtern. Gestosekinder und Kinder mit niedrigem Geburtsgewicht (Frühgeborene, Hypertrophe) sind besonders entwicklungsgefährdet, weshalb diese auch besondere Berücksichtigung erfordern.

Von den zahlreichen wertvollen Tabellen sei vor allem jene hervorzuheben, die die zwischen 1913 und 1972 in der Weltliteratur veröffentlichten Beobachtungen inbezug auf die somatopsychische Entwicklung der Kinder mit niedrigem Geburtsgewicht zusammenfaßt.

Die Monographie darf auf das Interesse von Pädiatern und Mitarbeitern von psychologischen, pädagogischen und Erziehungsberatungsstellen rechnen.

A. Pintér

H. Eggers und M. Möhr: *Die Ernährung gesunder Kleinkinder*. 236 Seiten mit 12 Abbildungen und 16 Tabellen. Volk und Gesundheit, Berlin 1976. Preis: M 5,50.

Das Ziel der Monographie ist, zur einheitlichen und vom wissenschaftlichen Standpunkt optimalen Ernährung der Kleinkinder im Alter von 1—3 Jahren praktische Ratschläge zu bieten. Sie wendet sich an die Familien und an Mitarbeiter von Krippen und Heimen und vermittelt in leicht verständlicher Form die Grundlagen und Prinzipien einer richtigen Kleinkinderernährung.

Das Buch gliedert sich in 13 Kapitel. Es erläutert das körperliche Wachstum, die Entwicklung des Bewegungsverhaltens, die altersgemäßen Eigenheiten des Stoffwechsels und die verschiedenen Nährstoffe. Ohne Anspruch auf Vollständigkeit werden von den Mineralstoffen Kalzium und Phosphor, von den Spurelementen das Eisen und von den Vitaminen das A, B und C, das Vitamin D dagegen nicht erörtert. Viel eingehender ist die Besprechung des Kalorie- und Nährstoffbedarfes, der Folgen der Fehlernährung und des Tagesrhythmus der Mahlzeiten.

Besonders lehrreich dürften jene Kapitel sein, die sich mit der Ernährungserziehung des Kleinkindes und der gegenwärtigen Ernährungslage der Kinder in der DDR befassen. Die Autoren weisen auf die zweckmäßige Auswahl der Lebensmittel hin und bieten Empfehlungen inbezug auf die Nahrungszubereitung, Einschränkung des Nährwertverlustes, das Lagern von Lebensmitteln, ferner Küchenhygiene und Organisation von Gemeinschaftsküchen.

Hervorzuheben sind noch die 56 Mustertageskostpläne mit Zubereitungshinweisen, Nährstoffzusammensetzung und Preisen. Der Text wird durch übersichtliche Tabellen und ein empfohlenes Schrifttum ergänzt.

S. Kassai

Tumours in Children. Eds. H. B. Marsden, J. R. Steward: 2nd edition. XVI + 500 pages with 295 figures and 119 tables. Springer-Verlag, Berlin—Heidelberg—New York 1976. DM 92,—.

This revised and considerably enlarged 2nd edition of the monograph contains all the important data published in the last 10 years. Since the first edition, the problems of the incidence and therapy of childhood tumours have come increasingly in the foreground, especially as the tumour deaths appeared to increase with the decrease in the other lethal diseases. It is well-known that the spectrum of

malignant tumours is much narrower in children than in adults, as the former have fewer forms, arise from fewer tissues and are less complex. It is in the paediatric field that team-work has been most fruitful between paediatricians, surgeons, radiologists, oncologists and pathologists and it is probably due to the collaboration of such teams, too, that survival has considerably lengthened in the last ten years. Another important factor in the prolongation of survival was the establishment of excellent and well-equipped paediatric centres specialized for optimum treatment.

The contents of this 2nd edition, apart from the chapters found in the first one, embraces reviews on the aetiology and epidemiology of tumours, data on tissue cultures, and the advances in oncological immunity. Some views and assumptions have been revised, for instance the alleged more favourable prognosis of Wilms tumour arising below two years of age.

The documentation is excellent. The photos are black-and-white but perfect in every respect. The book will be useful for both the specialist and the practitioner.

Z. Erdős

Kinderanästhesie. Herausgegeben von W. Dick und F. W. Ahnefeld. XI + 163 Seiten mit 26 Abbildungen und 20 Tabellen. Springer-Verlag, Berlin—Heidelberg—New York 1976. DM 21,80.

Dieses in der Reihe »Kliniktaschenbücher« veröffentlichte Büchlein enthält Beiträge von 7 Autoren über die Anästhesie bei Kindern. Das Ziel war, in den vielfältigen und manchmal verwickelten Problemen der Physiologie, Pathophysiologie, Pharmakologie und technischen Gefährdung der Früh- und Neugeborenen, Säuglingen, Kleinkindern und Kindern eine gewisse Systematik festzulegen und einem einheitlichen Prinzip entsprechend zu ordnen.

Das Buch gliedert sich in 8 Kapitel in denen 1. die physiologischen Grundlagen (K. D. Bachmann), 2. die pathophysiologischen Reaktionen (H. Ewerbeck), 3. die Pharmakologie der Anästhesie (R. Krebs), 4. die prä-, intra- und postoperative Infusionstherapie (F. W. Ahnefeld), 5. die Vorbereitung zur Anästhesie (P. Milewski), 6. die Anästhesieverfahren (W. Niederer), 7. die Anästhesie bei speziellen Eingriffen (W. Dick) und 8. die Komplikationen der Anästhesie und ihre Prophylaxe und Therapie (W. Dick) sehr gründlich bearbeitet wurden. Instruktive Abbildungen und Tabellen fördern die Verständlichkeit des ausgezeichneten Textes, der auch mit einem ausführlichen Literaturverzeichnis versehen ist.

Das Taschenbuch ist eine wertvolle Hilfe für Anästhesisten, Pädiatern und Kinderchirurgen, sowie für studierende Anästhesieschwestern und Studenten.

J. Jellinek

W. Plenert und U. Lehnert: *Säuglingsernährung.* 138 Seiten mit 3 Abbildungen und 33 Tabellen. G. Thieme Verlag, Leipzig 1977. DM 10,50.

Die in der bekannten Reihe »Moderne Pädiatrie« erschienene Monographie befaßt sich mit der zeitgemäßen Ernährung des gesunden Säuglings. Sie besteht aus 7 Kapiteln. Nach einem geschichtlichen Überblick wird in dem 2., wohl wichtigsten Kapitel der Energie- und Nahrungsbedarf des wachsenden Organismus besprochen. Der äußerst hohe Energiebedarf vor allem im 2.—3. Lebensjahr wird hervorgehoben, die Bedeutung der Spurelemente erörtert und die Notwendigkeit der konsistenten Nahrung, des 2. Kohlenhydrats stark bezweifelt. Ein Kapitel befaßt sich mit der natürlichen Ernährung, so z. B. mit der Zusammensetzung, den Enzymen, den gerinnungsaktiven Substanzen und mit der immunologischen Bedeutung der

Frauenmilch, ferner mit den Frauenmilchsammelstellen und dem Stillen selbst, dessen Wichtigkeit immer betont wird. Das 3. Kapitel ist der künstlichen Ernährung gewidmet; hier werden deren Kriterien und hygienische Forderungen, die klassischen und modernen Herstellungsmethoden und die in der DDR erhältlichen Fertignahrungen erläutert. Im 5. Kapitel werden die Fragen der Beikost behandelt und Ernährungsregime bei künstlicher Ernährung dargestellt. Es ist auffallend, daß die Autoren Fleisch und Eier erst nach dem 7. Lebensmonat empfehlen. Kapitel 6 erörtert die bilanzierte, synthetische und semisynthetische Ernährung, die aus einfachen, qualitativ und quantitativ gut definierbaren Baustoffen (Amino- und Fettsäuren, Vitamine usw.) besteht und bei oraler oder parenteraler Ernährung zur Anwendung kommt.

Die Verfasser bieten Konklusionen im Spiegel verschiedener Theorien, nicht aber Dogmen, und somit weite Möglichkeiten zur individuellen Weiterentwicklung des Themas, was als besonderes Verdienst des Buches zu betrachten ist.

S. Kassai

G. R. Fraser: *The causes of profound deafness in childhood.* XIII + 410 pages with 61 tables, 18 figures and 43 pedigree charts. Bailliere Tindall, London 1977. Price £ 17.00.

The genetic basis of deafness has long been evident from its familiar occurrence. This most serious life-long handicap has received remarkably little attention in contrast for example with blindness.

The main purpose of this large-scale study, based on the personal examination of 3535 affected patients in a 10-year period, was to discover the origin of deafness, its genetic relations as well as the possibilities of its prevention and therapy, emphasizing the serious hazards of the person involved.

The book is divided into 6 parts. The introduction is concerned with the aim of the work and the detailed description of the methods applied. The 7 chapters of the 2nd part deal with the various syndromes determined by Mendelian inheritance. This is a most valuable part of the book, because the majority of the cases of hereditary deafness belongs to this group. Many tables and impressive pedigree charts help the reader to become familiar with these heterogeneous syndromes. In the 3rd part we read about the various malformation syndromes in which deafness or hearing loss is only part of the symptoms, while the 4th part deals with the acquired forms of deafness. In this part the 12th chapter is of prominent value since it summarizes the problems in differentiating and evaluating the damages acquired in the perinatal period. The topic of the 5th part is the identification of deafness of unknown aetiology. With the development of our diagnostic and other procedures the number of such cases will diminish but reliable diagnosis is a fundamental criterion of all further therapeutic and preventive measures. The 6th part synthetizes the knowledge acquired through this large-scale study. Extensive investigation of each deaf individual immediately after the hearing loss has been detected is of fundamental importance in evaluating the therapeutic and prognostic problems of the patient. This can only be achieved if extrapolations are available in comparison to other groups of such persons. This is the real use of the work. Everybody who is concerned with genetic counselling may find it of real help in his work and a most valuable guide in the labyrinth of arising questions.

P. Kiss

Printed in Hungary

A kiadásért felel az Akadémiai Kiadó igazgatója — Műszaki szerkesztő: Zacsik Annamária
A kézirat nyomdába érkezett: 1977. IX. 2. – Terjedelem: 6,30 (A/5) ív, 24 ábra, (1 színes), 1 melléklet

78.4891 Akadémiai Nyomda, Budapest – Felelős vezető: Bernát György

ACTA PAEDIATRICA

ТОМ XIX—ВЫП. 1

РЕЗЮМЕ

СИНДРОМ СЛИЗИСТО-КОЖНОГО ЛИМФАТИЧЕСКОГО УЗЛА: ВТОРОЙ В ЕВРОПЕ СЛУЧАЙ

Г. НЬЕРГЕШ, М. БАРНА, Л. МОЛНАР

Авторы описывают случай девочки в 1 год симптомы больной соответствовали неблюдающемуся в Японии часто, на Северо-Американском материке только редко, а в Европе только в одном случае синдрому слизисто-кожного лимфатического узла. Титр связывания комплемента аденовирусом был во время болезни повышенны, но авторы не придают этому этиологического значения.

ЛЕЧЕНИЕ Д-ПЕНИЦИЛЛИНОМ ГИПЕРБИЛИРУБИНЕМИИ НЕДОНОШЕННЫХ ДЕТЕЙ

Г. КОРАНИ, Я. КОВАЧ и И. ВЁРЁШ

У 41 недоношенного ребенка, родившихся перед 38-й неделей беременности и страдающих гипербилирубинемией, проводилось лечение внутривенными инъекциями Д-пенициллина, который вводился ежедневно в дозе 300 мг/кг. Результаты лечения оценивались по относительному гипербилирубинемическому индексу. Как показали результаты сравнения с 41 ребенком контрольной группы, лечение оказалось успешным.

ПЕРИНАТАЛЬНАЯ АСФИКСИЯ И ЖЕЛТУХА НОВОРОЖДЕННЫХ

М. ФЕКЕТЕ, М. ХОРВАТ и М. ВИНЦЕЛЛЕР

Авторы настоящего сообщения измеряли уровень сывороточного билирубина в первые три недели постнатальной жизни у 114 доношенных и 199 недоношенных новорожденных. Среди зрелых новорожденных 22 ребенка, а среди недоношенных 89 детей страдали перинатальной асфиксией, у остальных была обнаружена непрямая гипербилирубинемия неизвестного происхождения. Желтуха у доношенных и недоношенных новорожденных с асфиксией не отличалась от желтухи контрольных больных. Поэтому авторы полагают, что перинатальная асфиксия сама по себе не утяжеляет желтуху новорожденных. Поскольку во всех исследованных группах отмечалась достоверная корреляция между максимальным уровнем билирубина и потерей в весе, постольку они предполагают, что степень упитанности и гидратации зависит от тяжести желтухи.

НЕЭСТЕРИФИЦИРОВАННЫЕ ЖИРНЫЕ КИСЛОТЫ (NEFA) В СЫВОРОТКЕ ДЕТЕЙ ПОНИЖЕННОГО ПИТАНИЯ В ПРОЦЕССЕ ВЫЗДОРОВЛЕНИЯ

М. ПЕНА, М. АМАДОР, П. ФЛОРЕС, Р. ГОНЗАЛЕЗ ГОТЕРА, Х. ПЕРЕЗ

Авторы провели обследование 71 ребенка в возрасте от 5 до 60 месяцев, страдающих белковой недостаточностью. При приеме в больницу у них определялся уровень сывороточных NEFA и сравнивался с уровнем NEFA у хорошо упитанных детей из контрольной группы (31 ребенок). Между группами обнаружена статистически достоверная разница. 20 детей из 30 с некомпенсированной пониженной упитанностью обследовались еженедельно. Среди них у 10 детей сразу наступило улучшение, и параллельно с этим быстро снизился уровень сывороточных NEFA. У остальных 10 детей закономерных изменений на отмечалось.

ДЕРМАТОЛОГИЧЕСКИЕ ИССЛЕДОВАНИЯ У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ

Л. БАРТА, А. РЕГЁИ-МЕРЕИ и Л. КАММЕРЕР

Авторы занимались изучением дерматоглифических отклонений у 290 детей и 180 взрослых, страдающих сахарным диабетом: результаты исследования сравнивались с отпечатками, снятых с ладоней пальцев 1000 детей школьного возраста из Будапешта и перифарии. Двойные петли в кожном рисунке пальцев встречались статистически достоверно чаще у детей и диабетом, узор рисунка кожи ладоней был достоверно беднее у некоторых детей-диабетиков. Что касается пропорции появления высокого TRC, то здесь только при диабете детского возраста наблюдались отклонения. TRC, превышающее 200, наблюдалось статистически достоверно чаще у детей с диабетом, как у мальчиков, так и у девочек.

СИНДРОМ ИВЕМАРК У СЕСТЕР

ДЬ. ЙЕЙАРТ и П. ФЕКЕТЕ

Авторы сообщают о синдроме Ивемарка (Ivemark), наблюдавшегося у сестер с аспленией. В семье не наблюдалось других нарушений развития или браков между родственниками. У обеих новорожденных девочек имелось сходные пороки развития, а именно: декстрокардия, двуполостное сердце, truncus arteriosus communis, трехдольчатое легкое с обеих сторон, симметричная печень и аспления. У одной из больных кроме того обнаружили еще частичное обратное расположение брюшных органов. Наследование синдрома с не выяснено.

АНТИГЕНЫ ХЛА Б8 И БВ15 ДИАБЕТИЧЕСКИХ ДЕТЕЙ

Л. БАРТА, Ш. ШИМОН, И. КОШНАИ

Антигены ХЛА Б8 и БВ15, а также БВ15 + Б8 чаще встречаются у диабетических детей, чем у взрослых. БВ15 отдельно не дифференцируется, но может быть потенциальным фактором. В том случае, если ХЛА Б8 и БВ15 встречаются вместе, возможный риск диабетического проявления наиболее высокий. Антигены Б8 и Б8 и/или БВ15 у близких родственников диабетических детей бывают чаще, чем у среди детей диабетиков.

ЧАСТОТА defectus sept ventricularis ПРИ РОЖДЕНИИ В ВЕНГРИИ

М. МЕСАРОШ, Э. ЦЕЙЗЕЛ

Тремя различными подходами (интенсивные измерения в Будапеште, материалы Детского Кардиологического Центра в г. Сольноке и так наз. оптимальная эпидемиологическая модель) были проведены определения частоты defectus sept ventricularis в Венгрии. Частота изолированной аномалии при рождении около 1,33—1,77‰, которую однако можно рассматривать как минимальное значение вследствие трудностей диагностики и пр. Представляется реальным значение 1,5‰. В дополнение к этому можно оценить в 1‰ частоту defectus sept ventricularis являющегося частью кардиоваскулярных, а также мультиплексных аномалий.

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22. III. 1978 HU ISSN 0001—6527 Index: 26.021

ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

VOLUMEN XIX * 1978 * NO. 2

AKADÉMIAI KIADÓ, BUDAPEST

Acta paediat. Acad. Sci. hung.

ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

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Kéziratok az alábbi címre küldendők:

Acta paediatrica Academiae Scientiarum hungaricae
1083 Budapest, Bókay János u. 53.

A szerzők közleményük honoráriumán felül költségmentesen 100 db különlenyomatot kapnak.

Megrendelés belföldre: *Akadémiai Kiadó* (1363 Budapest Pf. 24. Bankszámla: 215 11 448), a külföld számára *Kultura* (1389 Budapest 92, P.O.B. 149, Bankszámla: 218 10990).

Editorial office	Rédaction	Редакция	Redaktion
H-1083 Budapest, Bókay J. u. 53.			
Annual subscription (one volume)	Abonnement par an (un volume)	Подписная цена за год (один том)	Jahresabonnement (ein Band)
$ 36.00			

H-1389 Budapest 92, P.O.B. 149, KULTURA

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (2), pp. 71—92 (1978)

Interaction and interdependence of somatic organism and psyche in childhood

By

P. Gegesi Kiss

(Received June 27, 1977)

In order to clarify the interconnection and interdependence of the human somatic organism and psyche, their nature is discussed. The somatic organism is a specific morphological functional system, developing in every being. The psyche is a functional structure developing individually in the course of ontogeny, under the effect of internal processing influenced by the environment.

The function of conditioned and unconditioned reflexes is discussed including the way in which the conditioned reflexes are built up on unconditioned ones. The mechanism is described, by which the psyche develops in the individual and how its functions manifest themselves.

A concept is discussed concerning the structure of the human psyche, the system and nature of the conscious and unconscious functions.

The personality is the manifestation of the interconnections and the formation into a system of the somatic organism and the psyche. This interconnection brings about the socialized humanization of the vital processes in man living in society.

A concept concerning the essence of personality is discussed, emphasizing the "actual personality" and describing its structure.

Clinical examples are given concerning the interconnection of somatic organism and psyche and the somatopsychic and psycho-somatic processes, and conclusions are drawn for the purposes of education.

The interaction of the somatic organism, a morphological and functional system special to every human, and of the psyche, a functional structure determined by individual development, can properly be interpreted only if the individual formation and the nature of the two systems are taken into consideration.

I. The somatic organism

The human soma is formed in the course of fetal life, birth, infancy, childhood, adolescence, adulthood and senescence including maturation, development, stabilization of the developed characteristics, and regression, under the effect of basic laws realized in the chromosome set, in the zygote, and as programmed in the course of phylogeny. Under normal circumstances this system enforces the development of functional formations of morphological and physiological character, characteristic of the organism of every human, irrespective of its type or constitution. Starting from the zygote, all organs develop in a determined formal and functional form, the function of the organs

becomes co-ordinated, different functional systems come into existence, and a somatic entity develops which requires and at the same time secures the internal expediency of the function of these systems. This entity is probably more than a summation of its parts. In spite of deviations in the course of life, the basic balance of this entity, its somatic homeostasis, is secured neurally, by intero- and exteroceptors, and humorally, through the exchange of body fluids, where the different materials of the fluids influence the sensitive nerve cell groups, the transmission of information.

So there is a certain directing and executing system within the somatic organism. The directing system aims at ensuring survival of the organism, and after a certain maturation its self-repetition and thus survival of the human race. The system asserts itself both in health and in disease. In the latter case the system directs and activates the functions expelling foreign materials from the organism, or neutralizing these materials; and the functions balancing deficiency or satiety states, or those restoring morphologically traumatized parts, and the functions ensuring a bridging over of injured or lost parts.

Thus, the somatic organism develops and matures according to genetically determined rules valid for every human, even under the most different external circumstances, according to identical morphological, constitutional and functional patterns, with negligible individual differences.

The basic function of the somatic organism is to satisfy the actual needs and demands of physiologic character. While doing so, the partial functions and their co-ordination follow past experiences, everything happens according to previously established methods. This means that the perception of needs and demands in the course of life, the attempts at their satisfaction, and the ability to satisfy the internal conveyance of materials and the functions of movement, develop in different parts of the soma as programmed during phylogeny. All these activities aim at safeguarding the maturation and survival of the individual organism at a given time.

The unconditioned reflex system, one also programmed during phylogeny, means the internal mechanism meeting the needs and demands of physiologic character. At the beginning of ontogeny it corresponds to the ability to develop the unconditioned reflex system. The source of stimulus in this mechanism are the needs and demands caused by some vegetative change of physiologic character at a given time, and the reflex arc is the chain of unconditioned reflex processes in the first signalizing system. The end of the chain is an event covering the needs and demands. This concerns both the parts of the soma (cells, tissues, organs, systems) and the organism as a whole.

The important unconditioned reflex mechanism involves the responses of heart function, blood pressure, the tonicity of blood vessels, respiration, the activity of sweat glands, the func-

tions of the digestive apparatus, the systems of urination and defecation, cellular metabolism and the endocrine system. There are in addition the orientation reflex, searching and seizing by mouth, sucking and swallowing, signalling by crying (by uttering sounds), clinging, escape, protective movements, restlessness (torment) elicited by needs and demands and manifesting with crying and movement, and calming down (joy) elicited by the satisfaction of needs and demands. All these unconditioned reflex functions are constant characteristics of human life under healthy circumstances from birth to death. Thus, the basis of functional activity and manifestation of the soma is an endeavour to satisfy needs and demands of physiological character. The stimulus inducing the pulsation of life therefore arises from needs which have attained a certain intensity. The mechanism of functional movements is an unconditioned reflex process. The purpose of functions is a response to the stimulus by acquisition from the external world or by the mobilization of internal reserves. The guiding principle of starting and maintaining these functions is ultimately to secure the individual's survival, and through this the survival of the race.

The development of needs and demands, the mechanism of meeting them, the acquisition of materials from the outer world, the mobilization of internal reserves, and the purpose of satisfaction comply with general biological and physiological rules. Thus, the stimulus-excitement in the somatic organism, the internal and external processing of them, the relief and response,are all of biological-physiological character, i.e. specific to man as the direct manifestations of nature characterizing all living organisms. The organism ensures the biological continuity of human life, and it is this biological-physiological formation which opens the possibility for all human events. The specific functionality called higher nervous system, develops within that formation. The psyche, as a specific human formation, exceeds this merely biological sphere.

Some of the details concerning the soma as a separate entity are still disputed. These are, however, of minor importance. The theories relating to the development and nature of the human psyche are more complex.

II. The psyche

It was perhaps Platon who expressed most precisely the idealistic concept concerning the psyche. According to this concept, the spirit is eternal, the primary essence of human existence. The eternal spirit used to be considered separate from the body. This view cannot be maintained in the light of present theoretical knowledge and experience. It will suffice to mention that physiological changes can be brought about in the nerve cells without morphologic changes, merely by drugs or other agents binding specially to certain nerve cells, and thus the psyche can be influenced, changed through these physiological changes. The roughest influence of

this kind is general anaesthesia. The anaesthetics suspend the activity of certain nerve-cell groups, and in this way suspend the whole psychic function. Certain drugs cause depression, others may act as euphoriants. Phantastic visions and hallucinations, generally considered psychic manifestations, may also be elicited by chemical agents. Paediatric examples are the chromosome aberrations, when enzyme deficiencies, typical physiological disturbances, lead to mental retardation. There are some mental disturbances, which can be cured by specific diets. And, lastly, the "spirit" or some "spiritual" activity may totally change in certain illnesses due to morphological changes. On this basis we believe that the medical way of thinking can effectively be employed to understand the essence of the psyche.

The psyche in the living organism is the functional entity of certain special activities of the brain, of the central nervous system. The term, within the living organism, must be emphasized. The brain removed from the organism, or a tissue culture of nerve cells, do not have psychic functions. The co-ordinated activity of the peripheral nervous system, the organs of sense and locomotion, the endocrine system and the extero-interoceptor system are essential conditions of psychic function. Actions are not the result of merely the peripheral and central nervous system, but the musculature, the joints and the skeletal system too have an essential role in it.

The human psyche interpreted in this way is not eternal and not a primary matter. It develops individually in the course of man's life. During individual development it constantly undergoes changes, and at the end of man's somatic life it ceases to exist.

This view concerning human life includes the principle that as regards the psyche, everything starts anew in the individual at birth. The psyche is formed by the everyday human existence during ontogeny. The psyche is a functional unity of cybernetic character, which directs behaviour and action, it has the task to think and to perceive the world, to interpret and evaluate both the external and the internal world while building itself, governing itself and expressing itself in each phase of the individual's life. The psyche develops separately in each individual as a result of the events which have taken place until a certain moment of life, so that from birth each man lives in a specific natural and social environment together with the other subjects of this environment. It influences these environmental factors in an active and passive way, and in both ways. Thus, the psyche is an individual function corresponding to the level of maturation, the development of a given phase of life in every moment.

This view includes the fact that the human psyche does not come into being all of a sudden, but is the result of a certain process. The painters of the Middle Age illustrated in beautiful paintings on the basis of biblical de-

scriptions, how the Holy Ghost came down from heaven and gave spirit all of a sudden to people at Whitsuntide. However artistic the imagination and illustration of that kind is, it contradicts reality, since the psyche does not arrive into man from outside all of a sudden. This is not the way how the psyche develops. But not in the way either, as Pallas Athene had burst out from the head of Zeus on the stroke of Hephaistos' hammer, totally mature, ready for defence and attack, in full armour and beauty. In reality, the psyche is the result of a development in the course of individual life. The human psyche, as a special function, is an individual product, a product not of material character, but a function.

To elucidate this issue it has to be taken into consideration that today's human being is essentially of social character, though it has a biological basis. Environments of social character are decisive in development of the psyche. Environmental effects have the characteristics of human communities. In the newborn, infant, young child or the young man social environmental effects are realized through the mother, father, the sisters, brothers and relatives, through the family as a whole. In school age, effects are realized through schoolmates and adults, especially teachers. In adulthood, first of all the colleagues and the community of the working place are of influence, and this influence is realized in living together, acting, interpreting and evaluating every thing together with other people.

The main point of this coexistence is that the individual and his environment represent a functional unity. The younger the individual, the stricter the rule. The internal environment of natural and social character consists of physical and chemical elements, objects (instruments), persons, systems, structures, real actions, phenomena and abstract meanings (heritage and actual qualities) from the beginnings of individual life. Within this functional unity, the process of coexistence has a tripartite mechanism and function from the point of the individual.

1. The first is a system of events including the individual's efforts and activities to adapt himself to the environment actively or passively;

2. the second are the efforts and activities of the individual to change the environment;

3. the third are the conscious and unconscious efforts and activities at storage in the course of the previous two functions. Having reached a certain level of maturity, these systems become interwoven and affect the individual as a totality. The results of these actions are called adaptation and accommodation.

It belongs to the above interpretation that the result of the functioning of the psyche reacts secondarily upon both the individual and the social existence. Once the psyche is fully developed, the individual keeps connections with the external world and with his own internal world, his own remembrances, connections. Keeping connections with the external world

consists in giving and receiving signs of communication character. To keep connection with the internal world consists of codification and interpretation of signs as well as a subjective evaluation of informations.

The psyche as a function not only enables, directs, determines, regulates and manifests these connections, but also reflects them. It reflects them in somatic changes arising under the influence of the connections, and beside this passive reflection, it evaluates the stimuli and excitements derived from the connections actively and from the point of the individual. The psyche is, therefore, the unity of the activities of connection-keeping and of psychic contents accumulated until a given time at a certain level of development. The latter is the world of memory. This world of memory is partly static, being a system of knowledge and experience fixed verbally, and partly dynamic, being a complicated relationship between the activities of the inherited unconditioned and the individually acquired conditioned reflex processes. It is characteristic of this relationship that the past results persist as functional potentialities in the memory in the broader sense of the word. This persisting character of the experiences together with the continuous maintenance of existing connections is the subject of the individual.

The systems mentioned above are interconnected. The existing subject, one of the components of the psyche, is the result of the connection processes in the course of the individual's life. This determines the two processes of connection-keeping, from which the result basically originates: connection with the external world and with the internal world. The same connection is characteristic of evaluation. Evaluation takes place in the system of information, having developed from the results of connection-keeping based on the world of memory. Evaluation is to a certain extent subordinated to the object of life, which has developed individually. The object of life represents the future of the individual.

The psyche is therefore a) a dynamic system of energy fields, the world of memory; b) a kinetic system of actual processes of keeping connections (communication with the external world, giving and receiving information, connection with the own world of memory); c) a system of internal processing of impulses derived from connection-keeping; d) a system of evaluation of stimuli and excitements concerning the individual himself.

It is essential that both the internal model of the external objective and subjective world and the own model of man himself: the model of the body and that of the ego, are built up in the world of memory of the subject, as a result of the processes listed above under a) to d). The two models together make the internal human model, and there is the individual's world model, the model of existence. This model system makes it possible for the individual to control each phase of connection-keeping with the external and internal world, before every

activity, a preliminary internal consideration of the decision of starting the operative execution of actions, behaviour and activities. It also allows the necessary correction of originally scheduled activities, taking into consideration their expected effect on the models. Finally, it is also this system which affords the possibility of storing the results of events according to evaluation.

The psyche considering its mechanism is cybernetic in character. It is building up, correcting and improving itself steadily through feedbacks, ensuring the continuity of all partial activities according to a definite order and purpose. This cybernetic function of the human nervous system keeps connections with the external world and with the world of memory in order to ensure physiological and psychological homeostasis. The process of connection-keeping takes place mainly in the present, although the evaluation of stimuli, informations and impulses is made on the basis of both the past experiences and the consideration of future possibilities. The evaluation process makes use of the continuously integrated model of the external world and that of the subject formed about himself (world model), both developed with consideration of the future interests and purposes of the individual.

Mechanism of development of the human psyche

The psyche gradually becomes the specific function system of the brain, abstracted from the morphological, physiological systems of the individual's somatic organism. This ability of man developed during phylogeny makes this abstraction possible; that is why man is called an abstract sign producing being. The ability of abstraction has rendered man the most developed form of material motion.

The abstracting function is formed into a system under the influence of social and natural environmental effects in the course of maturation. The function develops while living together, acting together with the environmental effects, adapting oneself to them, striving at changing some of them, and storing certain things from the results. Individual experiences and acquired knowledges also belong among the results to be stored. So the psyche is the result of an external-internal integrated active-passive processing of stimuli and excitements elicited by three basic forms of events. In other words, the physiological events of the organism and the function of the organic physiological systems form the biological basis of the individual's morphology, upon which events of physiological character are built up and in which they are built in, from which they are then abstracted, and in the later periods of life these events are built on each other together with the previously developed ones.

The three events are 1. endeavours and activities aiming at adjustment; 2. endeavours and activities at changing the environment into one suited

better for the individual; 3. endeavours and activities aiming at storage develop and become characteristic under the conditions of everyday life in youth. At the beginning, all these are independent partial functions. Subsequently, with maturation, more and more partial functions unite into greater systems. On reaching full development, these systems are settled into a single complex functional entity. In this way the human psyche is the historical result of the individual processing of the life experiences acting on the individual and his social and natural environment, and the result of partial processes, purposes, successes and failures. At the beginning of life, the history of the individual psyche consists of abstractions of physiological functions built upon unconditioned reflexes and being built into them. Later, at a higher level of development, the psyche is made up of certain automatic processes. The different actions and expectations of the society and the adults of the environment: feeding, care, provision for satisfying needs, demands and requirements, habituation, teaching, living, education (rewarding, punishment) are the stimuli processed in the young individual. The psychic system is not static, but dynamic in character, the essence of which is a continuous functioning.

The human psyche after a certain level of development has a structure consisting of two basic functional systems: the system of conscious and that of unconscious functions.

a) The definition of the conscious is still debated. Its contents and functions are the results of events of life which have taken the form of sensations, ideas and notions. They can be expressed in words used in both external and internal speech. This definition of the conscious seems acceptable, since learning to understand and use words and speech develops a new partial functional system which is then built into the previous primitive, still unconscious psychic system. It means an abstraction of the actual situation and of the specific meanings. Speech means the function of abstraction of perception and sensation elicited by an actual event of physiological character, and at the same time the function of evaluation progressing from the unique towards the general. Internal and external speech provides means for the highest abstractive creative processes.

b) Similarly debated is the system of unconscious functions, the functional system of unconscious contents.

The unconscious functional contents of the human psyche are individual. As such, they are situated in the world of memory of the individual, in the form of individual memories of dynamic character. Individual life is a processing of the results of events of the common life of the individual and his environment.

These dynamic individual unconscious memories of the excitation-excitement processes elicited by certain stimuli are characterized by the possibility and compulsion of being repeated under the influence of a specific stimulus. According to this,

an individually determined form of memory takes place in internal repetition. These specific coded memories can be repeated at different levels of the unconscious. A closed form of the repetition process may take place in the fluid system and in the motion of materials, in the cells and tissues. It may take place in special primitive feelings and emotions. A previous individual state of existence may completely be repeated with the help of the unconscious memory. These individual memories in the unconscious are directed not only toward sex, but toward every field of the former life of the individual.

The contents of the unconscious are not inherited. They have been experienced, built in and fixed in the personality in a closed form, during the early phases of development. These primitive life experiences become fixed during the repetition of the stimulus-excitement processes, of the needs and demands of somatic character. Their fixation means that the same processes are repeated in functional unities by "remembering" certain actual stimuli.

In a more advanced stage of ontogenesis, but before the development of speech, primitive emotional demands of psychological character are abstracted from the physiological demands registered by the individual and from pleasant experiences of satisfaction of these needs and demands. Especially in this age are the repeated wishes and endeavours capable to satisfy the psychic demands, whether or not they had been successful and fixed in the unconscious in the form of closed unities, ready to be repeated through the memory, as elicited by primitive emotional motivations. The unconscious memories of this kind represent the possibility or compulsion of repetition under the influence of certain stimuli.

The unconscious memories are, accordingly, partly needs and demands of physiological character in the very early phase of life, and partly consequences of the fixation of the same processes of satisfaction or failure being continuously repeated, and consequences of demands of primitive physiological character having been abstracted from the earlier pre-speech age. In this way they are built up in the conditioned reflex systems in the course of repetition: These processes affect psychic function in the form of fixed motivations in the coming years of life.

The functional contents of the unconscious have a common point in future life: they cannot be abstracted and formed, composed into conscious sensations, ideas, words or internal speech. If the excitement is realized, it becomes active in the memory under the influence of some external or internal stimulus. If the excitement is repeated and its relief remains in the unconscious, it appears in a primitive form in the somatic events. As mentioned before, the somatic response can be a change of the materials in the body fluids, of organic functions, induction of moods, feelings and emotions in the preconscious with a full repetition of the former individ-

ual state of existence. The response may in addition be short-circuited and manifest with some external movement (physical exercise, unconscious action, outburst of emotion) in a more complicated form.

c) The conscious and the unconscious are not separate static, but dynamic systems in the human psyche. They have complex relations within the construction of the psyche, and have steady interconnections within the personality.

1. The psychic contents are not inherited, but acquired in the course of ontogeny. The abilities and aptitudes are inherited, and then make it possible for the psychic contents to develop, to settle in definite functional systems and to be organized into a cybernetic unit characteristic of the individual living and acting together with other people in society.

2. The basic principle of the psyche as a functional unit is the co-ordination of events and meeting present demands, although the mechanism of the internal process of satisfaction serves the demands of the objective life, the future. The dynamics of the search after possibilities to reach the desirable future, as an effect, is reflected in the present, but the character of the present is determined by the past.

3. The psyche functions by a special mechanism, the conditioned reflex system, i.e. the direct and indirect social connections. The social rules from the beginnings of ontogeny are built into the internal functional processes so that the conditioned reflexes are built upon the unconditioned reflex system, through the adults of the environment.

4. The two systems, the functions of the unconditioned and conditioned reflexes, remain in close connection in the course of life, in spite of the fact that sometimes and in certain dynamic situations one or the other becomes dominant within the personality. So they may seem to be independent. Under such circumstances the one may partially be blocked for a period of time as a result of a conditioned reflex function of inhibitory character. It may also occur that the influence of some too intensive stimulus releases the potential predominance of one or the other reflex function interference-like, manifesting itself in processing and the response to the stimulus.

5. When interpreting the reflexes concerning the psyche, the view of Anokhin is accepted against that of Descartes. According to that view, reflex arcs, reflex chains, and reflex rings constitute interconnected complex reflex systems.

6. Only the final result of the human reflex process, the response can be recorded by an outsider. The whole mechanism can be explored or followed only with complicated methods, by conclusions drawn from the response. Exploration is hampered by the fact that the end of the original primary reflex arc is the source of stimulus for the next link in the chain of internal processes. This occurs in a complex reflex process and the totality of the parts which can only be under-

stood through transmissions. This is the only way to detect the original stimulus and to explore the complicated processes of the internal function of stimulus and excitement and its relief by a response, and the activity of reflex system and the linking of its parts. The factors determining the behaviour of man cannot be understood without their knowledge.

III. The personality: Interconnection and interdependence formed into a system

When observing directly the interconnections of psychic and somatic factors, it must be stressed that interconnections of the human psyche and the somatic organism, the close connection and interdependence of their functions, are realized in the development and function of the human personality and its manifestations towards the external world. If the determinants and the functions of the personality are studied, the connections of the somatic and psychic factors can directly be explained.

The personality is the determinant unity of the morphological components of the individual, the functional form of living life, of the mentality, attitudes, manifestations and activities of the individual, that makes him unique in the social community where his personality has developed and in which he actually lives.

When examining the personality, the individual's somatic development and function and psychic development and function cannot be separated. The two features form a unity, they are closely connected and depend on each other in the course of individual life. They form a unity in individual development and in all functions. The personality is not only the totality of the individual psychic and unconscious psychic characteristics, but it comprises the general human and individual characteristics of the somatic organism as well. The human personality is a special, individually regulated entity of all morphologic and functional qualities of the individual within the frame of general human characteristics. It is this entity in which the somatic organism and the psyche are interconnected. The processing of stimulus-excitation-relief occurs into the somato-psychic and the psycho-somatic direction.

In order to understand these interconnections it is indispensable to determine the function of personality. The personality reflects the attitude of the individual towards the external world (subjects, structures, persons, individuals, groups, "other people", cultural heritage) on the one hand, and towards his own internal world, i.e. his soma and psyche to his present, past (world of memory) and future (object of life) on the other hand. It comprises and integrates the form, intensity and nature of the somato-organic and psychic stimulus-excitation processes elicited by external and internal stimuli (information); and it comprises the integrated forms of processing, of excitation processes

elicited by diverse stimuli. It is also the personality which emanates the results of the integrated results of processes towards the external world. The latter includes the characteristic external responses to stimuli and the individual characteristics of the intensity and nature of communications towards the external world.

The function of personality involves in addition the possibilities of modification of the previously developed personality form and content through feedbacks and internal evaluations, i.e. in the frame of self-development.

The personality develops and changes in the course of individual life. Use of the term personality is therefore incorrect for designing the unity of attitude, behaviour and manifestation of a mature adult individual only. What should then be called the manifestation entity of the infant, young child, and adolescent when it is evident that there are individual differences in the fetus, newborn, infant, young child and adolescent, too. Individuals in all these phases of life have their own unity of attitude, behaviour and manifestations: they are unique and have a personality. We therefore separate the personalities of the different phases of life and call actual personality the personality of an individual in the given phase of his life.

The actual personalities of different life phases are built upon one another in the course of individual development. The actual next one develops from the previous one, and so the consecutive personalities follow one another and are in close connection. The difference between them consists in the progress of information processing with age.

The progress of processing information, the quality and quantity of the processed contents in a given period and the connections of these contents; the sequence and form in which these connections are built up one upon the other constitute the course of human personality development. This development must be favourable, since the external world including other people and more or less the individual himself, judge a man on the basis of the manifestation, behaviour, attitude and actions of his personality in every phase of life.

The two basic systems in the individual, self-development of the soma and the psyche are subordinated to the development of the whole personality. Whether this relation of the two systems will be dominated by the soma or the psyche, depends on the stereotypes developed previously.

In the course of individual life a persisting personality structure develops through the function of remembering–forgetting. The personality structure is, corresponding to the rules of cybernetics, to be regarded as a functional structure. This is essential, as the interdependence of somatic and psychic factors and the function of the personality can only be understood if the personality is interpreted not as a strictly static construction, but as a dynamic functional system reacting upon itself and manifesting itself.

Within the personality structure several structural elements and partial functional unities exist. They are the vegetative, the kinetic (motor), the intellectual and the sexual personality elements. They all have complicated connections to the other ones. These specific personality elements each represent energy extension fields within the dynamic system and at the same time partial functional unities for preparing and for processing and solution of certain special tasks. It depends on the stable or actual character determined by the interconnections of the structural elements of the personality, whether an excitement elicited by a given stimulus will be concentrated or fixed during its processing in one of the elements within the structure and will be dominant in the response, or, on the contrary, the direction of the response, and the internal direction of processing mechanism will correspond to the balance of the personality. This means that the nature of the response to a given stimulus, i.e. the direct somatic process developed under the influence of the stimulus, and the motions of the material, the functional changes caused indirectly by a psychic process, and behaviour, attitude as well as activity all depend on the dynamic-energetic connections between the elements of the personality structure, and on the stereotype developed previously.

Thus, manifestations, attitudes and activities of the individual are phenomena representing the resultant of forces of the functional unities of which the personality structure consists. As a consequence, the internal movements determining the actions, behaviour, attitude and manifestations representing the everyday somatic processes and the psyche of man, and the energy transfers within the structure, are of two directions within the whole personality: the internal movements determining the response, and the results of energy transfer are of somato-psychic domination at one time, and psycho-somatic at another time.

I shall not quote case records to illustrate the psychic events arising under the influence of stimuli starting primarily from the somatic organism, or of somatic phenomena elicited by primarily psychic effects. In previous papers we have reported on observations, the reality of which has been proved by the success or failure of treatment. These cases showed that psychic changes in the personality can be elicited not only by grave and sometimes lethal somatic illnesses, but the younger the patient, the more do comparatively mild somato-organic functional disturbances (dehydration, acidosis, retention of certain materials in the body fluids) affect his psyche in a temporary or lasting manner. Secondary functional disturbances and complaints of physiological character may arise in nearly all somatic systems under a continuous psychic influence, and after lasting functional disturbance some tertiary morphological changes may develop.

Not only somatic and psychic factors continuously affect each other

within the personality; everyday processes also do so. The psychic effects of gastrointestinal function are well known. A pleasant dinner made up of favourite dishes of the individual will cause an euphoric state, even without any spirits. And, if we only think of our favourable dish, salivary secretion starts. Similar examples can be taken from the field of sexual life. The psyche is activated in partner search on the basis of an increased hormonal release and, on the contrary, if the individual thinks of his partner, which means a merely psychic stimulus, the same hormonal process starts in the organs as if the individual had in fact met the partner, as if a natural stimulus had affected him. These are examples of complicated somato-psychic and psycho-somatic processes with complicated interconnections. When e.g. a susceptible person has had a substantial dinner, his stomach becomes overfilled, his diaphragm pushed up and his heart is dislocated upwards and to the left. This abnormal situation of the heart may affect the coronary circulation, causing the symptoms of angina pectoris in the somatic organism. If there is fear of cardiac death in the conscious element of the individual's psyche, the sensation of the symptom mentioned above is stimulated in the conscious, causing an increased fear of death and eliciting anxiety in the emotional sphere. This anxiety as a psychic stress sets in motion a distress process, as a result the coronary disturbance increase, resulting secondarily in serious psychic angina pectoris, and without due intervention the vicious circle may cause not only functional but also morphologic disturbances of the heart.

In this way, processes of psycho-somatic direction involving sudden anger, fear or joy may lead to changes in the circulation of blood, in sweating, in the rhythm and depth of breathing, or may elicit urination or defecation.

As to the mechanism, by which the somatic organism and the psyche affect each other within the personality, it must be taken into consideration that the humanization of vital processes in modern individual life, the socialized humanization of vital processes is the key to the development of personality. It is essential for this humanization that the unity of the biological and social formations of man be realized in the personality in the course of individual life.

Human vital processes are direct and indirect reactions. It is characteristic of the living organism that if it is affected by a stimulus exceeding the excitability threshold, an excitation is stimulated in the organism. This state of excitation cannot be maintained permanently, it must be relieved, since the organism must regain its characteristic internal state of balance (homeostasis). The relief of excitation is a response to the stimuli processed internally. The stimulus-excitement, the processing ending in relief, including the nature of the processing system and the relief (action), are reflected in the vital process.

Human life is, of course, not a reaction to single stimuli, not a single response, either quantitatively or qualitatively. It is a number of reactions and responses, sometimes groups of them built up in a complicated way, being effective in an indirect and interwoven manner. Stimuli ellciting excitement in man may start both in the personality and in the external world. Both internal and external stimuli may be of natural, objective character or signals of abstract character, brought about by man.

Objective stimuli, those of natural character, elicit a response, once their intensity has exceeded the threshold. As to the stimuli of abstract character, it is a characteristic of man, in which he differs from any other living organism, that he creates abstract signals, using the created and learned signs for indications and can understand and perceive an abstract signal as a stimulus may be equal to that of objective natural one, which may have been the basis of the signal abstracted by man in general long ago.

The personality perceives the internal stimuli of natural character, the demands through interoceptors. These are parts and results of actual physiological or pathophysiological processes. Internal stimuli of abstract character derive from sources of stimuli such as thinking, evaluation, raving, perception-emotion, appearance in the memory, i.e. from the world of memory in the broader sense of the word.

External stimuli come from nature and society, and are received by man through exteroceptors. While stimuli of natural character originate from the environment, stimuli of social character may come directly from the society, and indirectly from the history of mankind and the heritage of culture and civilization. All these social effects are transferred in the form of sources of stimuli from other people, either directly from persons, or indirectly through activities like writing or reading. In possession of a certain knowledge, man seeks them as sources of stimuli.

Human life manifests itself with a diversity of stimuli, in complicated chains, rings, complexes of somato-organic, psychic reactions linked openly or in a concealed way.

Socialized humanization of life processes

To clarify this issue, it is necessary to repeat the interpretation of reflex processes, where the term reflex is not used in the sense as Descartes did it, but according to Anokhin. Reflexes are events activated by effective stimuli. In the course of man's development, reflex arcs, reflex chains, reflex rings and complex reflex systems arise. They are closely interconnected through somato-psychic and psycho-somatic functions. As to their nature, they can be divided into two groups, viz.

a) reflex forms of physiological character,

b) reflex forms of psychological character.

The physiological reflex forms are

a) inherited unconditioned reflexes,

b) acquired Pavlovian temporary conditioned reflexes, and

c) acquired definite reflexes relating to individual life.

Among the reflex forms of psychological character, there is no inherited unconditioned reflex. These reflex forms are conditioned ones, acquired in the course of individual life. They can be divided into three groups, viz.

a) acquired classical Pavlovian temporary conditioned reflexes,

b) acquired definite conditioned reflexes of the individual's life,

c) complex reflex forms, suitable for creating new responses; we term them creative response.

These forms are internal processes (partial functions, systems of partial functions), which mean not only the continuous mechanism of personality function, but also the mechanism of sozialized humanization.

Within the function of the personality as an entity, the function of one or the other of these reflex forms dominates in the individual, corresponding to his age and level of development. In the first ten days of life, only the inborn unconditoned physiological reflexes are functioning. The classical Pavlovian vegetative-somatic physiological conditioned reflexes (vegetative, visceral, motor, perception) are built in into these unconditioned reflex processes with events of feeding and somatic nursing. Later, after the 6th—8th week of life, the emotional, i.e. conditioned reflex-functions of primitive psychic character are built upon the previously developed reflexes, and fixed under the influence of life with the mother or her substitute. Later in infancy, after 6 months of age, and gradually in childhood and adolescence, or under unfavourable circumstances only in adulthood, the acquired unconditioned reflexes of psychic character are continuously built in into the personality function. Especially the creative responses, as the most differentiated partial functions of psychic character, are important among the reflex processes.

Speech, learnt with the help of adults, is of great importance in the development of reflex forms of high-level psychic character. This includes the understanding of words and speech, and learning to signal by means of words and speech, later in childhood, being acquainted with letters, learning to read, write and count, and being able to use these functions for giving and receiving signs. The basis of the development of these high-level psychic functions are the understanding of sounds as primitive signs, the understanding of daylight and darkness, learning to seize with the hands, creating means of subjects, standing and walking, and, parallel with these, understanding the meaning of actions by the help of adults.

The adults of the environment influence the internal process, and the totality of the result of this process leads to the socialized humanization of the vital processes of biological character through reflex functions of

high-level psychic character. The social meaning and evaluation of the vital processes are handed over, built in by words, writing, and signalizing, programmed into the functional system of the personality of the young impressionable individual. The programme becomes definitive, if the individual accepts and identifies himself with these effects of the adults in his environment and he builds in the manifestations into his system of interpretation in the form of an irresistibly directing stereotype.

The abstract world of signs becomes an equivalent source of stimuli with the natural phenomena of life and with the world of external objects. So the abstract signs may elicit an excitation equivalent, excitement with the letters and should also be relieved.

Knowledge of the internal stimulus-excitement-relief process preparing the kinetic response helps to understand the interconnection of the somatic organism and the psyche, the mechanism of the socialized humanization. A simple example will suffice to point out the essence of interactions. A young girl goes to a party. As the room is hot, an unconditioned stimulus-excitement process starts under the influence of the high temperature and beside other phenomena she begins to perspire, especially in the axillary region. The process would have no consequence if the girl were alone at home, but at the party where she desires to have success, if she becomes aware of the intensive smell of her sweat, this starts a conditioned reflex process in her psyche. She believes that her friends will smell the unpleasant odour. This thought of fear of failure is elicited by primary somato-organic factors. The conditioned reflex chain in her conscious elicits anxiety in the emotional sphere. She is worrying about being put to shame, being ridiculed, and she becomes disappointed. Anxiety, a psychic distress, reacts upon the somatic organism and instead of being stopped or relieved, the perspiration further increases. In this example a primary somato-organic unconditioned reflex process was the stimulus, which started a psychic process.

The direction of the interconnections can also be opposite. Let us take a young man who participates at a contest of gymnastics. He feels an eagerness to compete in his psyche, this means that he is anxious to score a success. The anxiety, a primary psychic distress process, increases the activity of the sweat glands and makes his palms sweat. The conditioned reflex process is followed by a further chain-reaction. The competitor knows that his hands may slip and therefore makes mistakes in the exercise, endangers his success in the competition, he will be disappointed and will fail. These psychic factors are further stimuli (effects of distress) to the somatic organism, and the perspiration is increasing further. The above two examples show convincingly the pattern of interconnection and interdependence of the somato-organic and psychic factors on a previously established stereotype.

These examples will help to understand more complicated somato-psychic and psycho-somatic processes of different directions. The fact must be borne in mind that everyday life cannot be compared to that of a test animal. People do not live in sound- and light-proof, air-conditioned laboratory rooms, but in open social and natural environments, where their personality is developing and where there are developed adults, and all stimuli including the teaching and education by adults, are processed in their specific individual personality by their specific evaluating system. The stimuli of natural and psychic character, i.e. the effects eliciting excitement, become equivalent. Thus, the natural vital processes will be humanized in the way as are the adults of the environment. Parallel with teaching to speak and write, they gradually teach, build in the traditionally developed evaluations of social character a system of meanings generally valid for man, the meanings of good and bad, valuable and valueless, to be punished or to be rewarded and have them accepted by the developing individual. The acceptance of this system of social meanings as a function determining the young individuals' actions, represents the socialized humanization.

The fact, which form of response to a stimulus, to needs and demands, will be dominant in the function of the personality, how the individual responds to the majority of stimuli, and which of the vital processes will be socially humanized, depends on the factors which have formed the specific life of the individual. A possibility for the functioning of all four reflex forms and forms of response mechanism will persist throughout the life of the individual, while the primordial forms endanger the effectiveness of the younger ones. It depends on complex processes, how effective the socialized humanization will be in the interpretation of vital processes, and in the system of meanings; and also how effective the younger forms of processing and response will be in the direction of the individual's manifestations. It is known that the psyche makes use of a coding system to estimate the meaning of the stimulus before the actual personality begins to function and a kinetic response is given. The key to this coding system are the estimates "good for me" and "bad for me".

The "good for me" and "bad for me" estimates are either somatic or psychic in character. The meaning of the decoded stimuli is different: somatic pain or good feeling, favourable or unfavourable physical conditions. It may be of psychic character, like emotional pleasure, sorrow, pain; or of intellectual character: material, ethic, aesthetic values. As to the nature of the decoded meaning, the most important question is whether it endangers or protects the existence of the somatic organism, or whether it means annihilation, help or support for the psyche.

Even the most sensitive, mature human personality follows the fundamental rules of the ancient living or-

ganism, when processing a stimulus-excitement, or when taking stand in actions, activities, attitudes, i.e. when he responds to a stimulus. The ancient law is: one should escape from the "bad for me" and approach the "good for me". The "bad for me" should be attacked, destroyed; the "good for me" should be kept and protected.

It is not simple to realize the escape from the "bad for me" and the approach to the "good for me" in everyday life and to develop a view concerning action, activity, motion, behaviour and attitude for the complex human personality including his psyche. It is not so simple as for an amoeba: The amoeba moves from the dry place, a "bad for me", towards the wet place, which is a "good for me", thus his choice is based exclusively on chemical and physical effects. The human response to a stimulus, the manifestation of personality, is realized in a complicated chain of transmissions in the form of taking stand, action, behaviour and attitude. There are men who can stand dangerous somatic "bad for me" states, stand physical pain, even death, because the action, activity and behaviour realized in the processing of the stimulus in his personality causes a "good for me" of psychic character, and this kind of "good for me" is considered the most important human attitude and to arrive at it is the object, the sense of life for that man. The complicated transmission can be an opposite one, too. There are men who can endure psychic "bad for me" states, or an existential annihilation of psychic character unbearable for other people; all this only for the sake of attaining a somatic "good for me".

Clinical experience shows that the younger the individual, the less developed the social humanization of his personality, the more are his manifestations, standpoints, actions, activities, behaviour and attitude dominated by the somato-organic "good for me". The more mature, sensible and complicated his personality, the more do the endeavours at reaching the psychic "good for me" states dominate in the subject's manifestations, actions activities, behaviour and attitude. In general, the latter form of living life develops merely with ageing. It blossoms out in the phase of development, when not the importance of the age is in the centre of the personality dynamism (function system), but the importance of *I* is included in the importance of *we* together with the importance of *you*, *he*, *she*, *they*. On that level of development *we* takes the most important places in the personality and the "good for us" and "bad for us" instead of the "good for me" and "bad for me" are the keys of coding the interpretation of stimulus. *We* means *I* and *you*, the unity of mother and child on a lower level of development. Later the other members of the family join this unity, and much later *we* includes the totality of people belonging to the communities, working place, country, then mankind and ideas and ideas without any material.

IV. Practical conclusions

The somatic organism, the vegetative soma, one of the two systems constituting personality, develops in a specific morphologic and functional form as a manifestation of inborn characteristics, programmed genetically in the course of biologic maturation. On the other hand, development of the psyche is strictly dependent on the environmental effects surrounding the individual after birth. The psyche develops during ontogeny while living; acting with the people in the social and natural environment in the course of internal processing is induced by actual effects: stimulus-excitement-relief (emotional, ideal, action). The form and content developed are definitely the result of environmental effects. Of external effects, the evaluation of persons emotionally close to the individual are important for him and his actions. The conclusion for doctors and educators is that the characteristics of the somatic organism programmed in phylogeny cannot be altered at will under normal circumstances. The only thing that can be done is to strengthen the favourable somatic qualities and to suppress the unfavourable ones. In contrast, in the psyche the characteristics programmed during ontogeny can be altered with the help of feedbacks and the development of unfavourable characteristics can be prevented. In order to apply this in practice one should consider the methods to be used and remember that immediately after birth the individual is merely biologic in character and later the extra-uterine maturation process follows biological rules. In the early phase of life the dominance of somatic factors is characteristic. Through them, the environment may influence the individual. Thus, the methods of education in early age are concealed in the mode executing the everyday activities of nursing and feeding. Since the life of the individual starts and continues in a social frame, one must consider this when choosing the methods of education. Immediately after birth through the mother and other adults, then indirectly through different institutions, social effects of psychic character start to develop, to form later the functional system called psyche. Parallel with ageing, from fetal life through infancy, childhood, school age, adolescence until adulthood the role of the increasingly developed psychic system is increasingly established within the personality. In order to ensure appropriate progress in the personality from the point of view of both the individual and the society, it is essential that factors of psychic character, educational environmental effects should increasingly dominate beside the effects of nursing, feeding, and the other activities of physiological character, before reaching adulthood. In the consecutive phase of life the internal powers which dominantly direct the vital processes of the individual, also undergo changes. While in the earlier phases of life it is the emotional personality element which has the directing function, in

the course of development the intellectual personality element gradually takes charge of the functions of the system. Under normal circumstances the intellectual character of the psychic effect dominates in the interconnections of the somatic organism and the psyche of a properly developed adult personality. Accordingly the methods of education should contain more and more psychic elements (teaching of verbal character) gradually increasing the load with the progress of life. In addition, education should strive at ensuring the dominance of conscious elements among the psychic ones in the interconnections, considering expectations, needs and demands of modern society. In order to achieve this aim, both the individual, the one who is educated, and the whole society, the environment and the educators should make every effort to observe one another's points of view.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (2), pp. 93—98 (1978)

Serum iron level in acute lymphoblastic leukaemia

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(Received July 11, 1977)

Serum iron level (SIL) was studied by atomicabs orption spectrophotometry in 57 children with acute lymphoblastic leukaemia. SIL depended on the activity of the disease. Mean SIL was highest in untreated children. Normalization of myelograms during treatment was accompanied by a decrease of SIL. A significant decrease was observed in organ localizations and in infections during remission of the leukaemia. SIL may be helpful as an auxiliary test in the management of leukaemic children.

Serum iron level (SIL) as well as that of other trace metals in neoplastic proliferations of the lymphoreticular system and leukaemias in children and adults has been the subject of numerous papers [2—5, 8—11, 13, 18—21]. An increase of SIL during the active period of acute leukaemia results from diminished utilization of iron in erythropoiesis which becomes inhibited by leukaemic metaplasis of bone marrow [4, 11, 13, 20]. Moreover, increase of SIL in acute leukaemia is caused by red cell haemolysis [3, 11, 20] and by release of the iron bound to the ferritin of destroyed leukaemic cells [3, 21]. Drugs applied in therapy can also inhibit the uptake of iron for haemoglobin synthesis [4, 14, 15]. The object of the present study was to investigate the SIL in the course of acute lymphoblastic leukaemia (ALL), to establish whether SIL could be used as an index of the activity of the disease, the efficacy of treatment, and of prognosis.

MATERIAL AND METHODS

SIL was studied in 57 children (31 boys and 26 girls) ranging in age from 2 to 15 years, treated for ALL [1, 15] from June 1, 1973, to October 15, 1974. In 24 untreated children with ALL, the SIL was determined on admission together with the haemoglobin level, red cell and thrombocyte count, quantitative and qualitative leukocyte count, bone marrow count and liver tests. The total number of SIL examinations was 267 (from 3 to 12 per case during the whole observation). SIL was not analysed in those children who 9 weeks before the examination had had a blood transfusion.

As a control group, 59 healthy age-matched children were studied (Table I). Venous blood samples were prepared and stored according to the norms required for iron determination [17].

SIL in serum deproteinized with 20% trichloroacetic acid was estimated by

TABLE I

Serum iron levels (in μg/dl) in controls, in marrow involvement and in complete remission in age groups A, B and C

Age group		A (2—5 yrs)			B (6—9 yrs)			C (10—15 yrs)		
		Normal	Marrow involvement	Remission	Normal	Marrow involvement	Remission	Normal	Marrow involvement	Remission
Number of observations		18	24	29	20	44	71	21	30	48
(Number of children)		(18)	(14)	(16)	(20)	(14)	(21)	(21)	(10)	(16)
Fe	$\bar{x}$	85.8	146.7	90.2	90.3	136.6	88.4	82.3	123.0	85.0
	(SD)	(13.2)	(63.6)	(28.9)	(16.3)	(42.5)	(23.0)	(14.8)	(37.6)	(19.8)

normal = SIL in healthy children
marrow involvement = SIL in children with ALL and more than 5% paralimphoblasts in the bone marrow
$\bar{x}$ = mean value
SD = standard deviation

means of atomic absorption spectrophotometry (Hilger-Watts Model H 1170) [7, 17]. The results were expressed in μg/dl iron as read from standard curves prepared by the use of metallic iron, trichloroacetic acid and deionized water [7, 17].

Mean SIL values were analysed according to age (Table I), the clinical stage of the disease (Table II) and to the degree of ALL activity (Table III). For statistical analysis, Student's *t* or the Welch test were applied after analysis of variance according to the F-Snedecor test [16].

RESULTS

I. SIL in controls, in bone marrow involvement and remission in age groups A, B, C (Table I)

Mean SIL values showed no significant differences between the particular age groups A and B, and C, c and A in healthy children, in bone marrow involvement and in remission, as well as between the control groups and the values obtained in remission of ALL. Values of SIL in all these age groups displayed an increase which was highly significant statistically ($p < 0.001$) in marrow involvement in comparison to the levels obtained in remission and in the controls.

II. SIL in the leukaemic stages (St) I to VIII (Table II)

The highest mean SIL value was obtained at the beginning of the first marrow involvement of ALL (169.3 μg/dl in St I). The mean SIL at the onset of the successive marrow relapses (131.8 μg/dl in St III) was significantly lower ($p < 0.01$) than in stage I. During treatment (St II, IV) leading to remission (St Va, Vb, V, VIII) SIL reached normal values. During treat-

TABLE II

Serum iron levels (μg/dl) in clinical stages of acute lymphoblastic leukaemia

No. of stage	Clinical stage of ALL	Number of observations (of children)	SIL $\bar{x}$ (SD)	Per cent marrow parablasts
I	1st marrow involvement (before treatment)	24 (24)	169.3 (52.8)	89.4
II	1st marrow involvement during intensive treatment	18 (14)	108.0 (41.4)	38.6
III	Onset of marrow relapses (2nd to 7th) during remissive treatment	34 (18)	131.8 (47.1)	70.7
IV	Marrow relapses (2nd to 6th) during intensive treatment	23 (13)	121.4 (37.1)	34.4
Va	1st complete remission	74 (34)	89.7 (25.2)	2.5
Vb	Remissions: 2nd to 6th	21 (11)	83.7 (23.1)	3.2
V	Remissions (jointly) from 1st to 6th	95 (41)	88.4 (25.4)	2.8
VI	Extramedullary relapse of ALL in marrow remission (CNS leukaemia, tumour of testes, kidneys)	25 (14)	71.6 (29.0)	3.6
VII	Bacterial or viral infections during remission	24 (16)	70.8 (21.7)	2.3
VIII	1st long lasting marrow remission over 3 years (6 observations after cessation of treatment)	26 (8)	93.1 (15.0)	2.5

ment, the values decreased, but differed significantly ($p < 0.001$) when compared in the following order: I and II, I and Va, IV and Vb, III and Vb. Mean SIL in stage I (169.3 μg/dl) was almost twice as high as that obtained during the first remission (St Va), 89.7 μg/dl. The decrease of SIL in the extramedullary relapse of ALL (St VI) amounted to 71.6 μg/dl and in the course of infections during remission (St VII) to 70.8 μg/dl; the difference was significant statistically ($p < 0.005$) in comparison to the 88.4 μg/dl mean value during the 1st to 6th remission in St V. SIL in St Va (1st remission) when compared with that in St Vb (2nd to 6th remissions) as well as that in St Va with St VIII did not differ significantly ($p > 0.5$).

III. SIL and marrow parablast percentage in relation to ALL activity (Table III)

The increase of SIL with progression of the disease appeared to be significant statistically and went almost parallel to the increase in the marrow parablast count. In the more

TABLE III

Serum iron values and marrow parablast percentage in relation to the degree of disease activity

Group range of marrow parablasts — per cent		I (0—5)	II (6—25)	III (26—100)	IV (26—100)
Number of observations (of children)		31 (23)	23 (17)	54 (27)	20 (15)
Fe μg/dl	$\bar{x}$	83.1	100.3	122.4	164.0
	(SD)	(20.9)	(33.2)	(20.6)	(47.0)
Parablasts per cent	$\bar{x}$	3.1	14.3	73.4	90.25
	(SD)	(1.52)	(5.4)	(18.7)	(9.55)

I. Complete remission. Results of SIL excluded in VIth and VIIth stage of ALL (Table II)
II. Imminent relapse or improvement during treatment
III. 1st bone marrow involvement or relapse
IV. Marrow involvement with peripheral hyperparablastosis from 21 to 231 thousand/mm^3 and/or leukaemic infiltration of testes, kidneys, mediastinal tumours and hepatosplenomegaly

advanced stages the differences in SIL were greater and more significant statistically ($p < 0.001$). The highest mean value, 164.0 μg/dl, was observed in marrow involvement with peripheral hyperblastosis and extramedullary localization of ALL (group IV).

DISCUSSION

The significant prolongation of survival of children with ALL has made it necessary to work out tests of the disease activity and efficacy of treatment.

For that reason the following tests have been recommended: 5-amino-4-imidazole carboxamide level in urine, fetal haemoglobin in blood, cytochemical PAS reaction, ferritin, transferrin and coeruloplasmin levels in serum as well as serum iron, copper, zinc, magnesium and silver [3, 4, 5, 8, 9, 11, 18—21] estimations. The data on SIL in ALL mostly deal with the period before treatment [3, 11, 13] and some with the period following remission [20].

The values shown in Table I indicate that mean SIL values are influenced by the disease itself and not by the age of the patient.

The classification into clinical stages from I to VIII is an attempt at systematizing the clinical course of ALL (Table II). The highest SIL was seen in St I, i.e. before therapy. The mean value obtained in that stage (169.3 μg/dl) was the highest beside that noted in the stage of marrow relapse with peripheral hyperparablastosis and/or leukaemic tumours (Table III). The decrease of SIL to normal during treatment is connected with the clinical and haematological improvement and with the gradual fall of marrow parablasts to below 5% (Table II).

SIL in bacterial or viral infections during remission (St VII) was similar as in other neoplastic conditions [3, 4, 11, 13]. The decrease of SIL in cases of an isolated organ localization of ALL (St VI) was like that observed in Hodgkin's disease and in other solid tumours [4, 10, 11, 13].

In the present work, it has been attempted to determine whether the SIL was influenced during the course of ALL. As it is seen in Table III, the mean SIL values increased parallel with the increase in the marrow parablast count. This must have been due to the inhibition of erythropoesis by the leukaemic marrow metaplasia [4, 11, 13, 20]. One of the highest mean SIL values (164.0 μg/dl) was observed in marrow involvement accompanied by peripheral hyperparablastosis and/or leukaemic infiltration of the organs (Table III), i.e. prognostically unfavourable signs [1, 6]. The cause of this is probably the fact that iron originates from the ferritin of parablasts circulating in the blood after their destruction [3, 21]. The highest SIL in group IV may have resulted from neoplastic infiltration of the liver which may additionally disturb iron metabolism.

The presented results do not fully explain the disorders of iron metabolism in ALL. They allow, however, some practical conclusions. Thus,

(i) increased SIL in ALL shows a positive correlation with the activity of the disease;

(ii) effective therapy and haematological improvement cause a decrease of SIL to normal values;

(iii) a high SIL value early in ALL may point to an unfavourable prognosis;

(iv) SIL may give some information of the degree of marrow involvement by the leukaemic process as well as of organ localizations and infections during remission.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (2), pp. 99—104 (1978)

Physical growth of children born small for gestational age

By

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(Received November 1, 1977)

In a longitudinal study the postnatal physical growth of 188 small for gestational age and 225 appropriate for gestational age children was compared. A significant retardation in weight, stature, head circumference and osseous development of SGA children was observed even at the age of 3 years.

The physical development of children with low birth weight and/or intrauterine growth retardation has attracted great interest in paediatric literature [1, 2, 3, 4, 5, 6, 7, 9, 10, 14, 15]. The results being equivocal, we undertook a prospective investigation of small-for-gestational age (SGA) subjects with special reference to weight, stature, circumference of the head and osseous development.

Material and Methods

In the year 1972, 2840 liveborn babies were born in our hospital. Out of them 250 singletons (165 girls and 85 boys) proved to be SGA, i.e. their birth weight fell below the 10th percentile of the local growth chart. Of these 188 were followed-up and examined at the age of 6, 12, 18, 24 and 36 months: 120 girls including 48 with a birth weight of less than 2500 g, and 68 boys involving 32 with a birth weight under 2500 g. Their distinction by birth weight and not by gestational age was justified by the fact that all official statistics consider the 2500 g border, irrespective of gestational age. At each examination weight, height and head circumference were measured, and at the age of 3 years an X-ray picture of the right wrist was taken. The latter was evaluated according to the standards of Tanner and Whitehouse [16].

Randomly selected 225 appropriate-for-gestational age (AGA) babies, among them 49 true prematures with a birth weight under 2500 g, served as controls. They were followed-up in exactly the same way as the SGA children.

A summary of the material is shown in Table I.

Results

As shown by the figures of Table II, the mean weight values for AGA girls and boys corresponded to the European standards [11, 12]. Whereas the average weight of AGA premature babies reached the mean value of full-term eutrophic infants by the end of the first year, a significant retardation of SGA children was still visible at the age of 3 years. As Figs. 1 and 2 show, the differences in weight

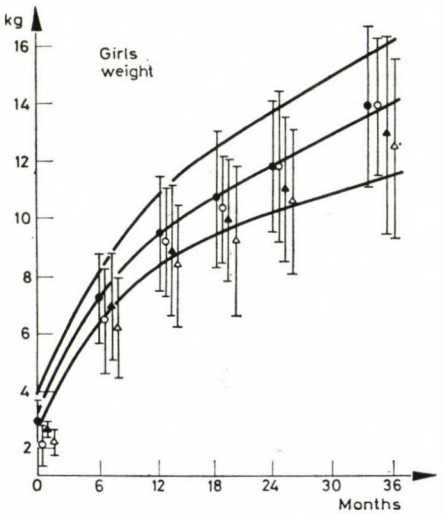

FIG. 1. Postnatal weight gain of girls. Mean ± 2 S.D. —●— AGA, birth weight ⩾ 2500 g; —○— AGA, birth weight <2500 g (true prematures); —▲— SGA, birth weight ⩾ 2500 g; —△— SGA, birth weight < 2500 g

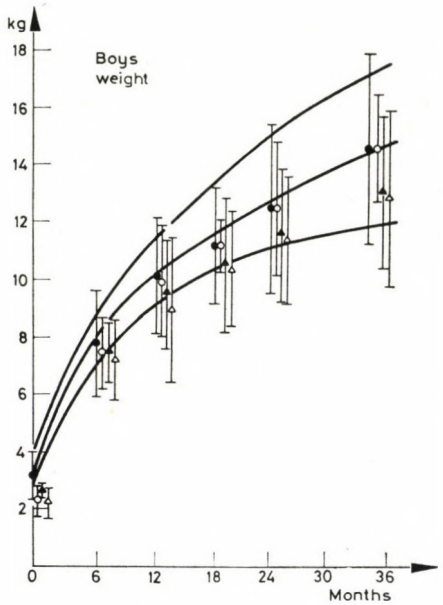

FIG. 2. Postnatal weight development of boys. Mean ± 2 S.D. The symbols are the same as in Fig. 1

TABLE I

Survey of material

	Birth weight		Total
	< 2500 g	⩾ 2500 g	
Small for gestational age			
Girls	48	72	120
Boys	32	36	68
Total	80	108	188
Appropriate for gestational age			
Girls	29	90	119
Boys	20	86	106
Total	49	176	225

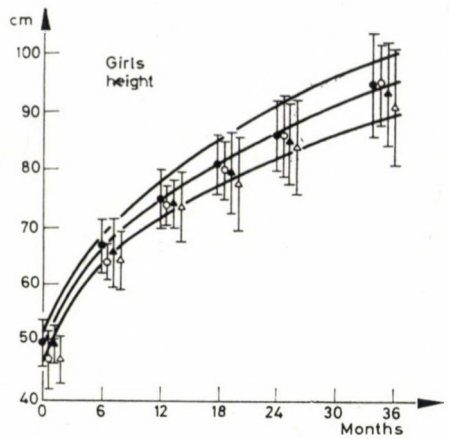

FIG. 3. Height development of girls. Mean ± 2 S.D. For symbols see Fig. 1

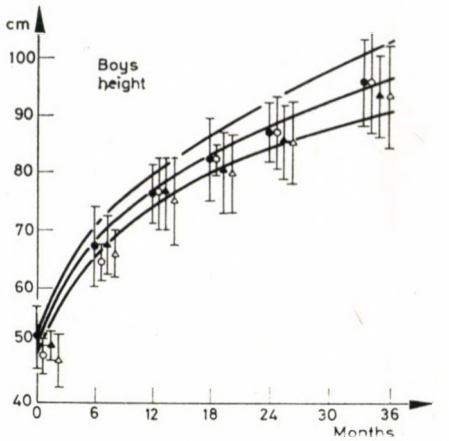

FIG. 4. Postnatal height values of boys. Mean ± 2 S.D. The symbols are the same as in Fig. 1

were more expressed in boys than in girls.

A similar tendency for height could be observed, although the average length of SGA subjects was only slightly less than that of the AGA children (Table II, and Figs 3 and 4).

Mean head circumference was smaller in all SGA girls and in low birth weight SGA boys throughout the 3-year period of the investigation. No significant differences among the other groups were found (Table II).

Compared with full-term AGA infants, both SGA babies and true preterm infants had a lower skeletal age at the age of 3 years (Table III). Because of the wide range this was only slightly or not significant statistically.

DISCUSSION

The present findings support the view that in addition to the well-known acute risks of the SGA newborn, attention should be focussed on the importance of gestational age and birth weight as a factor influencing postnatal growth and development.

In agreement with many authors [4, 5, 10, 14, etc.] we found that SGA children were retarded in postnatal weight, stature and osseous development. This could be demonstrated not only in SGA children whose birth was less than 2000 g [1], but to a moderate extent also in SGA subjects with a birth weight above 2500 g. Bjerre [4] reported a normal head circumference of SGA children at the age of 5 years. In our material head circumference was less than expected in all groups of SGA children during the 3-year period of observation.

A high postnatal growth rate in true prematures was found also in the present material. By the end of the first postnatal year, weight, height and head circumference of these children corresponded to the values of full-

TABLE II

Mean weight, length and head circumference at birth and at 6, 12, 18, 24 and 36
circumference in cm. P means significance compared

Age (months)	AGA controls					
	Girls			Boys		
	Weight	Length	Head	Weight	Length	Head
Birth	2 980	51.5	33.5	3 090	51.5	33.5
6	7 260	67.0	42.0	7 720	66.5	43.0
12	9 470	75.0	45.5	10 130	76.0	46.5
18	10 710	81.0	47.0	11 070	82.0	47.5
24	11 840	85.5	48.0	11 940	85.0	49.0
36	14 000	96.0	49.0	14 500	96.0	50.0
						Birth weight <
Birth	2 010***	47.0***	31.0***	2 230***	47.5***	31.5***
6	6 450***	64.0***	41.0**	7 470*	64.5*	42.5
12	9 200	74.0*	45.0	9 960	76.0	46.5
18	10 370	80.0	46.5	11 470	82.5	48.0
24	11 940	86.0	48.0	12 440	87.0	49.5
36	14 000	96.0	49.0	14 700	96.0	50.0

* = $p < 0.05$, ** = $p < 0.01$,

term AGA babies. This seems to be at variance with previous investigations in which permanent height retardation of low birth weight children was described [8, 13, 15, 17]. The discrepancy is probably due to sampling differences: the comparatively high birth weight of our AGA prematures might account for their rapid catch-up growth.

Investigations of the skeletal age of SGA children in later life are scanty. The data suggest that low birth weight of all types results in a later retardation of osseous development [4, 10]. This was confirmed in the present study, and the results are all the more convincing, since in evaluating the X-ray pictures our method differed from those of both Fitzhardinge [10] and Bjerre [4].

Although some sampling bias, and the role of environmental factors, except for significant malnutrition, cannot be excluded, our data provide further evidence that gestational age

months of age in the groups of children investigated. Weight is given in g, length and head with corresponding values of full-term AGA controls

Small for gestational age children

Girls			Boys		
Weight	Length	Head	Weight	Length	Head
2 650***	50.5***	33.0**	2 650***	50.0***	33.5
6 950*	65.5*	42.0	7 485*	66.5	43.0
8 900**	74.0*	44.5***	9 470**	76.0	45.5**
9 970*	79.5	46.5**	10 430*	80.0*	47.0
11 100***	84.5	47.5**	11 480*	85.0	48.5
13 000**	93.0*	48.5*	13 100***	93.0*	49.5
2500 g					
2 160***	47.5***	32.0***	2 160***	47.5***	32.5***
6 240***	64.5***	41.5*	7 190**	67.0	42.5*
8 400***	73.5**	44.0**	8 930***	75.0*	45.0***
9 250***	77.5**	45.5**	10 500*	80.5*	47.0*
10 640***	84.0*	47.5**	11 440*	85.0	48.0*
12 500***	91.0***	48.5*	13 100***	93.5*	49.0*

*** = $p < 0.001$

TABLE III

Skeletal age in 3-year old children

	Girls			Boys		
	Skeletal age (years)	Percentile position	P	Skeletal age (years)	Percentile position	P
AGA > 2500 g	3.11 ± 1.40	50		3.10 ± 1.52	50	
AGA < 2500 g	2.68 ± 0.68	25	< 0.02	2.65 ± 1.06	25	n.s.
SGA > 2500 g	2.85 ± 1.04	25—50	n.s.	2.85 ± 1.14	25—50	n.s.
SGA < 2500 g	2.52 ± 1.16	25	< 0.02	2.67 ± 0.74	25	n.s.

and birth weight should be considered in estimating the later physical development of a given child.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 18 (2), pp. 105—112 (1977)

100 Jahre des sekulären Trends in einem Bezirk Ungarns

Von

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(Eingegangen am 5. Juni 1977)

Die Gestaltung des Längenwachstums der 18—20jährigen männlichen Population des Landesbezirks Somogy in den letzten 100 Jahren wurde aufgrund von Musterungsdaten analysiert. Es wurde festgestellt, daß die Akzeleration des Längenwachstums in den letzten 14 Jahren zum Stillstand gekommen ist. Daraus ergab sich die Folgerung, daß die männliche Population des untersuchten Gebietes das unter den gegenwärtigen Verhältnissen optimale Längenwachstums-Niveau erreicht hat. Es wird somit jene frühere Feststellung bekräftigt, laut der die Akzeleration des Längenwachstums die Folge der Eliminierung der hemmenden, retardierenden Verhältnisse ist.

Zur Registrierung des Wachstums der Jugend bieten sich zwei Möglichjeiten: die Untersuchung der Schuljugend sowie die periodische Ermessung der körperlichen Entwicklung der Militärpflichtigen. In der vorliegenden Arbeit wollen wir über die Ergebnisse unserer auf dem letzterwähnten Gebiet durchgeführten Studien berichten.

Zuerst berichteten wir 1953 über die Gestaltung der Körperhöhenwerte der zwischen 1852 und 1927 Geborenen. In dieser Periode machte die Zunahme des Längenwachstums der 20jährigen 10jährlich 7,88 mm aus, während die Wachstumsakzeleration bei den zwischen 1927 und 1936 Geborenen 10jährlich 8,33mm betrug. Nach dem letzten Krieg, zwischen 1945 und 1963, erhöhte sich diese Beschleunigung von dem vor 1945 registrierten Wert von 8 mm/10 Jahre sprungartig auf 18 mm/10 Jahre. Da diese Erhöhung den verbesserten Lebensbedingungen zugeschrieben wurde, haben wir darauf hingewiesen, daß in der Gestaltung des Längenwachstums eigentlich nicht die Akzeleration, sondern die Eliminierung der Retardation von Bedeutung sein dürfte.

Im Landesausmaß betrug bis 1967 der Anstieg der körperlichen Entwicklung der damals 18—20jährigen männlichen Population (Geburtsjahre 1937—47) 6,7 mm. Wenn man die Daten der Hauptstadt Budapest und die der Provinz voneinander trennt, ergibt es sich, daß in Budapest praktisch kein Unterschied besteht (Differenz —0,55, in der Provinz +8,0 mm). Aus dieser Tatsache, daß nämlich bei der Budapester Bevölkerung inbezug auf die Körperhöhe von 172,5 cm keine nennenswerte Differenz nachzuweisen war, erhob sich die Frage, ob nicht etwa diese Körperhöhe es ist,

TABELLE I

Angaben der Körperhöhe, des Körpergewichts und des Brustumfangs der zwischen 1944 und 1958 geborenen männlichen Population

Nr.	Geburts-jahr	n	Körperhöhe, cm			Körpergewicht, kg			Brustumfang, cm		
			x	s	V	x	s	V	x	s	V
1.	1944	223	171,00	6,71	3,92	61,82	7,99	12,92	86,48	5,98	6,91
2.	1946	233	169,64	6,51	3,84	60,80	6,84	11,25	87,76	5,01	5,71
3.	1948	225	170,06	6,69	3,94	61,63	7,60	12,33	87,86	5,27	6,00
4.	1950	200	169,33	6,99	4,13	60,82	7,74	12,73	84,18	6,39	7,60
5.	1952	218	169,79	6,73	3,96	61,53	7,68	12,48	85,90	6,40	7,45
6.	1954	219	171,21	6,72	3,92	62,47	7,92	2,69	86,80	5,49	6,77
7.	1956	207	170,50	6,72	3,88	62,94	8,30	13,19	86,00	6,67	7,75
8.	1958	225	170,75	6,78	3,97	64,18	7,76	12,10	86,95	5,65	6,50
Insgesamt		1750	1362,28			496,18			691,93		
Durchschnitt			170,285			62,22			86,49		

Abweichung von der Regressionsgerade

$SQ_x = 162{,}0 - 162{,}0 = 0{,}0$

$SQ_y = 3{,}24$

$SP = 0{,}80$

$a = 170{,}285$

$b = 0{,}0$

Streuung:

+	−
2,32	2,32

die unter den gegebenen Verhältnissen als optimal gilt und die Akzeleration des Wachstums deshalb zum Stillstand kam, weil die Population diesen Wert erreicht hat.

Angesichts dieser Daten hielten wir die Wiederholung der Untersuchung der 18—20jährigen Population als angezeigt.

MATERIAL UND ERGEBNISSE

Aus den Protokollen des Landesbezirks Somogy haben wir 1976 die Abmessungen für Körperhöhe, Körpergewicht und Brustumfang der zwischen 1944 und 1958 geborenen militärpflichtigen Jungen analysiert (Tab. I). Es konnte folgendes festgestellt werden.

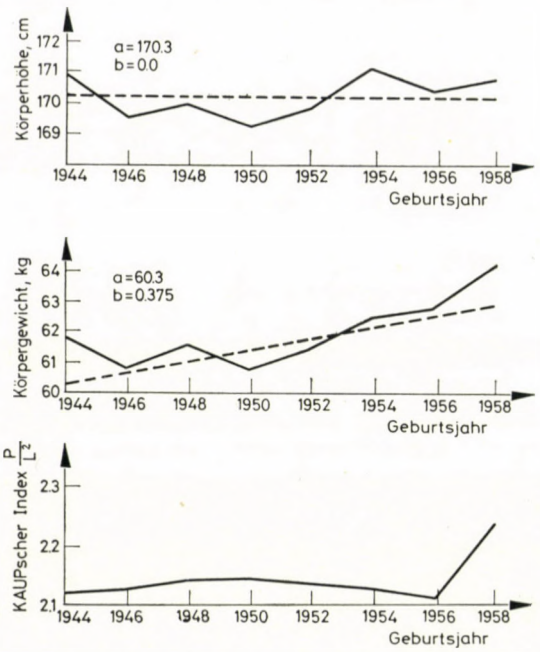

ABB. 1. Entwicklung (Körperhöhe, Gewicht, KAUPscher Index) der zwischen 1944 und 1958 geborenen 18jährigen männlichen Population

Körperhöhe. Laut der linearen Regressionsanalyse betrug das »a« der Funktion, d. h. die Regressionskonstante 170,285 cm, während der Regressionskoeffizient »b« = 0 ausmachte. Die Genauigkeit dieses Ergebnisse manifestiert sich in dem Umstand, daß die + und — Abweichung von der Regressionsgerade gleichfalls 2,32 beträgt. Das bedeutet soviel, daß inbezug auf die Werte der Körperhöhe unter den zwischen 1944 und 1958 geborenen bzw. zwischen 1962 und 1976 vorgestellten Männern kein Unterschied besteht, d. h. daß die Wachstumsakzeleration zum Stillstand kam.

Körpergewicht. Dieser Wert erhöht sich. Das »a« der Regressionsgerade zeigt einen Wert von 60,32, und das »b« beträgt 0,375 (Abb. 1).

Brustumfang. Wie darauf die Werte der linearen Regression hinweisen — »a«: 86,93 und »b«: — 0,095 — hat sich der Brustumfang verkleinert. Die Ergebnisse der Bestimmung des relativen Brustumfangs bekräftigten diese Feststellung. Die Werte der Gerade machten »a«: 51,1 und »b«: — 0,075 aus.

Die Richtlinie des KAUPschen Indexes verläuft fast waagerecht, eine Erhöhung zeigt sich nur in den letzten Jahren (Abb. 2).

Ein beachtenswertes Ergebnis ist, daß der Trend die waagerechte Richtung eingeschlagen hat, d. h. die Populationszunahme, der sekuläre

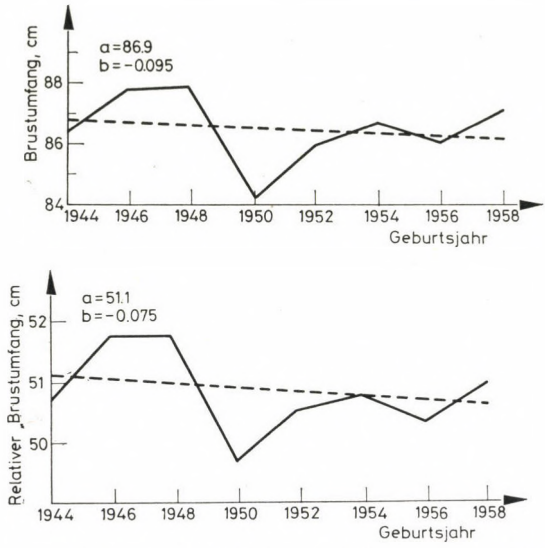

Abb. 2. Brustumfang der zwischen 1944 und 1958 geborenen 18jährigen Männer

Trend zum Stillstand kam. In Anbetracht der früheren sich auf die Stellungspflichtigen beziehenden Feststellung, war diese Angabe zwar bedeutend, doch nicht überraschend.

Wie darüber Bakwin [3] 1964 berichtete, übertreffen die neuesten Meßdaten die in den Grundschulen der Vereinigten Staaten 1939 ermittelten Körpergewicht- und Körperhöhenwerte, während die Gewichts- und Körperhöhenwerte, der unter guten finanziellen und hygienischen Verhältnissen lebenden Kinder der Privatschulen die höheren Werte bereits 1930 erreicht haben und sich von den neuesten Daten im wesentlichen nicht unterscheiden.

Im Landesbezirk Somogy kam der sekuläre Trend nicht in den untersuchten und erläuterten 14 Jahren, sondern bereits früher, praktisch im Geburtsjahr 1940 — das sind die 1960 vorgestellten Jungen — zum Stillstand. Die Körperhöhe der 1943 Geborenen betrug im Alter von 20 Jahren im Durchschnitt 171,52 cm.

Bei den Mädchen des erwähnten Gebietes kam die Akzeleration früher zum Stillstand. Es stehen uns die Ergebnisse von drei bewertbaren Schuluntersuchungen zur Verfügung. Die erste aus 1930 enthält die Körpergewichts- und Körperhöhenwerte der 4—12jährigen, die zweite aus 1948 die Körpermaße der 4—18jährigen. Eine dritte berichtet über 1974 durchgeführte Messungen. Aus den beiden letzterwähnten Untersuchungen geht hervor, daß die Körperhöhe der 18jährigen Mädchen im Jahre 1948 161,2 cm und im Jahre 1975 160,9 cm betrug, während das Körpergewicht der gleichaltrigen Mädchen 1948: 54,82 kg und 1975: 54,83 kg ausmachte (Abb. 3, 4).

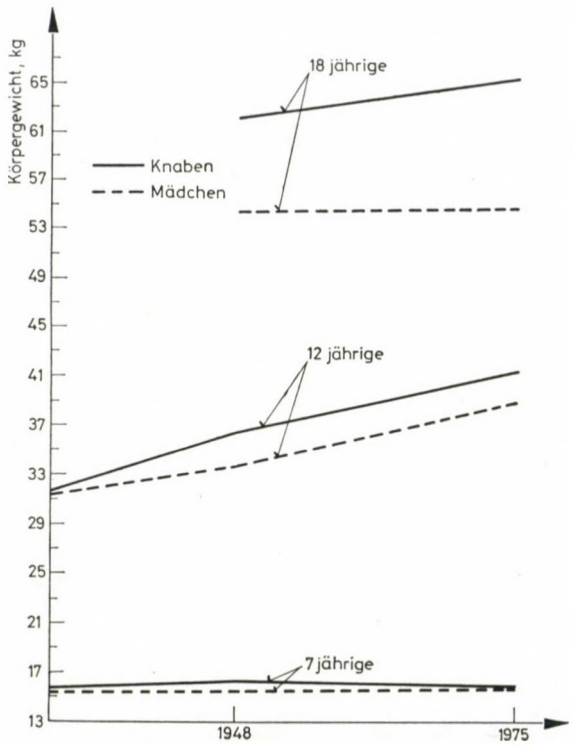

Abb. 3. Körperhöhe der zwischen 1930 und 1975 untersuchten 4, 12 und 18jährigen Jungen und Mädchen

Bei den Mädchen kam also die Akzeleration bereits vom Jahre 1930 an zum Stillstand. Die Tatsache, daß das Abbremsen der Wachstumsakzeleration der Mädchen der der Knaben voranging, kann wahrscheinlich auf die sich früher meldende Menarche — durch die das Längenwachstum gehemmt wird — zurückgeführt werden.

Tabelle II veranschaulicht die durchschnittlichen Körperhöhenwerte der zwischen 1852 und 1958 geborenen 18—20jährigen Population des untersuchten Landesbezirks. Somit beziehen sich unsere Angaben aufgrund von 51 Mustern auf 100, genauer gesagt 106 Jahre.

Besprechung

Wenn man die Ergebnispunkte dieser 106 Jahre in einem Diagramm miteinander verbindet, bildet sich eine Zickzacklinie, die wir mit Hilfe der Richtlinie (Trend) zu veranschaulichen trachteten. Die 10jährlichen Elemente der Geraden »a« 161,43 und »b« 0,849 sind Ausgangspunkt des Trends: 161,43 beim Geburtsjahr 1952 und Endpunkt 171,63 cm im Jahr

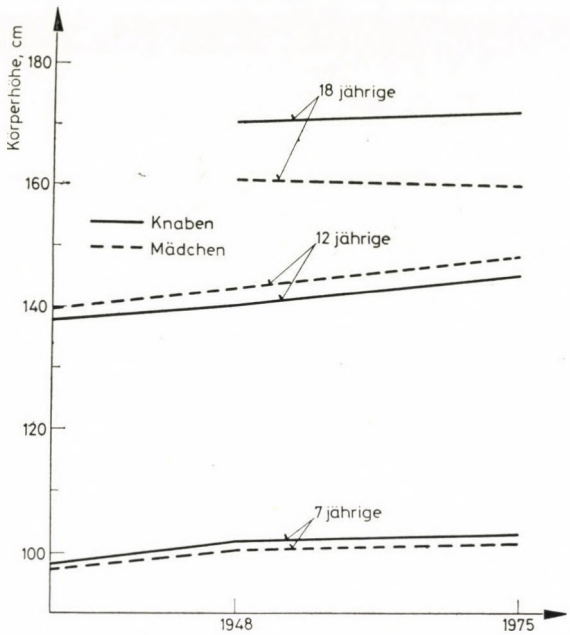

Abb. 4. Körpergewicht der zwischen 1936 und 1975 untersuchten Jungen und Mädchen

1958. Die Gerade paßt sich besonders in den mittleren Regionen ziemlich gut den empirischen Werten an, dies ist jedoch irreführend; es führt nämlich zu der fehlerhaften Hypothese, daß sich der sekuläre Trend gleichmäßig abspielt und noch eine unbestimmbare Zeit lang anhält. Aufgrund des sich in der empirischen Zahlenreihe meldenden rascheren Anstiegs und der in den letzten 20 Jahren registrierten Verflachung nahmen wir an, daß sich der empirischen Reihe an dieser Stelle am besten eine parabolenförmige Linie anpassen wird. Eine sich gut anpassende Kurve zu finden, gelang uns aber nicht, obwohl wir sämtliche Sorten der linearen Regression erprobten. Eine graphisch konstruierte Kurve brachte schließlich folgendes Ergebis: Nach einer anfänglichen provisorischen Abnahme meldet sich bei den zwischen 1852—1875 geborenen (zwischen 1872 und 1895 gemusterten) jungen Männern ein Anstieg, während sich die Akzeleration bis zum Geburtsjahr 1915 (Musterungsjahr 1935) mäßigt. Vom Geburtsjahr 1940 (Musterungsjahr 1960) an verläuft die Richtlinie wieder steiler, um sich schließlich zu verflachen (Abb. 5).

Früher haben wir darauf hingewiesen, daß der sekuläre Trend nicht gleichmäßig ist, d. h. daß raschere und langsamere Wachstumsperioden nacheinander folgen und sogar nennenswerte Rückfälle vorkommen. Daraus erhebt sich die Frage, ob der dargestellte Stillstand der letzten Jahre ein einfaches Innehalten oder ein definitiver Zustand ist. Der letzter-

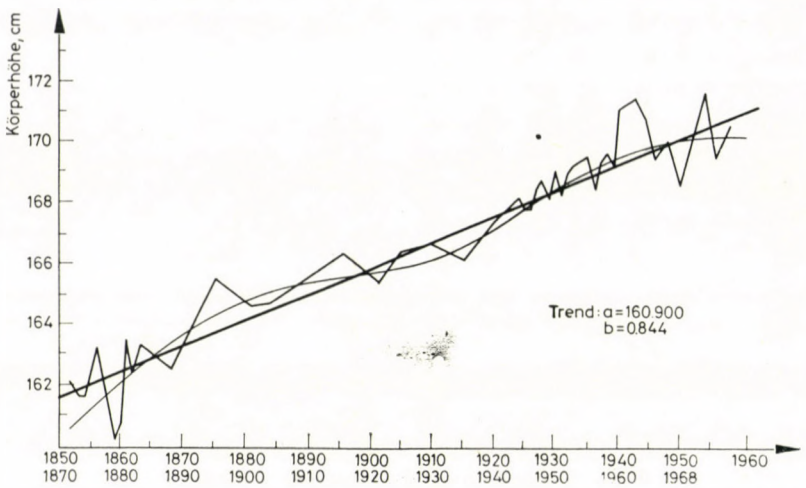

Abb. 5. Körperhöhe der zwischen 1852 und 1958 geborenen stellungspflichtigen Männer

Tabelle II

Durchschnittliche Körperhöhenwerte der zwischen 1852 und 1958 geborenen 18—20jährigen männlichen Population

Geburtsjahr	Durchschnittliche Körperhöhe, cm	Geburtsjahr	Durchschnittliche Körperhöhe, cm	Geburtsjahr	Durchschnittliche Körperhöhe, cm
1852	162,06	1905	166,59	1939	169,37
1853	161,72	1910	166,79	1940	171,08
1854	161,67	1915	166,23	1941	171,11
1855	162,65	1920	167,53	1942	171,40
1856	163,62	1924	168,13	1943	171,52
1857	162,14	1925	167,90	1944	171,00
1859	160,30	1926	167,90	1946	169,64
1860	160,87	1927	168,55	1948	170,06
1861	163,46	1928	168,90	1950	168,80
1862	162,42	1929	168,30	1952	170,25
1863	163,40	1930	169,06	1954	171,67
1868	162,59	1931	168,48	1956	169,72
1871	163,80	1932	169,02	1958	170,75
1875	165,64	1933	169,33		
1881	164,70	1934	169,48		
1884	164,80	1935	169,60		
1895	166,40	1936	168,77		
1901	165,61	1937	169,34		
1904	166,28	1938	169,72		

wähnte Fall könnte seine Erklärung darin finden, daß die unter den gegenwärtigen Verhältnissen mögliche optimale Körperhöhe annähernd erreicht worden ist. Dies unterstützt unsere sich auf die Retardation beziehende Theorie, besonders wenn man auch die lange Zeitdauer berücksichtigt. Vom Geburtsjahr 1944 bis zum Geburtsjahr 1958 sind 14 Jahre vergangen, und der Stillstand der Akzeleration des Längenwachstums der Mädchen umfaßt eine noch längere Zeit, in unserem Nachweis 28 Jahre.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (2), pp. 113—123 (1977)

Remnants of vitelline duct: analysis of 66 cases

By

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(Received October 7, 1977)

In twenty years, 66 infants and children with remnants of vitelline duct requiring surgery have been admitted. The patients were classified into three groups: patent vitelline duct (20 cases); Meckel's diverticulum as the primary surgical disease (19 patients); and Meckel's diverticulum found incidentally at surgery (27 patients).

The male preponderance in the groups of patent vitelline duct and symptomatic Meckel's diverticulum was 9 : 1. In contrast with other data, Meckel's diverticulum requiring surgery occurred with nearly equal frequency up to fourteen years. The gravest complication in the cases of patent vitelline duct were a T-shaped protrusion of ileum and a small bowel volvulus around the fibrous cord or the patent duct; and in the cases of Meckel's diverticulum causing symptoms, intestinal obstruction, bleeding peptic ulceration or inflammation.

Three deaths occurred in newborn age in connection with patent vitelline duct, and one patient died who belonged to the group of asymptomatic Meckel's diverticulum.

The vitelline duct (vitello-intestinal duct or omphalomesenteric duct) connects the primitive midgut and the embryonic yolk sac in early intrauterine life. At about the fifth week, once placental nutrition has become established, a progressive narrowing of the duct occurs; it is completely obliterated by the seventh week of fetal life. Arrest of this obliterative process at different stages results in a variety of congenital abnormalities capable of producing a wide variety of clinical disturbances.

If the vitelline duct remains widely patent (Fig. 1a) a prolapse or intussusception of the ileum through the abdominal wall (Fig. 1b) may occur. This is the most terrifying complication of this congenital malformation. The prolapse causes a T-shaped protrusion of the small bowel (Fig. 1c). If the duct is narrowly patent, it may discharge mucus, gas bubbles or faeces.

If the distal end fails to obliterate, an incomplete fistula (Fig. 1f), or a so-called sinus develops (Fig. 1e) which opens at the umbilicus and usually secretes mucus. On inspection a bright red, slightly haemorrhagic polypoid formation with a central opening is seen. The anomaly often leads to inflammations which are usually diagnosed as omphalitis, umbilical granuloma, or umbilical sepsis.

The vitelline duct cyst is a rare anomaly; it appears as an abdominal

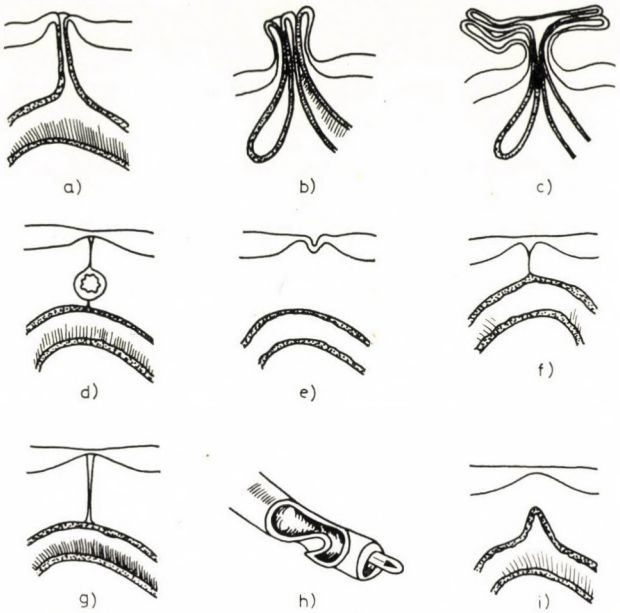

FIG. 1. Remnants of vitelline duct; a) persistent vitelline duct; b) intussusception through vitelline duct; c) T-shaped protrusion of the duct; d) incomplete duct; e) umbilical sinus; f) vitelline duct cyst; g) Meckel's diverticulum, h) Meckel's diverticulum causing ileal intussusception; i) fibrous band between ileum and umbilicus

mass, mainly in newborn infants (Fig. 1d).

The totipotential cells of the vitelline duct sometimes persist and thus the duct fails to obliterate and gives rise to ectopic tissue. The most common form of this is Meckel's diverti- or culum (Fig. 1i). Gastric mucosa, pancreatic tissue, duodenal glands colonic mucosa may be found in it. This ectopic tissue accounts for at least two of the complications occurring in the diverticulum with resulting haemorrhage or perforation. The diverticulum may invaginate into the lumen of the small bowel and serve as the leading point of ileal intussusception (Fig. 1h). Acute inflammation of the duct may be due to peptic ulceration or non-specific inflammation, the pathogenesis being probably similar to diverticulitis elsewhere.

Around the obliterated or patent duct (Fig. 1g) a small bowel volvulus or internal herniation may develop resulting in life-threatening intestinal obstruction, strangulation or ischaemic necrosis.

The aim of the present study is to analyse the main features of the remnants of the vitelline duct with special reference to its clinical signs, radiological and histological appearance, and variations. The operative findings and procedures and the follow-up studies are also detailed.

MATERIAL

During the twenty year period 1956 to 1976, 66 infants and children with various

forms of remnants of vitelline duct requiring surgery were admitted. Because of the wide variations in the clinical appearance and the problems presented by these malformations, the material was classified into three groups: patent vitelline duct, Meckel's diverticulum requiring emergency surgery, and Meckel's diverticulum found incidentally at surgery. Each group will be considered separately.

Patent vitelline duct

Twenty patients belonged to this group.

Sex distribution: there was a marked male preponderance (male : female = 17 : 3).

In age, the patients ranged from a few hours to seven years; 15 were under three months of age (Table I).

In most cases the diagnosis on admission already indicated or suggested the kind of congenital anomaly (Table II).

Diagnosis

In five patients there was a widely patent duct discharging gas bubbles or faeces, or a duct with partial ileal prolapse, or a T-shaped small bowel intussusception. These cases did not require diagnostic manoeuvres. In further ten patients where the diagnosis was obscure, injection into the duct of radio-opaque material demonstrated its connection with the intestine (Fig. 2) or showed a sinus or indicated a patent urachus duct. In two patients diagnosis was made in the course of surgery.

Associated anomalies

Major congenital abnormalities were encountered in one patient (oesophageal atresia, rectal agenesis, and severe heart failure). Other anomalies were exomphalos (3 patients), persistent urachus duct, cleidocranial disostosis, mesenterial defect (1 patient each) and malrotation of intestines (2 patients) (Table III).

All the findings were proved and classified at surgery. One persistent vitelline duct and one fibrous cord resulted in volvulus and severe subsequent intestinal obstruction. In a newborn infant the proximal part of the persistent vitelline duct was

Table I
Age at admission

	No. of patients		No. of patients
< 24 hours	3	1— 3 months	2
1—7 days	6	3—12 months	1
1—4 weeks	4	> 1 year	4

Table II
Diagnosis at admission

	No. of patients		No. of patients
Vitelline duct	6	Umbilical hernia	1
Omphalitis	2	Abdominal emergency (ileus)	2
Exomphalos	2	Appendicitis	1
Umbilical granuloma	4	No data	1
Umbilical sepsis	1		

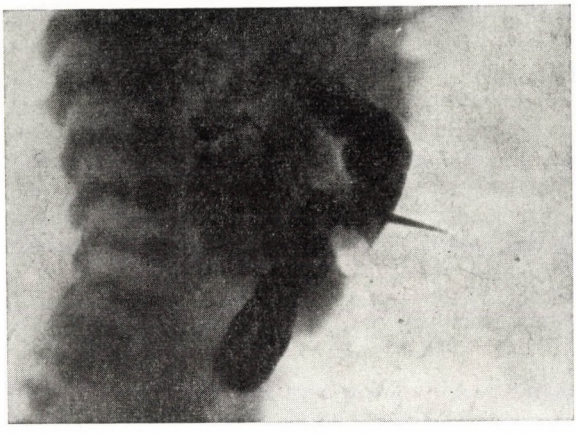

FIG. 2. Fistulography demonstrating the connection between umbilicus and small intestine

TABLE III

Types of patent vitelline duct

	No. of patients
Persistent vitelline duct without prolapse	7
Partial prolapse of ileum	2
Intussusception with T-shaped protrusion	2
Persistent vitelline duct + exomphalos	3
Fibrous cord + volvulus	1
Persistent vitelline duct + Meckel's diverticulum	1
Incomplete vitelline duct (sinus)	3

as wide as a Meckel's diverticulum and continued in a narrow but still patent duct to the umbilicus, this being patent on the abdominal wall (Table III).

In most cases, the vitelline duct was removed by careful wedge resection of the ileal wall. Manual reduction of the ileal prolapse followed by a resection of the duct was performed in two patients. Infants with T-shaped intussusception of ileum and one patient with volvulus required partial resection of the small bowel. The continuity of the ileum was re-established by single layer end-to-end anastomosis. The smallest patient of this group was a 2000 g premature infant. The newborn infant with multiple congenital anomalies was operated on only for treatment of its oesophageal atresia and rectal agenesis. (Table IV).

Type of mucosa

In five patients out of the eight with ileal mucosa in the vitelline duct, inflammatory changes were seen. In a newborn infant gastric mucosa was found. In the remainder no histological examination was carried out.

The patient with mechanical obstruction had to be subjected to repeated laparotomy in the early postoperative period

TABLE IV

Surgical procedures

	No. of patients
Removal of the duct	11
Removal of the duct + a segment of ileum	3
Removal of the duct + exomphalos	3
Removal of the duct + appendix	1
Incision of an abscess and later removal of the duct	1
Thoracotomy, gastrostomy, colostomy	1*

* No surgery for vitelline duct was carried out.

TABLE V

Postoperative period

Healing without complication		14
Healing with complication		3
Long-term suture suppuration	1	
Intestinal obstruction	1	
Sepsis	1	
Death		3
Persistent vomiting	1	
Generalized sepsis	1	
Multiple anomalies	1	

because of strangulation. A 30 cm length of small bowel was ischaemic and required resection; following ileal reanastomosis the patient recovered.

In this group there were three deaths. The cause of death in one case remained unclear even at necropsy. This infant, following resection of the vitelline duct, had a free intestinal passage but continued to vomit and failed to thrive, eventually dying of marasmus. The second death occurred after segmental small bowel resection, due to leakage of the suture line with subsequent peritonitis and generalized sepsis. (Table V).

The surviving patients were followed for an average of 11 years with a maximum of 20 years. All the surviving patients showed a good or sufficient physical development. Two of them have constipation and one is moderately retarded mentally.

MECKEL'S DIVERTICULUM

There were 46 patients with Meckel's diverticulum. Nineteen presented with various complications and required emergency surgery. In the remaining twenty-seven the diverticulum was found incidentally at surgery for some other condition.

MECKEL'S DIVERTICULUM CAUSING SYMPTOMS

Sex incidence: there was a very suggestive male to female ratio (18 : 1).

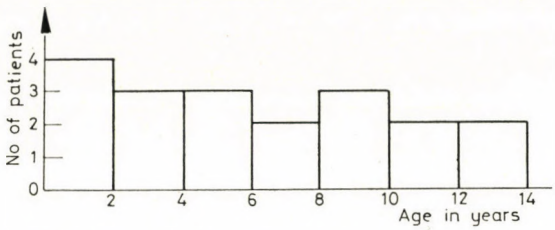

FIG. 3. Age distribution in manifest diverticulum

TABLE VI

Complaints before requiring hospitalization and surgery

Chronic paraumbilical colic	2
Dyspepsia	1
Chronic anaemia	2
Melaena	1
Vomiting	3
No previous complaints	8
No data	2

TABLE VII

Presenting complaints and findings on admission

Melaena	7
Vomiting	13
Abdominal colic pain	4
Abdominal distension, meteorism	9
Localized or diffuse peritonitis	7
Palpable abdominal mass	8
Bulging pouch of Douglas	1

Patients with symptomatic diverticula ranged in age from under two years to 14 years, mean 5.2 years. There was a slightly greater incidence in the first two years of life, which then remained steady with increasing age (Fig. 3).

Table VI demonstrates that half of the patients had had some complaints before hospitalization suggesting the possibility of Meckel's diverticulum.

The most characteristic presenting symptom was rectal bleeding which varied from mild to massive and was usually painless. Pain appeared in the older age group. One-third of the patients were seriously ill on admission, with fever, marked dehydration and some evidence of shock (Table VII).

Clinical picture

The patients displayed one of three clinical pictures verified at surgery (Table VIII).

TABLE VIII

Clinical picture of manifest diverticula

I Obstruction		8
Intussusception	6	
Band + volvulus	2	
II Peptic ulceration		8
Massive bleeding	6	
Perforation	2	
III Inflammation		3
Non-perforated	2	
Perforated	1	

In six patients with intestinal obstruction, an ileo-ileal or ileo-ileo-colonic intussusception with Meckel's diverticulum as the leading point was seen. The history of one of these patients was remarkable: a 6-year-old boy presented with severe abdominal pain. A fortnight before he had sustained a mild blunt abdominal injury producing no clinical symptoms. On admission, abdominal rigidity could not be estimated due to the very extensive pain in the abdomen. On rectal examination on the right side of the pouch of Douglas a bulging mass was palpated. Since the X-ray showed no opacity in the upper left abdomen, the mass was thought to be the spleen with a long pedicle squeezed into the small pelvis. At surgery it proved to be an ileo-ileo-colic invagination; its leading point was a Meckel's diverticulum with ectopic gastric tissue. Because the intussusception was irreducible, a segmental resection of ileum together with the diverticulum was performed. Fig. 4 shows the resected intestine with a phalliform Meckel's diverticulum.

In two patients the obstruction was due to volvulus of the small bowel around a Meckel's diverticulum which was attached by a fibrous band to the underside of the umbilicus.

Peptic ulceration caused usually painless intestinal bleeding in six patients. In the remaining two patients belonging to this group, the ulcer had perforated resulting in peritonitis and shock but no melaena.

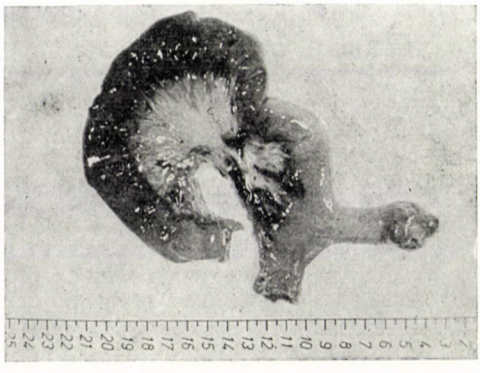

FIG. 4. Resected segment of small bowel with Meckel's diverticulum

Inflammation of Meckel's diverticulum was seen in three patients. Here, pain was the major presenting symptom and the clinical picture was indistinguishable from acute appendicitis. In one of the three patients inflammation led to a perforation of Meckel's diverticulum and subsequent severe peritonitis.

Mucosal histology. From the 19 patients, 13 had heterotopy (12 gastric and one colonic mucosa). In line with the literature a heteropic predominance was found in children with peptic ulceration.

Therapy

Simple diverticulotomy was performed if the diverticulum could be removed without compromising the lumen of the small bowel. In the four patients in whom the adjacent bowel was necrotic as a result of intussusception or volvulus, a segmental resection and an end-to-end anastomosis of the ileum was made. There was no death in this group of patients but complications developed in three children: septic infection, intestinal paralysis lasting for ten days, and mechanical obstruction requiring a temporary ileostomy for a couple of weeks. Follow-up showed a good mental and physical development in all patients.

Asymptomatic Meckel's diverticula

In 27 patients, Meckel's diverticulum was an incidental finding at surgery for other conditions like appendicitis, intestinal obstruction, mesenteric adenitis, Hirschsprung's disease, strangulated hernia, intra-abdominal testis, intussusception.

The age incidence was different from that of the diverticula causing symptoms. More than half of the patients were over ten years of age. In all but two Meckel's diverticulum was removed when it was detected. We only leave a diverticulum in place if there is a ruptured appendicitis, severe peritonitis, intestinal paralysis or mechanical obstruction, or in poor risk patients, etc. In a 5-month-old infant who was operated on for intussusception and a Meckel's diverticulum was found, a few months later a second operation was performed to remove the diverticulum.

As to mucosal histology, in only two children of the 27 patients was gastric mucosa found in the diverticulum; in the rest, normal ileal mucosa was detected in it.

There was one death in this group. An infant of three months was referred to us with strangulated irreducible inguinal hernia. At herniotomy a loop of small bowel and the adherent sac were not reducible and so a hernio-laparotomy was performed. During hernia repair a Meckel's diverticulum without associated pathology was found. Simple diverticulotomy was carried out and the closure was with 5—0 atraumatic silk thread. Unfortunately, in the postoperative period leakage of the suture-line with subsequent peritonitis led to the death of the infant.

Discussion

A considerable variation in the types of remnant vitelline duct has been found in our patients, and the incidence of the anomaly in our material amounted approximately to 1 : 2000 in the last twenty years.

The persistent vitelline duct including Meckel's diverticulum shows a marked male preponderance. Soderlund [16] reported a male to female ratio of 7 to 1 in a series of 54 cases causing symptoms, while in the asymptomatic cases the incidence in the two sexes was equal. Gross [5] observed a male to female ratio of 3 to 1 in a group of 149 manifest cases, while in our 66 children the ratio was about 4 : 1. If we consider the cases which required emergency surgery the ratio was 9 : 1, but in the asymptomatic diverticula only 3 : 1.

As with some other types of congenital malformation, prematurity was found to be a relevant factor in the patients with patent vitelline duct; only four of Singer's [15] ten infants with the anomaly weighed more than 2500 g at birth.

The different forms of remnant vitelline duct show a characteristic age distribution [9]. A patent duct was

found mainly immediately after birth, or in early infancy. If Meckel's diverticulum gives rise to symptoms, it will do so at any age but it occurs in over 50% of children before the second year of life [1, 5, 11]. Asymptomatic diverticula are inconsistently found in later childhood. In contrast, in our material Meckel's diverticulum requiring surgery displayed a nearly equal frequency up to 14 years of age.

It is easy to recognize a patent vitelline duct if there is a wide connection between intestine and umbilicus, especially in the early postnatal period. In a quarter of these patients a partial or total T-shaped prolapse of the small bowel developed, which is a life-threatening complication. Apart from two emergency cases with volvulus, all the patients were admitted with a diagnosis of omphalitis, exomphalos, umbilical granuloma, umbilical sepsis, or umbilical hernia.

In the manifest cases, a mainly painless rectal bleeding, sometimes intestinal obstruction or abdominal inflammation were the symptoms. These patients had a long history of repeated paraumbilical pains or of occult intestinal haemorrhage. This could have led to the diagnosis earlier. The most frequent preoperative diagnosis was intussusception or appendicitis.

Fistulography with contrast material will mostly demonstrate or disprove the connection between umbilicus and intestine. The diverticulum is not revealed by radiological examination but if intussusception occurs, it will be demonstrated by a barium enema [11]. Serious and painless rectal bleeding points to Meckel's diverticulum if sigmoidoscopy excludes rectal and sigmoid polyps [12]. Helpful in diagnosis is an abdominal scintigram with ^{99m}Tc [7, 8] owing to the affinity of technetium to the parietal cells of the gastric mucosa.

The therapy of choice of the patent vitelline duct is its removal. The operation is urgent if the ileum is prolapsed. Efforts should be made to limit the surgery to removal of the duct, avoiding to resect an ileal segment.

The diagnosis of Meckel's diverticulum is complicated by the variability of the symptoms [4, 14]. When no cause for the bleeding can be identified, an exploratory laparotomy is indicated; it often reveals a diverticulum [6]. Intestinal obstruction, secondary to intussusception of the diverticulum, is easily overlooked. Perforation of the diverticulum is an uncommon but most serious complication. In our material there was a single such case and we could not diagnose it preoperatively. Canty et al. [3] reported nine infants with perforated Meckel's diverticulum of which none was diagnosed preoperatively. For treatment, simple diverticulotomy with wedge resection of the ileum is usually sufficient. Cases with advanced obstruction resulting from intussusception or volvulus require a segmental resection of the small bowel with end-to-end anastomosis [2, 3].

The high incidence of ectopic mucosa, mostly gastric, is responsible for the majority of characteristic clinical

features such as peptic ulceration with bleeding or inflammation and probably for intussusception, too [9]. There is uncertainty as to how to proceed if a Meckel's diverticulum is discovered at surgery carried out for some other condition. Although many authors recommend diverticulotomy in such cases [2, 4, 9, 13] even in neonates [10], it is contraindicated in the presence of acute inflammation or severe disease of other abdominal organs. On the other hand, the fact that pathological changes (intussusception, torsion, inflammation, gangrene, peritonitis, adhesive stricture, etc.) develop in about 20% of all Meckel's diverticula [2, 13] encourages every surgeon to remove it, even if it is found incidentally. The death of an infant with Meckel's diverticulum in our material is a warning event. Our policy now is as follows. Under the age of one year we do not remove an incidentally found Meckel's diverticulum if other changes may endanger the suture line since in infants the greater omentum is not sufficiently developed to afford protection in the case of leakage After one year of age, intestinal obstruction due to some cause other than Meckel's diverticulum contraindicates the emergency resection of an incidentally found diverticulum in the dangerously ill patient. In these cases a second operation is indicated to remove the diverticulum.

Overall mortality amounted to 7% in the 66 patients with different forms of remnant vitelline duct. Three of the deaths were in connection with patent vitelline duct in neonates. No death occurred in the group of manifest Meckel's diverticula. One infant with asymptomatic Meckel's diverticulum with incarcerated hernia may have lived had we not removed the incidentally found diverticulum.

Thus, the prognosis is favourable in all forms of remnant vitelline duct. After due treatment these patients recover and develop well both physically and mentally.

In summary, the mortality risk associated with the various types of remnant vitelline duct must be borne in mind together with the experience that early diagnosis and proper surgical treatment can only prevent the life-threatening complications. Dr. Charles W. Mayo's statement "Meckel's diverticulum is frequently suspected, often looked for, and seldom found" is still and will remain actual probably forever.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (2), pp. 125—135 (1978)

Eigenschaften und Antigenität der aus Brot isolierten Gluteneiweisse

Von

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(Eingegangen am 15. Oktober 1977)

Aus dem wässerigen bzw. mit 0,01 M Essigsäurelösung verfertigten Extrakt des Brotes wurden Gluteneiweiße, Gliadin und Glutenin isoliert.

Mit Na-dodecylsulfat-Akrylamid-Gelelektrophorese wurde festgestellt, daß das Molekulargewicht der aus Brot isolierten Gliadine 30 000, 55 000 bzw. 35 000, 52 000 und das der Glutenine 100 000, 80 000 bzw. 70 000 Dalton ausmacht. Inbezug auf die Aminosäurezusammensetzung sind die Gliadin- und Gluteninfraktionen einerseits einander, anderseits den aus Mehl isolierten Fraktionen ähnlich; sowohl der Glutaminsäure- (43,9% bzw. 38,4%) als auch der Prolingehalt (17,6% bzw. 16,5%) der Gliadin- und Gluteninfraktionen ist hoch. Das Absorptionsmaximum der aus Brot mit Essigsäureextraktion isolierten Gliadinfraktion liegt bei 275 nm, während sich das Absorptionsspektrum der Gluteninfraktion von dem des Gliadins in bedeutendem Maße unterscheidet. Die isolierten Gluteneiweiße reagieren mit dem Serum der Zöliakie-Kranken als Antigene.

Es konnte festgestellt werden, daß die Gluteneiweiße gegenüber der beim Brotbacken angewandten hohen Temperatur resistent sind, indem sie zumindest inbezug auf die untersuchten Parameter ihre ursprünglichen physikochemischen und immunchemischen Eigenschaften beibehalten.

Die Untersuchung der Gluteneiweiße des Weizens ist nicht nur in der Lebensmittelindustrie bzw. der Ernährungswissenschaft, sondern auch vom Standpunkt der theoretischen und klinischen Immunologie eine im Vordergrund des Interesses stehende Frage geworden, besonders seitdem Dicke [5] auf ihre Rolle im Zusammenhang mit dem Zöliakie-Syndrom bzw. Singh und Kay [12] mit der Schizophrenie hingewiesen haben. Die Gluteneiweiße — Gliadin und Glutenin — sind bekanntlich weder in Wasser noch in neutraler Salzlösung löslich, während sie sich in 50—70%-igem Alkohol, dünner Säure oder Lauge lösen.

Wie wir darüber früher berichteten [13], reagiert die von uns »A« genannte aus dem wässerigen Extrakt des Weizenmehls auf der Sephadex G-75 Säule mit Gelfiltration isolierte Fraktion mit dem Serum der Zöliakie-Kranken antigenartig; was die Aminosäurezusammensetzung und das Molekulargewicht anbelangt, entspricht die Fraktion A im wesentlichen den Weizen-Gliadinen.

Unsere Untersuchungen richteten sich auf die Klärung der Frage, ob bzw. inwiefern durch das Brotbacken

die physikochemischen Eigenschaften und die Antigenität der Gluteneiweiße beeinflußt werden.

Material und Methoden

Isolierung der Gluteneiweiße aus Brot mit Methode I. 50 g zerstückeltes Brot wurde in 500 ml Wasser suspendiert und die Suspension 120 Minuten bei Zimmertemperatur gründlich durchgemischt, sodann 14—16 Stunden im Kühlschrank (2—4°C) aufbewahrt. Zwecks Entfernung der unaufgelösten Teilchen wurde die Suspension durch einen gewaschenen Wattebausch gefiltert. Zunächst wurde die reine Suspension bis zur 66—68% Äthylalkohol-Endkonzentration mit 96%igem Alkohol versetzt und 1—2 Stunden im Kühlschrank aufbewahrt. Es folgte die Entfernung des Stärkepräzipitats mittels Filtration. Zunächst wurde das Gluteneiweiß enthaltende Filtrat bei 38 °C unter Vakuum mit Hilfe von Rotadest auf 10—12 ml einkonzentriert, während auch das Alkohol größtenteils verdampfte. Die Eiweißlösung (10—12 ml) wurde mit 3—4 ml 70%igem Alkohol versetzt und das pH mit 0,1 M Essigsäure auf 4 eingestellt. (Diese Manipulation hatte zur Folge, daß ein großer Teil des sich auf die Wand des Rotadest-Kolbens ausgefällten Eiweißes ebenfalls in die Lösung überging.) Die eiweißhaltige Alkohollösung wurde hiernach gegenüber 1,5—2 l demineralisiertes Wasser dialysiert und das während der Dialyse ausgefällte Präzipitat mit Zentrifugieren (3000 *g*, 25°C, 15 Minuten) entfernt. Des weiteren wurde der Supernatans angewandt. Aus 50 g Brot können etwa 70—90 mg Eiweiß isoliert werden.

Isolierung der Gluteneiweiße aus Brot mit Methode II. Das Verfahren ist eine Modifikation der von Beckwith und Mitarb. [3] beschriebenen Methode. 100 g zerstückeltes Brot wurden in 1000 ml 0,01 M Essigsäure 120—180 Minuten kräftig umgerührt, sodann für 14—16 Stunden in den ühlschran k (2—4°C) gestellt. Demnach wurde die Suspension durch vierschichtigen Gaze gefiltert und das Filtrat in einer Kühlzentrifuge (MSE 25 Super-Speed) bei 4°C 120 Minuten mit 25 000 *g* zentrifugiert. Das Präzipitat (größtenteils Stärke) wurde verworfen, und aus dem reinen Suparnatans wurden die Gluteneiweiße bei einer 0,2 M NaCl Endkonzentration ausgefällt. Das Präzipitat wurde in 0,01 M Essigsäurelösung gelöst, mit 96%igem Äthylalkohol bis zu einer Endkonzentration von 66—68% versetzt und das pH mit N KOH-Lösung auf 6,5—6,8 eingestellt. Nachdem das Gemisch eine Nacht in kaltem Zimmer stand, präzipitierte sich das Glutenin, während das Gliadin in aufgelöstem Zustand blieb. Nach erneutem Zentrifugieren (2000 *g*, 4°C, 45 Minuten) und Zurücklösen des Gluteninpräzipitats in 0,01 M Essigsäure und Dialyse gegenüber 0,01 M Essigsäurelösung stand uns das isolierte Glutenin zur Verfügung.

Zunächst wurde der Alkoholgehalt des Gliadin enthaltenden Supernatans mittels Zugabe von kaltem, ionfreiem Wasser auf 35—37% herabgesetzt, die Lösung einige Stunden auf 0°C abgekühlt (bei einer um 2—3°C höheren Temperatur klärt sich die Suspension auf), in der Beckmanschen präparativen Ultrazentrifuge mit 100 000 *g* 50 Minuten zentrifugiert, das ausgefällte Gliadin in 0,01 M Essigsäure gelöst und gegenüber 0,01 M Essigsäure dialysiert. Mit der Methode können aus 100 g Brot 80—90 mg Gliadin und 50—60 mg Glutenin isoliert werden.

Polyakrylamid-Gelelektrophorese

Die Homogenität der aus dem Brot isolierten Eiweiße wurde unter Anwendung einer 7%igen Polyakrylamid-Gelkonzentration + Tris-Glycinpuffers (pH 8,3, Ionstärke 0,05) kontrolliert.

Natrium dodecylsulfat-Polyakrylamid-Gelelektrophorese (pH = 7)

Diese Methode [13] diente zur Untersuchung des Molekulargewichts bzw. der

molekulargewichtgerechten Homogenität der Polypeptidketten der aus dem Brot isolierten Eiweiße.

Die Analyse des Absorptionsspektrums der Eiweiße erfolgte mit Hilfe des Spektrophotometers Opton PM 2 DL. Der Eiweißgehalt wurde mit dem Biuretverfahren bestimmt.

Aminosäureanalyse

Zur Bestimmung der Aminosäurezusammensetzung von Glutenin und Gliadin diente unsere vorangehend beschriebene Methode [13].

Agardiffusion

Das Antigen (Gliadin, Glutenin) wurde mit NaCl-Lösung auf 0,6—0,7 mg Eiweiß/ml Konzentration verdünnt und zwar so, daß die NaCl-Endkonzentration 0,9% ausmache (die unter Wirkung der NaCl-Lösung enstandene Trübung der Antigenlösung läßt stufenweise nach). Nach einigen Stunden wurde diese Antigenlösung mit auf 50—55 °C aufgewärmte 3%ige wäßrige Agarlösung vermischt (hiernach betrug die Eiweißkonzentration der Lösung 0,3—0,35 mg/ml, die NaCl-Konzentration 0,45% und die Agarkonzentration 1,5%) und je 2,2 ml wurden auf Objektträger pipettiert. Am darauffolgenden Tag wurden in das Agar Löcher mit einem Durchmesser von 4 mm gebohrt und in diese Löcher die aus den Seren verschiedener Individuen — Normalpersonen, Zöliakiekranken usw. — verfertigte unterschiedliche — 1 : 4, 1 : 8, 1 : 12, 1 : 16, 1 : 32 — Verdünnungen gemessen (in diesen verdünnten Seren betrug die Endkonzentration des Kochsalzes ebenfalls 0,45%). Nach 24 Stunden wurde diese Manipulation wiederholt. In der Zwischenzeit haben wir die Objektträger in der Feuchtkammer, bei Zimmertemperatur aufbewahrt. Am Ende der 48stündigen Inkubationszeit wurden die sich an der Bildung des Immunpräzipitats nicht beteiligenden Eiweiße aus dem Agar mit 0,45%iger Kochsalzlösung ausgewaschen, die Objektträger getrocknet, mit Säurefuchsin gefärbt, differenziert, usw.

Ergebnisse

Im ersten Teil der Versuche wurden die mit der Methode I aus Brot isolierten Eiweiße auf Sephadex G-75-Säule fraktioniert (Abb. 1). Im oberen Teil der Abbildung 1 sieht man das Elutionsdiagramm (M), der mit der in unserer vorangehenden Mitteilung [13] beschriebenen Methode aus Mehl extrahierten Eiweiße, während im unteren Teil das Elutionsdiagramm der aus Brot (B) mit der Isolierungsmethode I extrahierten Eiweiße, dargestellt ist. Die beiden Elutionsdiagramme unterscheiden sich voneinander nur darin, daß aus den aus Brot isolierten Eiweißen den Eiweißen mit niedrigem Molekulargewicht, den einige Kettengliede enthaltenden Polypeptiden und Nukleotiden entsprechende Fraktion D fehlt. Unzweifelhaft ist dagegen die Anwesenheit der Fraktion A, die sich als Antigen verhält [4].

Die nach Akrylamid-Gelelektrophorese verfertigten Densitogramme der aus Mehl und Brot extrahierten Eiweiße unterstützen die bei der Gelfiltration ermittelten Ergebnisse (Abb. 2). Im Gegensatz zum Densitogramm M findet man auf dem Densitogramm B keine in Richtung der Anode wandernde Komponenten mit niedrigem Molekulargewicht, während die für die Antigenität verantwortlichen Komponenten auf den Polyakrylamid-Gelen in Kathodenähe dort erscheinen, wie bei den kontrollhalber aus Mehl extrahierten Eiweißen.

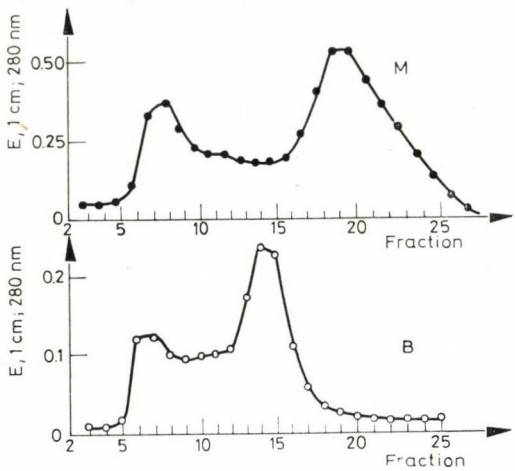

Abb. 1. Elutionsdiagramm der aus Mehl (M) und aus Brot (B) mit Wasser extrahierten Eiweiße bei Gelfiltration auf Sephadex G-75-Säule. Die Elution erfolgte mit NaN_3-haltigem (0,005%) demineralisiertem Wasser. Parameter der Gelsäule: Durchschnitt 1,6 cm, Höhe: 30 cm, Volumen: 60,5 cm^3. Elutionsgeschwindigkeit: 20 ml/St, Volumen der eluierten Fraktionen: je 2,5 ml

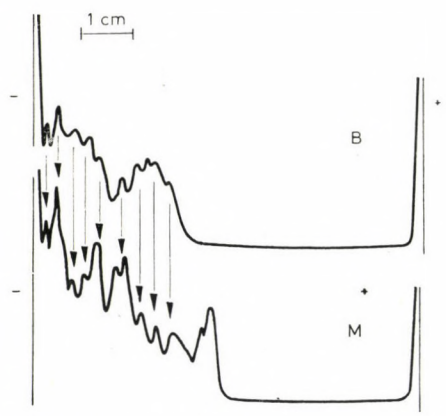

Abb. 2. Polyakrylamid-Gelelektrophorese und nach der Färbung verfertigte Densitogramme der mit Wasser aus Mehl (M) und aus Brot (B) extrahierten Eiweiße. (Weitere Angaben s. [4])

In der Folge haben wir das Molekulargewicht der aus Brot extrahierten mit dem Serum der Zöliakiekranken antigenartig reagierenden Fraktion A mittels Na-dodecylsulfat-Polyakrylamidgel-Elektrophorese bestimmt. Auf den Densitogrammen der aus Mehl (M) bzw. Brot (B) isolierten Fraktionen A waren Komponenten mit fast übereinstimmenden Molekulargewichten — 50 000—56 000 bzw. 30 000—35 000 Dalton — ersichtlich (Abb. 3).

Mit der Isolierungsmethode II haben wir aus dem mit 0,01 M Essigsäure verfertigten Brotextrakt mit

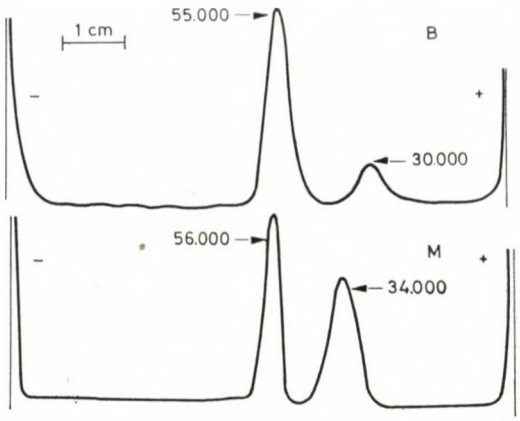

ABB. 3. Densitogramme der aus dem wässerigen Extrakt des Mehls (M) bzw. des Brotes (B) mittels wiederholter Gelfiltration isolierten Fraktionen A, nach mit Natrium-dodecylsulfat-Polyakrylamid-Gelelektrophorese (pH 7,0) und Färbung. (Weitere Angaben s. [13])

der weiteren Fraktionierung der bei einer Kochsalzendkonzentration von 0,2 M präzipitierbaren Gluteneiweiße, unter gut definierbaren Verhältnissen Glutenin- und Gliadin-Fraktionen abgesondert und die Eigenschaften bzw. die Antigenität dieser Fraktionen untersucht.

Das mit 0,01 M Essigsäure hergestellte Brotextrakt (Abb. 4, 1) enthält weniger ein niedrigeres Molekulargewicht aufweisende, in Richtung der Anode wandernde Eiweißkomponenten als das wässerige Extrakt (Abb. 2, B). Dies ist aus dem Vergleich der Densitogramme 1 bzw. B der Abbildungen 4 bzw. 2 deutlich zu entnehmen. Auf dem nach Elektrophorese der aus dem Essigsäureextrakt bei 0,2 M Kochsalzendkonzentration abgetrennten Gluteneiweiße verfertigten Densitogramm findet man bereits keine anodwärts wandernden Komponenten mit niedrigerem Molekulargewicht (Abb. 4 »2«). Diese Tatsache spricht dafür, daß diese Eiweiße bei einer Kochsalzkonzentration von 0,2 M bereits nicht ausgefällt werden. Das Densitogramm der isolierten Gliadinfraktion (Abb. 4, Densitogramm 4) ist dem der Glutenfraktion (Abb. 4, Densitogramm 2) ähnlich. Da die Gluteninfraktion bei der Akrylamid-Gelelektrophorese nicht wandert, oder wahrscheinlich wegen ihres hohen Molekulargewichts nicht in das Gel gelangt, sind auf dem Densitogramm (Abb. 4, Densitogramm 3) keine Eiweißkomponenten ersichtlich. Aus diesem letzterwähnten Umstand kann auch darauf gefolgert werden, daß anläßlich der Elektrophorese des Extrakts bzw. der Eiweiße der Glutenfraktion (Gelkonzentration 7%, pH = 8,3, Elektrodenpuffer) auf den Densitogrammen weder die Gluteninfraktion, noch ihre Komponenten in Erscheinung treten. Diese Feststellung stimmt mit den Literaturangaben überein, laut deren das Glutenin nicht einmal bei der Stärke-Gelelektrophorese wandert [1, 15]. Nach NILSEN

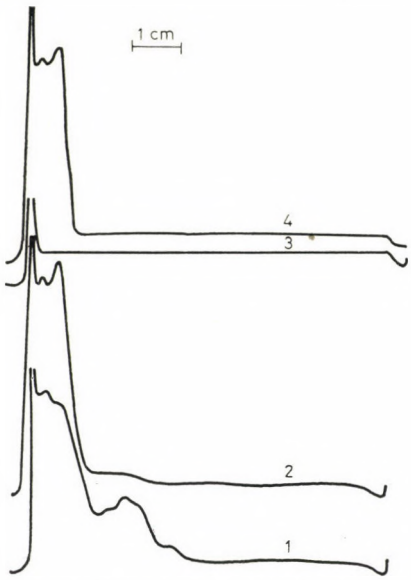

Abb. 4. Densitogramme der aus dem Essigsäureextrakt des Brots mit der Methode II isolierten Eiweiße nach Polyakrylamid-Gelelektrophorese und Färbung. 1. Essigsäureextrakt; 2. Glutenfraktion; 3. Gluteninfraktion; 4. Gliadinfraktion

und Mitarb. [10] schwankt nämlich das Molekulargewicht des Glutenins zwischen einigen 10 000 und 1 Million. Dieses hohe Molekulargewicht ist nicht auf die physikalische Aggregation zurückzuführen, es ist vielmehr die Folge der durch die zwischen den SH-Gruppen der Zysteine entstehende Kreuzbindung — Disulfidbindung — bedingten Entwicklung der Polymerstruktur [14].

Anläßlich der zwecks Bestimmung des Molekulargewichts durchgeführten Na-dodecylsulfat-Akrylamid-Gelelektrophorese wurden die in den Gluteneiweißen befindlichen Disulfidbrücken in der Anwesenheit von Na-dodecylsulfat mit Merkaptoethanol reduziert; im Laufe dieser Manipulation zerfiel das Polymermolekül in Polypeptidketten. In der Glutenfraktion können mit abnehmendem Molekulargewicht, in zunehmender Menge Polypeptidketten — mit einem Molekulargewicht von 100 000, 80 000, 52 000 und 36 000 Dalton — beobachtet werden (Abb. 5, Fraktion 1). Die Gluteninfraktion enthält die Eiweißkomponenten mit höherem Molekulargewicht (Abb. 5, Fraktion 2) und die Gliadinfraktion diejenigen mit niedrigerem Molekulargewicht (Abb. 5, Fraktion 3). Diese Angaben sprechen ebenfalls dafür, daß das Glutenin — trotz der Reduktion der Disulfidbrücken — ein Eiweiß mit verhältnismäßig hohem Molekulargewicht ist, und demzufolge ohne Reduktion und Denaturierung im Polyakrylamid- bzw. Stärkegel nicht wandert.

Das Absorptionsspektrum von Gliadin und Glutenin wurde im 0,01 M

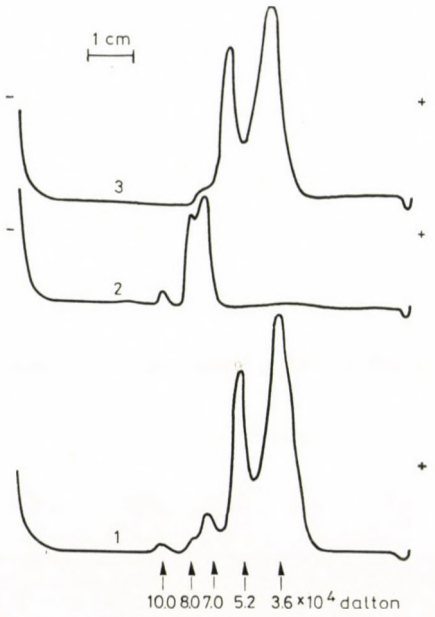

ABB. 5. Densitogramme der aus dem Essigsäureextrakt des Brots mit der Methode II isolierten Fraktionen: 1. Gluten, 2. Glutenin, 3. Gliadin, nach Natrium-dodecylsulfat-Polyakrylamid-Gelelektrophorese (pH 7) und Färbung

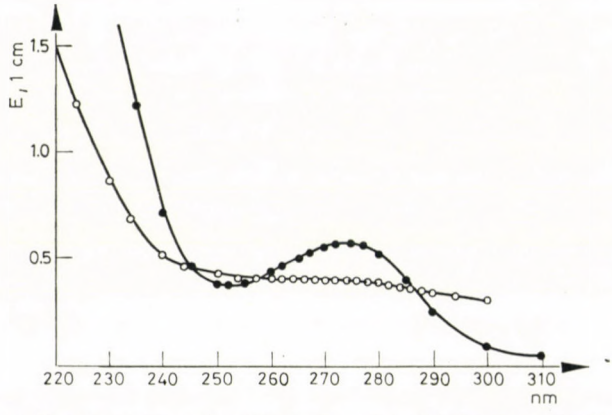

ABB. 6. Absorptionsspektrum von aus dem Essigsäureextrakt des Brots isolierten Gliadins und Glutenins. ●–● 0,79 mg/ml Gliadin; ○–○ 0,76 mg/ml Glutenin

Essigsäure enthaltenden Medium untersucht. Das Absorptionsmaximum von Gliadin liegt bei 275 nm (Abb. 6). In den in verschiedenen Jahreszeiten, vom September bis Juni verfertigten Präparaten schwankt der Wert von $E_{280}^{1\%}$ zwischen 6,5 und 8,05. Für die aus in essigsäure- und ureahaltigem Lösungsmittel gelöstem Mehl präparierte Gliadinfraktion haben MERE-

TABELLE I

Aminosäurezusammensetzung von Glutenin und Gliadin

Aminosäure	Glutenin		Gliadin		Aminosäure	Glutenin		Gliadin	
	L^+	S	S	L^{++}		L^+	S	S	L^{++}
	Mol %					Mol %			
Lys	1,15	0,90	1,40	1,50	Gly	9,10	4,77	2,20	3,00
His	1,50	1,35	1,48	1,70	Ala	3,30	1,80	2,00	3,40
Arg	3,20	1,44	1,81	1,80	Val	4,00	2,98	2,52	4,80
Cys			1,34						
Asp	2,00	1,98	1,60	2,90	Met	1,30	2,25	0,55	1,10
Thr	2,70	1,89	1,60	2,10	Ile	3,30	3,61	3,40	4,20
Ser	5,40	4,86	5,53	5,40	Leu	6,15	6,05	5,80	7,70
Glu	36,40	38,41	43,90	37,50	Tyr	2,40	2,70	2,10	2,70
Pro	14,30	16,50	17,60	15,00	Phe	3,80	8,44	5,10	4,20

L^+ : Gluteninwerte aus der Mitteilung von WU und DIMLER [16]
S : Aminosäurezusammensetzung von Brot-Glutenin und -Gliadin (eigene Isolierungsangaben)
L^{++} : Aufgrund der Aminosäurezusammensetzung der III. Fraktion (Gliadin) berechnete Werte (BECKWITH und Mitarb. [3]

DITH und WREN [9] ähnliche Werte gefunden. Das Absorptionsspektrum von Glutenin unterscheidet sich in bedeutendem Maße von dem des Gliadins bzw. von dem der Eiweiße im allgemeinen (Abb. 6). Die Absorption, die sich zwischen 230—260 nm verringert, bleibt bis 260—280 nm praktisch unverändert. Hierzu sei erwähnt, daß während das Gliadin in einem 0,01 M essigsäurehaltigen Medium bei der zur Aufnahme des Absorptionsspektrums angewandten Eiweißkonzentration von 0,8 mg/ml eine vollkommen reine Lösung ergab, die Gluteninlösung bei derselben Eiweißkonzentration mit identischem Essigsäuregehalt keineswegs als rein bezeichnet werden konnte.

Im Interesse der weiteren Charakterisierung der mit der Isolierungsmethode II aus Brot hergestellten Gliadin- und Gluteninpräparate haben wir auch ihre Aminosäurezusammensetzung bestimmt (Tab. I). Wie aus Tabelle I ersichtlich, sind die aus Brot isolierten Glutenin- und Gliadinfraktionen der von BECKWITH und Mitarb. [3] aus Mehl isolierten Gliadinfraktion (Fraktion III) sehr ähnlich. Alle drei Fraktionen verfügen über einen hohen Glutaminsäure- (38—44%) und Prolingehalt (16,5—17,6%). Im Laufe der Aminosäureanalyse wurde auch der Ammoniakgehalt der Präparate bestimmt und aus diesem Wert auf das proportionale Verhältnis von Glutamin + Asparagin (Amidierungsgrad) gefolgert. Die im Laufe der Aminosäureanalyse der Gliadinpräparate bestimmte Glutaminsäure + Asparaginsäure — die

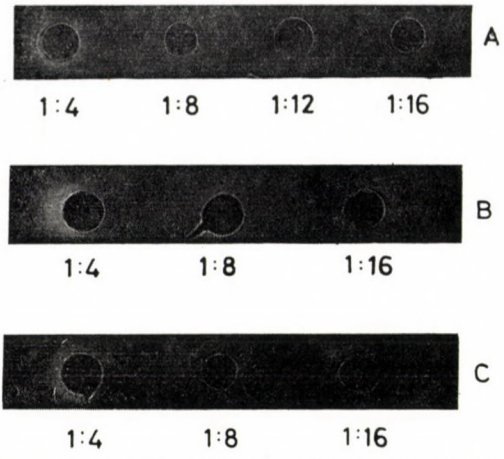

ABB. 7. Immunreaktionen des aus Essigsäureextrakt des Brots mit Methode II isolierten Glutenins und Gliadins mit den aus Zöliakiekranken (A, B) und Normalpersonen (C) stammenden Seren. Antigen im Agar A: Glutenin, B: Gliadin, C: Gliadin

45,5% des gesamten Aminosäuregehalts ausmacht — besteht zu 53—60% aus Glutamin + Asparagin. Was die Gluteninpräparate anbelangt, ließ sich feststellen, daß 80—90% der Glutaminsäure + Asparaginsäure aus Glutamin-Asparagin besteht. Unter der Teilnahme der im Glutamin und Asparagin befindlichen Amidgruppen können sich Wasserstoffbindungen entwickeln, welche unter Berücksichtigung der in den Gluteneiweißen anwesenden verhältnismäßig großen Zahl der Amidgruppen — nebst anderen Verbindungen (Ion-, Hydrophobbindung, usw.) — auch in der Bestimmung der Eiweißstruktur eine wichtige Rolle spielen.

Die Immunreaktion von Glutenin und Gliadin — dessen Aminosäurezusammensetzung aus Tabelle I ersichtlich ist — mit dem Serum von Zöliakiekranken veranschaulicht Abbildung 7 (Abb. 7 A, B). Die erwähnten Gluteneiweiße ergeben als Antigene selbst in Serumverdünnungen von 1 : 12 bzw. 1 : 16 positive Immunreaktionen. Gleichzeitig reagiert das Kontroll-Normalserum nur in einer Verdünnung von 1 : 4 (Abb. 7, C) — manchmal 1 : 8 — aber im Vergleich zum Zöliakieserum mit identischer Verdünnung nur mit halber Intensität.

BESPRECHUNG

Durch den Prozeß des Brotbackens werden die Eigenschaften der im Mehl befindlichen Eiweiße — die sich voneinander in mancher Beziehung unterscheiden (z. B. — Wasser- und Salzlöslichkeit) — von ihrer Empfindlichkeit abhängig auf unterschiedliche Weise beeinflußt. In der Technologie der Brotherstellung ist das Backen der wichtigste Prozeß. Während der 60—90minutigen Backdauer beträgt, bei einer Ofentemperatur von rund 200°C die Temperatur im Brotinne-

ren 100°C. Ein großer Teil der Eiweiße wird aber bekanntlich im Laufe einer kurzen Wärmebehandlung mit nur 40—50°C denaturiert [8]. Laut unserer Versuchsdaten sind die Gluteneiweiße resistent gegenüber der Wärmedenaturation. Was Mobilität, Verhalten bei der Elektrophorese (Abb. 2, 4) Molekulargewicht (Abb. 3, 5) und Aminosäurezusammensetzung (Tab. I) anbelangt, besteht zwischen den aus Brot hergestellten Gluteneiweißen und den aus Mehl isolierten Gluteneiweißen kein bzw. ein nur minimaler Unterschied. Nach den Literaturangaben zeigen die Gliadine der Samen der Grasarten — deren Molekulargewicht zwischen 35 000—60 000 Dalton liegt — eine ähnliche Aminosäurezusammensetzung [1, 2, 6, 11]. Mit der Isolierungsmethode I können in erster Linie Eiweiße mit einem Molekulargewicht von 35 000—60 000 Dalton — d. h. Gliadine — isoliert werden (Abb. 3), während die mit der Methode II isolierten Fraktionen inbezug aus das Molekulargewicht sowohl den Gliadinen, als auch den Gluteninen ähnlich sind. Dieser Umstand ermöglichte, daß wir nebst den physikochemischen Eigenschaften des Gliadins auch die des Glutenins untersuchen. Wie darauf Wu und Dimler [16] hingewiesen haben, sind das aus Mehl isolierte Gliadin und Glutenin hinsichtlich ihrer Aminosäurezusammensetzung einander ähnlich. Wie aus Tabelle I ersichtlich, bezieht sich diese Feststellung auch auf die von aus Brot isolierten Gliadin- und Gluteninfraktionen. Die Unterschiede manifestieren sich vor allem in dem Molekulargewicht der Polypeptidketten (Abb. 5, 2, 3) und dem Absorptionsspektrum der Fraktionen (Abb. 6). Aus Abbildung 7 geht hervor, daß die aus Brot isolierten Gliadin- und Gluteninfraktionen mit den von Zöliakiekranken stammenden 1 : 12 bzw. 1 : 16 verdünnten Seren als Antigene reagieren, während mit den von Normalpersonen stammenden Seren nur in Verdünnungen von 1 : 4 — bzw. selten 1 : 8 — positive Immunreaktionen ergeben [in mehreren Fällen gaben auch die im Verhältnis 1 : 12, 1 : 16 verdünnten, von verschiedenen Kranken (Myelom, Schizophrenie, Schilddrüsentumor) stammende Seren positive Reaktionen mit den Gluteneiweißen; diese positiven Reaktionen waren aber nicht unbedingt konsequent. Unseres Erachtens könnte die Frage, ob es sich in diesen Fällen um echte bzw. konsequente Reaktionen handelt, durch eine serienweise Untersuchung der Seren der an den erwähnten Krankheiten leidenden Patienten geklärt werden].

Die angeführten Versuchsergebnisse liefern einen Beweis dafür, daß die mit Pepsin und Trypsin nicht oder nur in geringem Maße hydrolysierbaren [7] Gluteneiweiße auch gegenüber der beim Brotbacken dauerhaft angewandten hohen Temperatur resistent sind, indem sie ihre ursprünglichen physiko- und immunochemischen Eigenschaften sowie ihre nährungsphysiologische Bedeutung beibehalten.

*

Unser herzlicher Dank gebührt Frau E. Korom und Frl, M. Debreczeni für ihre technische Hilfe.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (2), pp. 137—143 (1978)

Mild variant of maple syrup urine disease

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(Received November 1, 1977)

The case of a three-year-old boy with mental retardation, moderate muscular hypotony and speech delay is presented. The mild form of maple syrup urine disease was suspected at the first blood screening test by means of ion-exchange thin-layer chromatography. The diagnosis was confirmed by quantitative serum amino acid analysis and protein loading. On a low protein (2 g/kg body weight) diet completed with leucine–isoleucine–valine free formula prompt and lasting normalization of the serum amino acid level ensued with steady improvement of the clinical and neurological status.

Since the first report of maple syrup urine disease (MSUD) in 1954 [10] several papers were concerned with the recognition, biochemical and genetic background, treatment and prognosis of this inborn error of amino acid metabolism.

According to the latest surveys its incidence is about 1 : 2—500 000 [12, 16]. Since the world-wide organization of routine screening procedures for detecting the various inborn errors of amino acid metabolism, much knowledge has accumulated concerning the nature and biochemical differences of the different aminoacidopathies, and it was discovered that MSUD has four different forms. These are,

1. classical form
   complete lack of branched chain keto acid decarboxylase activity;
2. intermittent form
   the enzyme activity is 5—15% of normal and manifests in episodes during intercurrent diseases;
3. mild form
   the enzyme activity is below 50% of the normal;
4. thiamine responsive form
   high doses of thiamine are sufficient to control the serum amino acid levels.

In the present paper we shall report a case of the mild variant of MSUD in which the changing pattern of the serum amino acid level has led to the correct diagnosis.

REPORT OF A CASE

A 3-year-old boy was referred to genetic counselling in order to ascertain the cause of somato-mental retardation. The child had been born from the second pregnancy of healthy non-consanguineous 29 and 23

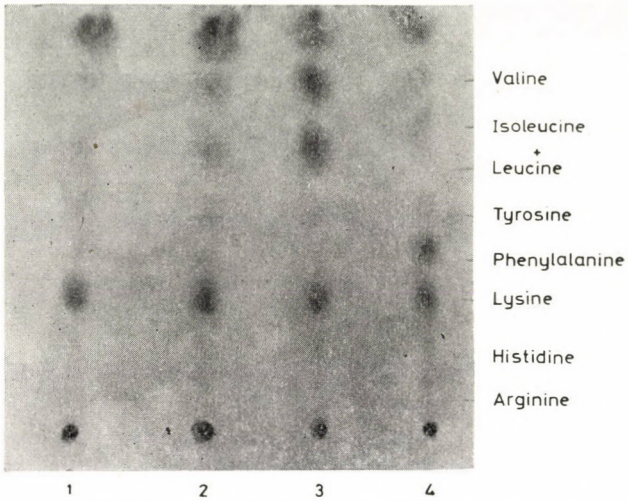

FIG. 1. Thin-layer ion-exchange chromatographic screening test for aminoacidaemias, on 10 × 10 cm IONEX 25 SA chromatoplate: No. 1. normal serum; 2. normal serum; 3. serum of patient with MSUD: pathologically increased level of valine and isoleucine + leucine; 4. serum of a patient with PKU: pathologically increased level of phenylalanine

years old parents. His only brother is apparently healthy.

After uneventful pregnancy a mature baby had been delivered with a birthweight of 3000 g. In the first week of life the baby was admitted to a neonatal ward on account of failure to thrive, apnoeic and cyanotic spells. X-rays had revealed aspiration pneumonia and RDS. A Robin anomalad has been supposed to be responsible for the feeding difficulties. After a couple of weeks of tube feeding and treatment with alkali-glucose infusions the infant had slowly recovered but at discharge his bodyweight was only slightly over the birthweight. Except a bilateral inguinal hernia and strange posture of the forearms, no other pathological signs had been observed. A Guthrie test had not been performed.

The child's somatic and mental development was delayed. He had begun to walk at 2 years of age. He does not speak, but hears well and is house-trained. At 2 years of age bilateral herniotomy and adenotomy were performed without complications. Convulsions or other neurological disorders or acidotic attacks had never occurred. His appetite was always poor and the parents never observed any strange smell of the urine.

Clinical findings and laboratory data. A routine blood sample was drawn for aminoacidopathy screening. Thin-layer ion-exchange chromatography [4, 8] showed a well-distinguishable spot in the region of valine and leucine (Fig. 1), and the child was admitted for clinical and biochemical evaluation. He was then three years and two months old, with fair complexion, blonde hair and eyelashes and a gracile constitution. His body weight was 11.7 kg, height 89 cm (both values below the third percentile), head circumference 48 cm (Fig. 2).

He had moderate general muscular hypotony which was particularly remarkable in the facial region, manifesting itself with blepharophimosis and poor mimicking. The child did not speak, although his hearing was adequate, he obeyed simple calls. Audiological examination revealed no organic hearing loss. Ophthalmological

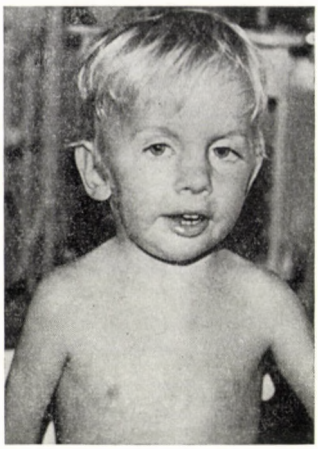

FIG. 2. Three years old mentally retarded boy with mild variant of MSUD

examination showed marked hypermetropy and astigmatism, which was corrected later with 6—7 Ds eye-glasses. No other internal or neurological disorder could be detected, except the strange posture of the hands which was supposed to be the consequence of the muscular hypotony.

Routine laboratory tests showed normal values.

Quantitative serum amino acid analyses were carried out by Beckman Unichrome Amino-Acid Analyser and the values were expressed in μmoles/litre.

Table I shows the complete serum amino acid pattern on admission and 3 days later after the ingestion of 200 ml cow's milk, in comparison with normal values [9]. The elevated levels of valine, leucine and isoleucine were remarkable.

In order to establish the type of branched chain amino acid disorder, after 3 weeks of low-protein diet and 12 hours fasting a protein load was performed with 3 g/kg protein. Results are shown in Table II. The initial values for all three branched chain amino acids were in the normal range and the increase following the protein load was moderately above the upper limit of normal. Subsequently, the level of the branched chain amino acids persisted in this range, failing to return to the initial level, whereas no marked change occurred in the pattern of the other amino acids.

A low-protein diet (2 g/kg protein) completed with valine–leucine–isoleucine free formula (Maizena) was introduced immediately after the first result of serum amino-acid analysis had become known. It had a striking effect on the neurological status. The child's behaviour, the muscular hypotony and his speech showed a slow but steady improvement. He became more alert and the most obvious sign was the improvement of his appetite. After six weeks of diet he gained 1.5 kg. The former unsuccessful logopaedic attempts were promising and the child soon learned to speak a few simple words.

DISCUSSION

The biochemical disturbances leading to the full clinical picture of MSUD are well-known. The main enzymatic defect is a deficient branched-chain keto acid decarboxylase activity, which can be demonstrated in the leukocytes and fibroblasts of patients [2, 3].

The consequence is a highly elevated plasma level of the branched chain amino acids valine, leucine and isoleucine, and the elevated urinary excretion of these substances and their metabolites. The latter are responsible for the characteristic sweet maple syrup odour.

In the classical form the clinical symptoms are present in the early newborn period. The outcome of undetected and therefore untreated cases is fatal [10, 13].

The improvement of diagnostic methods and the spread of knowledge in the field of amino acid disorders led to the discovery of several forms of MSUD. In a variant the accumulation of keto acids occurs intermittently under the effect of febrile diseases. These attacks are usually accompanied with severe acidosis and coma [1, 6, 17].

In a third variant the elevation of branched chain amino acids in the serum is moderate but constant. In spite of this it involves no serious neurological damage [7, 11, 14].

A fourth variant [15] is the thiamine responsive form. This variant resembles in many of its aspects the third one, with the exception that thiamine in high doses is effective in maintaining the control of the serum amino,acid level.

The present case resembles the third MSUD variant. In this form of the condition a moderate but consequently elevated valine, leucine and isoleucine level could be demonstrated [7, 13]. In our patient the initial values for the serum valine, leucine and isoleucine level were threefold of the normal (Table I). On three weeks protein restriction the level returned to almost normal. A challenge with 3 g/kg protein caused a moderate but constant increase in the level of these three amino acids and the elevated level persisted well beyond 24 hours (Table II). As it is seen in Fig. 3, compared to the healthy control, the protein load did not cause any significant change in the level of the other amino acids. It was remarkable that the 2,4-dinitrophenylhydrazine test in the urine was always negative.

The said changes were quite distinct if the quantities of the branched chain amino acids (valine, leucine, isoleucine) as well as of the basic ones (lysine, histidine, arginine) were added and the values expressed in percentage of the initial values. In MSUD (Fig. 3, curve No. 1) the rise of branched chain amino acids after 24 hours was more than 200%, compared to that of the basic amino acids (curve No. 3). In a healthy child (curves Nos 2 and 4) the flat curves point to a normal enzymatic and metabolic activity. This fact is interpreted as an indirect sign of diminished branched chain keto acid decarboxylase activity, supporting the diagnosis of the mild form of MSUD in our patient.

In the literature available, only three cases of the mild variant of MSUD have been reported [5, 7, 13]. Comparing to these the serum amino acid pattern of our patient (Table III), it is noteworthy that in this case the level of branched chain amino acids

TABLE I

Serum amino acid pattern on admission and after ingestion of 200 ml cow's milk
All values expressed in μmoles/litre

	On admission	After ingestion of 200 ml milk	Normal values [9]
Lysine	227	161	162 ± 23.2
Histidine	98	101	73.9 ± 17.1
Arginine	126	66	85.3 ± 18.5
Serine	202	158	147 ± 34.9
Proline	399	245	215 ± 69.7
Glycine	310	152	253 ± 70.8
Alanine	325	289	365 ± 103.1
Valine	486	571	211 ± 34.8
Isoleucine	149	178	47.1 ± 18
Leucine	229	267	106 ± 19.1
Tyrosine	105	83	60.9 ± 13.3
Phenylalanine	83	80	51.1 ± 9.5
Methionine	40	40	16.7 ± 4.2

TABLE II

Serum amino acid pattern after 5 weeks protein restriction, 12 hours fasting, and after 3 g/kg protein loading

	Serum amino acid levels at hours			
	0	2	4	24
Lysine	120	228	177	124
Histidine	67	115	108	88
Arginine	59	93	104	83
Serine	133	143	166	142
Glutamic acid	89	55	89	86
Glycine	261	240	226	170
Alanine	250	288	236	164
Valine	89	101	160	200
Isoleucine	41	60	96	91
Leucine	56	93	128	124
Methionine	20	33	34	17
Tyrosine	29	68	77	56
Phenylalanine	30	65	72	62

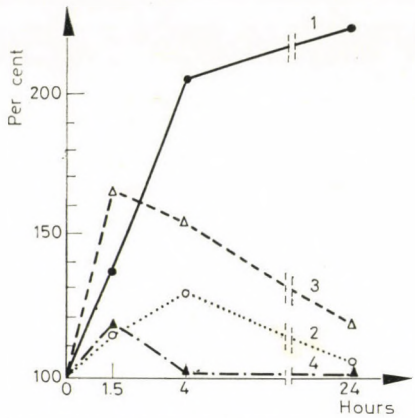

FIG. 3. Serum amino acid pattern after 3 g/kg protein load in MSUD and healthy control. The changing pattern of all branched chain as well as basic amino acids is expressed in per cents of the fasting levels. Curve 1. branched chain amino acids in MSUD; 2. branched chain amino acids in control; 3. basic amino acids in MSUD; 4. basic amino acids in control

TABLE III

Branched chain amino acids in serum (μmoles/l) in four cases of mild variant of MSUD

	Schulman et al. [13]	Fischer, Gerritsen [5]	Kodama et al. [7]	Present case	Normal values [9]
Leucine	1930	723	1988	229	106.0 ± 19.1
Isoleucine	630	287	867	149	47.1 ± 18
Valine	1040	776	914	486	211.5 ± 34.8

was considerably lower, although still distinctly higher than the normal values. This finding may explain the moderate mental retardation as well as the lack of the characteristic sweet odour of the urine. This is one of the reasons why the mild form of MSUD is easily overlooked. Only a reliable serum amino acid analysis combined with appropriate loading tests ensures the correct diagnosis and consequently the adequate therapy.

ACKNOWLEDGEMENTS

Thanks are due to Dr. T. Dévényi (Institute of Biochemistry of the Hungarian Academy of Sciences) for quantitative amino acid analyses, as well as to Mrs. I. Midrák for technical assistance.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (2), pp. 145—148 (1978)

Enterobiasis and urinary tract infection

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(Received October 21st, 1977)

The correlation between enterobiasis and urinary tract infection was studied in girls aged 6—14 years. Enterobius ova were demonstrated in anorectal scrapings, carried out three times in each case. Of the 84 patients suffering from urinary tract infection, 55 were Enterobius positive, as compared to 60 among 100 control girls. The difference was not significant. Enterobiasis was not found to be more frequent even when urinary tract infection reappeared within 6 months. There was no significant difference among patients with monosymptomatic bacteriuria and pyuria either. Enterobiasis thus seems to play no pathogenic role in urinary tract infection of girls.

A large proportion (20—80%) of children all over the world are infested with pinworm [2, 3, 5, 10] and it has been reported that children affected by urinary tract infection show a higher rate of enterobiasis than the average population [5, 7]. In view of the small number of reported cases it was felt justified to examine the relationship between the two conditions.

Patients and Methods

Eighty-four girls suffering from urinary tract infection were examined. Their age ranged from 6 to 14 years (average, 9 years and 7 months). The diagnosis of urinary tract infection was made if the freshly voided midstream urine, examined twice on consecutive days, contained more than 10^6 per ml of bacteria and the same bacteria could be cultured repeatedly from the urine; their antibiotic sensitivity had to coincide. Of the girls, 51 had pyuria; their urinary sediment contained more than 5 leukocytes per field. Thirty-three girls had monosymptomatic bacteriuria, and reinfection occurring within 6 months was observed in 37 patients.

Hundred girls aged 6 to 14 years (average, 9 years and 6 months) were examined as controls. These girls had no sign of urinary tract infection and no history of such complaints.

The diagnosis of enterobiasis rested on the presence of ova in the anal scrapings examined 3 times on consecutive days. Of infested persons, 90% are expected to give a positive result when examined in this way [10].

Enterobius ova were examined in anorectal scrapings, obtained by parting the cheeks and exposing the anal area. The short side of a laboratory slide was used for scraping both sides of the anus. If no material was obtained, the perianal area was wetted with a drop of water and the scraping repeated. The material thus obtained was transferred to a clean slide, smeared and examined under the microscope at ×70 magnification. The whole surface of the slide was screened as well

TABLE I

Comparison of the results of anorectal scraping and tape method in enterobiasis

Scraping	Tape method		Total
	Positive	Negative	
Positive	19	2	21
Negative	0	29	29
Total	19	31	50

TABLE II

Frequency of enterobiasis among girls with urinary tract infection and among controls

	Enterobius		Total
	Positive	Negative	
Urinary tract infection	55	29	84
Control	60	40	100
Total	115	69	184

as the edge of the one used to prepare the smear. In order to standardize results, all scrapings and examinations were carried out by the same person.

The procedure was compared to the generally used cellulose tape method [4]. In 50 cases the two methods were used simultaneously. Material was obtained from one side of the anus using the first method and from the other using the second method. Results are shown in Table I. It appears that the first method is at least as reliable as the tape method. Its advantages are that it is easier to obtain material, and the material collected from a larger surface area is concentrated in a smaller spot on the slide. Viewing the slides therefore takes less time. It is also easier, since with the tape method the pattern created by the adhesive and the curling up of the tape are somewhat disturbing for the examiner. On the other hand, transportation of the tape on slides is much simpler, and this is a considerable advantage if the material has to be sent to the laboratory.

RESULTS

Of the 84 girls affected with urinary tract infection, 55 were found to have Enterobious ova in the anorectal scrapings. In the control group, 60 had pinworm infestation. The difference was not significant ($\chi^2_{[1]}=0.5843$; $P > 0.3$; Table II).

Among the 37 girls who had reinfection, 24 had enterobiasis, while 31 were positive among the 47 who had had no reinfection. The difference was not significant ($\chi^2_{[1]} = 0.10985$; $P > 0.7$).

Of the 33 girls with monosymptomatic bacteriuria 19 were Enterobius positive, while of the 51 patients with pyuria 36 were positive. The difference was not significant ($\chi^2_{[1]} = 1.4114$; $P > 0.2$). There was no significant difference either if we compared the rate of Enterobius infestation among the patients with pyuria and the controls ($\chi^2_{[1]} = 1.093$; $P > 0.2$).

Discussion

There are two ways to explain the pathological role of enterobiasis in urinary tract infection of girls. According to the first view, the pinworms enter the urethra and the bladder carrying the bacteria of the gut [7]. Pinworms, however, are enteric parasites and rarely invade the organism outside the gut [1, 6, 9]. The number of such cases is extremely small if one takes into consideration that 209 million people in the world were said to be infected with Enterobius vermicularis [8], and the number of Enterobius infections in the USA is estimated at 42 million [10].

The other explanation seems more plausible: the worms cause perianal itching and the patient forces the bacteria into her urethra when scratching herself [5].

Reviewing the literature we found two papers claiming for enterobiasis a pathogenic role in urinary tract infection. Mayers and Purvis [5] found 10 positive cases among 26 girls with bacteriologically proven urinary tract infection, while 24 of the 100 controls were infested. If we analyse these data statistically, the difference was not significant ($\chi^2_{[1]} = 2.19$; $P > 0.1$). Of Simon's [7] 28 patients with urinary tract infection, 16 had enterobiasis, against 6 out of the 113 controls. As Welch [11] pointed out, the diagnosis of urinary tract infection in these cases was unequivocal: no bacteriological tests were carried out.

In the present material we found no correlation between either urinary tract infection and enterobiasis or between monosymptomatic bacteriuria, pyuria and enterobiasis. There was also a lack of correlation between pinworm infection and urinary tract reinfection.

Thus, according to our results, enterobiasis plays no pathogenic role in the urinary tract infection of girls.

Since completion of this paper, 35 new female patients suffering from urinary tract infection have been studied. Thus, of a total of 119 girls with urinary tract infection 80 had pinworms (67%) while in the control group of 120 patients 77 were positive for pinworms (64%). The difference was not significant ($x^2_{[1]} = 0.2482$; $P > 0.5$).

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (2), pp. 149—156 (1978)

The baseline data of the Hungarian Congenital Malformation Register, 1970–1976

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(Received October 1, 1977)

The baseline data of the Hungarian Congenital Malformation Register 1970—1976 are published for national and international use and evaluation

The renewed Hungarian Congenital Malformation Register (HCMR) was launched January 1st, 1970. Its aim and function were described earlier [1]. The classification of categories and subcategories of congenital anomalies is based on the International Classification of Diseases (ICD), VIIIth Revision, 1965 [3], mainly on its Chapter XIV entitled "Congenital Anomalies". But the HCMR shows some deviations from the ICD:

(i) All *notified* congenital anomalies, e.g. congenital rubella syndrome, inborn errors of metabolism, congenital hernias and tumors, etc., have been included.

(ii) A new type of subcategory has been established, of the so-called "*complex*" congenital malformation which involves two or more notified congenital malformations within the *same* organ, e.g. heart, eye, bowels, etc.

Table I

Number and occurrence of malformed babies in Hungary, 1970—1976

Year	Live births		Stillbirths		Total births		Number of babies with congenital malformations	Occurrence of malformed babies per 1000 total births
	No.	%	No.	%	No.	%		
1970	151,819	99.01	1520	0.99	153,339	100.00	3304	21.55
1971	150,640	99.00	1519	1.00	152,159	100.00	4355	28.62
1972	153,265	99.10	1423	0.90	154,688	100.00	4802	31.04
1973	156,224	99.11	1399	0.89	157,623	100.00	4780	30.33
1974	186,288	99.11	1669	0.89	187,957	100.00	6301	33.52
1975	194,240	99.18	1607	0.82	195,847	100.00	6909	35.53
1976	185,395	99.19	1521	0.81	186,916	100.00	6844	36.56

TABLE II

Number and occurrence of registered congenitally malformed newborn infants according to categories and subcategories of ICD VIIIth revision in the Hungarian Congenital Malformations Register, 1970—1976

ICD code number	Categories and subcategories	1970		1971		1972		1973		1974		1975		1976	
		No.	‰	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰
740.	Anencephalus	145	0.95	130	0.85	156	1.00	117	0.74	181	0.96	128	0.66	118	0.63
741.	Spina bifida	189	1.23	184	1.21	164	1.05	146	0.93	192	1.02	156	0.81	140	0.75
742.	Congenital hydrocephalus	48+	0.31	98	0.64	93	0.60	100	0.63	148	0.79	149	0.77	114	0.61
743.0	Encephalocele	38	0.25	37	0.24	48	0.31	37	0.24	44	0.23	31	0.16	31	0.16
743.1	Microcephalus	12	0.08	23	0.15	22	0.15	10	0.06	28	0.15	29	0.14	22	0.12
743.2**—743.9	Other anomalies of nervous system	2	0.01	7	0.05	16	0.11	12	0.08	19	0.10	17	0.09	12	0.06
744.0—744.1	Anophthalmos and microphthalmos	4	0.03	11	0.07	5	0.03	1	0.01	3	0.02	0	—	3	0.20
744.3 744.2	Congenital cataract	10	0.07	8	0.05	5	0.03	3	0.02	9	0.05	3	0.01	9	0.05
744.4—744.9	Other anomalies of eye	13	0.08	24	0.16	22	0.15	28	0.18	21	0.11	23	0.11	15	0.08
745.0 745.2	Anomalies of ear	18	0.12	20	0.13	19	0.12	17	0.11	24	0.13	33	0.17	30	0.16
745.1	Accessory auricle	11	0.07	11	0.07	8	0.05	6	0.04	10	0.05	7	0.03	11	0.06
745.4	Branchial cleft cyst, or fistula; preauricular sinus	8	0.05	10	0.07	9	0.06	10	0.06	6	0.03	13	0.07	6	0.03
745.7* 745.5	Torticollis	1	0.01	6	0.04	48	0.31	31	0.20	30	0.16	23	0.11	7	0.04
745.8—745.9	Other anomalies of face and neck	4	0.03	6	0.04	7	0.05	3	0.02	5	0.03	7	0.03	9	0.05
746.0	Common truncus	6	0.04	6	0.04	10	0.06	6	0.04	13	0.07	13	0.07	9	0.05
746.1	Transposition of great vessels	11	0.07	19	0.12	17	0.12	18	0.11	38	0.20	31	0.17	30	0.16
746.2	Tetralogy of Fallot	16	0.10	26	0.17	14	0.09	17	0.11	19	0.10	18	0.09	22	0.12
746.3	Ventricular septal defect	94	0.61	119	0.78	162	1.05	148	0.94	159	0.85	181	0.93	170	0.91
746.4	Atrial septal defect	37	0.24	33	0.22	31	0.20	37	0.24	41	0.22	43	0.22	40	0.21
746.5—746.8	Other specified anomalies of heart	9	0.06	11	0.07	23	0.15	38	0.24	56	0.30	35	0.18	27	0.14
747.7*	Complex congenital anomalies of heart	33	0.22	48	0.31	44	0.28	63	0.40	67	0.36	73	0.38	61	0.33

746.9	Unspecified anomalies of heart	116	0.76	182	1.20	166	1.07	170	1.08	237	1.25	348	1.78	307	1.65
747.0	Patent ductus arteriosus	18	0.12	14	0.09	31	0.22	33	0.21	20	0.11	36	0.18	53	0.28
747.1	Coarctation of aorta	1	0.01	4	0.03	6	0.04	7	0.04	6	0.03	13	0.07	9	0.05
747.2	Other anomalies of aorta	4	0.03	21	0.14	18	0.12	15	0.10	24	0.13	30	0.15	21	0.11
747.3	Stenosis or atresia of pulmonary artery	3	0.02	8	0.05	0	—	11	0.07	15	0.08	15	0.07	15	0.08
747.4—747.6	Other anomalies of circulatory system	1	0.01	2	0.01	3	0.02	7	0.04	7	0.04	10	0.05	6	0.03
747.8—747.8															
748.	Congenital anomalies of respiratory system	13	0.08	25	0.16	29	0.19	26	0.17	28	0.15	31	0.16	29	0.16
749.0	Cleft palate	44	0.29	49	0.32	43	0.28	45	0.29	60	0.32	58	0.30	63	0.33
749.1—749.2	Cleft lip; cleft palate with cleft lip	123	0.80	145	0.95	163	1.05	149	0.95	171	0.91	169	0.87	171	0.91
749.3*	Robin anomalad	5	0.03	7	0.05	6	0.04	8	0.05	14	0.07	16	0.08	9	0.05
750.1	Pyloric stenosis	44	0.29	87	0.57	58	0.37	44	0.28	57	0.30	*48*	0.25	57	0.30
750.2	Tracheo-oesophageal fistula, oesophageal atresia and stenosis	19	0.12	27	0.18	30	0.19	19	0.12	32	0.17	32	0.16	40	0.21
751.1	Atresia and stenosis of small intestine	7	0.05	30	0.20	28	0.18	27	0.17	24	0.13	34	0.17	43	0.23
751.2	Atresia and stenosis of rectum and anal canal	24	0.16	32	0.21	16	0.11	35	0.22	33	0.18	39	0.20	31	0.16
751.2	Hirschsprung disease	5	0.03	11	0.07	23	0.15	16	0.10	10	0.05	17	0.09	13	0.07
751.6—750.0**750.8—751.0	Anomalies of gallbladder, bile ducts, liver and pancreas	8	0.05	13	0.08	13	0.09	14	0.09	22	0.12	22	0.11	21	0.11
751.4—751.5751.8—751.9	Other anomalies of digestive system	5	0.03	22	0.14	18	0.12	17	0.11	43	0.23	21	0.11	29	0.16
752.1	Undescended testicle	26	0.17	38	0.25	90	0.58	88	0.56	110	0.59	169	0.87	168	0.90
752.2—752.3	Hypospadias and epispadias	77	0.50	164	1.08	153	0.99	200	1.27	235	1.25	303	1.55	336	1.80
752.4	Congenital hydrocele	77	0.50	93	0.61	93	0.60	78	0.49	156	0.83	169	0.87	239	1.28
752.0**752.5—752.9	Other anomalies of genital organs	26	0.17	12	0.08	18	0.12	17	0.11	16	0.09	21	0.11	19	

TABLE II (Cont.)

ICD code number	Categories and subcategories	1970		1971		1972		1973		1974		1975		1976+	
		No.	‰	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰
753.0**	Renal agenesis	4	0.03	12	0.08	7	0.05	8	0.05	11	0.06	4	0.02	13	0.07
753.01*	Caudal regression anomalad	1	0.01	4	0.03	8	0.05	15	0.10	9	0.05	10	0.05	20	0.11
753.02*	Triad anomalad	1	0.01	0	—	2	0.01	1	0.01	5	0.03	4	0.02	5	0.03
753.1	Cystic kidney disease	3	0.02	10	0.07	21	0.14	16	0.10	11	0.06	21	0.11	15	0.08
753.2	Obstructive defects of urinary tract	0	—	3	0.02	11	0.07	19	0.12	28	0.15	17	0.09	17	0.09
753.5	Exstrophy of urinary bladder and cloacae	5	0.03	0	—	5	0.03	8	0.05	8	0.04	12	0.06	9	0.05
753.3—753.4 753.8—753.9	Other anomalies of urinary system	8	0.05	22	0.14	23	0.15	19	0.12	26	0.14	38	0.19	26	0.14
754.0	Clubfoot (congenital)	170	1.11	239	1.57	247	1.60	258	1.64	326	1.73	378	1.94	337	1.81
755.0	Polydactyly	46	0.30	85	0.55	97	0.63	71	0.45	123	0.65	91	0.47	98	0.53
755.01*	Polydactily + syndactyly	7	0.05	4	0.03	8	0.05	8	0.05	13	0.07	11	0.05	18	0.10
755.1	Syndactyly	19	0.12	38	0.25	46	0.30	34	0.22	44	0.23	67	0.34	43	0.23
755.2—755.4	Reduction deformity of limbs	28	0.18	44	0.29	37	0.24	45	0.29	63	0.34	89	0.46	82	0.44
755.6 755.5	Congenital dislocation of hip	572	3.73	722	4.75	809	5.23	854	5.42	1142	6.08	1422	7.26	1514	8.10
755.7—755.9	Other anomalies of limbs	12	0.08	7	0.05	16	0.11	14	0.09	9	0.05	18	0.09	15	0.08
756.**	Other congenital anomalies of musculoskeletal system	20	0.13	22	0.14	15	0.10	23	0.15	30	0.16	25	0.13	23	0.12
757.1	Pigmented naevus	37	0.24	20	0.13	44	0.28	35	0.22	52	0.28	74	0.38	102	0.55
757.0 757.2—575.9	Other anomalies of skin, hair and nails	3	0.02	11	0.07	15	0.10	8	0.05	13	0.07	18	0.09	5	0.03
758.2	Anomalies of thyroid gland	6	0.04	8	0.05	15	0.10	24	0.15	34	0.18	16	0.08	15	0.08
758.0—758.1 758.3	Anomalies of spleen and other endocrine glands	1	0.01	2	0.01	0	—	5	0.03	5	0.03	9	0.04	2	0.01
758.9	Unspecified congenital anomaly	0	—	5	0.03	0	—	5	0.03	3	0.02	9	0.04	0	—
759.0	Situs inversus	5	0.03	2	0.01	2	0.01	2	0.01	5	0.03	15	0.07	2	0.01
759.1*	Conjoined twins	2	0.01	2	0.01	2	0.01	1	0.01	7	0.04	1	0.00	5	0.03

759.2*	Relatively frequent heterogeneous multiple malformations														
759.211*	Chondrodystrophia	3	0.02	12	0.08	17	0.12	11	0.07	8	0.04	14	0.07	21	0.11
759.212*	Osteogenesis imperfecta	7	0.05	4	0.03	9	0.06	5	0.03	4	0.02	7	0.03	5	0.03
759.213*	Arthrogryposis	4	0.03	4	0.03	5	0.03	4	0.03	0	—	3	0.01	4	0.02
759.22*	Structural syndromes due to major gene defect	11	0.07	13	0.08	10	0.06	12	0.08	18	0.10	26	0.13	10	0.05
759.23*	Inborn errors of metabolism	6	0.04	9	0.06	15	0.10	12	0.08	24	0.13	33	0.17	28	0.14
759.23*	Heredoneuromuscular anomalies	1	0.01	3	0.02	1	0.01	3	0.02	4	0.02	4	0.02	8	0.04
759.3	Down disease	87	0.57	111	0.73	128	0.83	136	0.86	175	0.93	168	0.86	169	0.90
759.4	Other syndromes due to autosomal abnormality	7	0.05	4	0.03	12	0.08	13	0.08	10	0.05	10	0.05	12	0.06
759.5	Syndromes due to sex chromosome abnormality	3	0.02	3	0.02	5	0.03	3	0.02	5	0.03	5	0.02	6	0.03
759.6*	Structural syndromes due to environmental agents	3	0.02	4	0.03	0	—	4	0.03	15	0.08	11	0.05	10	0.05
759.71*	Postural associations	83	0.55	110	0.72	128	0.83	133	0.85	97	0.52	61	0.31	35	0.21
759.82*	Combinations														
759.821*	Persons with two malformations														
	Cardinal malformations														
759.8211*	First group														
	Anencephalus	8	0.05	9	0.06	16	0.11	22	0.14	18	0.10	18	0.09	16	0.08
	Encephalocele	5	0.03	6	0.04	3	0.02	6	0.04	11	0.06	9	0.04	1	0.01
	Spina bifida	14	0.09	17	0.11	18	0.12	20	0.13	31	0.16	26	0.13	19	0.10
	Cleft lip; cleft lip with cleft palate	13	0.08	14	0.09	19	0.12	30	0.19	11	0.06	22	0.11	24	0.13
	Cleft palate	6	0.04	10	0.07	10	0.06	9	0.06	9	0.05	6	0.03	10	0.05
	Reduction deformity of limbs	5	0.03	3	0.02	6	0.04	13	0.08	10	0.05	7	0.03	9	0.05
	Polydactyly	3	0.02	8	0.05	14	0.09	8	0.05	9	0.05	12	0.06	10	0.05
	Syndactyly	7	0.05	9	0.06	4	0.03	6	0.04	13	0.07	17	0.09	8	0.04
	Exomphalos	2	0.01	8	0.05	6	0.04	9	0.06	3	0.02	7	0.03	9	0.05
	Oesophageal atresia	8	0.05	5	0.03	5	0.03	7	0.04	6	0.03	8	0.04	3	0.02
	Atresia of anal canal	8	0.05	9	0.06	9	0.06	7	0.04	4	0.02	7	0.03	9	0.05
759.8212*	Second group														
	Microcephalus	8	0.05	5	0.03	7	0.05	8	0.05	6	0.03	12	0.06	9	0.05
	Hydrocephalus	7	0.05	13	0.08	16	0.11	18	0.11	15	0.08	14	0.07	16	0.08
	Anomalies of eye	4	0.03	5	0.03	7	0.05	8	0.05	3	0.02	6	0.03	1	0.01
	Clubfoot	6	0.04	10	0.07	10	0.06	6	0.04	9	0.05	6	0.03	21	0.11
	Congenital dislocation of hip	6	0.04	7	0.05	19	0.12	15	0.09	26	0.14	26	0.13	34	0.18
	Hypospadias	12	0.08	10	0.07	17	0.12	12	0.08	22	0.12	27	0.14	23	0.12

TABLE II (Cont.)

ICD code number	Categories and subcategories	1970		1971		1972		1973		1974		1975		1976+	
		No.	‰	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰
	Undescended testicles	5	0.03	3	0.02	11	0.07	5	0.03	9	0.05	10	0.05	11	0.06
	Diaphragmatic hernia	5	0.03	5	0.03	4	0.03	5	0.03	4	0.02	6	0.03	7	0.04
	Anomalies of heart	19	0.12	29	0.19	43	0.28	40	0.25	36	0.19	43	0.22	48	0.26
	Anomalies of urinary system	0	—	1	0.01	3	0.02	5	0.03	10	0.05	6	0.03	2	0.01
	Hernias	11	0.07	11	0.07	14	0.09	11	0.07	10	0.05	12	0.06	18	0.10
	Anomalies of skin	7	0.05	8	0.05	4	0.03	6	0.04	4	0.02	6	0.03	3	0.02
	Other anomalies	1	0.01	0	—	1	0.01	1	0.01	0	—	0	—	0	—
759.822*	Persons with three or more malformations														
759.8221*	First group														
	Anencephalus	3	0.02	7	0.05	3	0.02	6	0.04	6	0.03	9	0.04	9	0.05
	Encephalocele	1	0.01	3	0.02	1	0.01	4	0.03	0	—	4	0.02	5	0.03
	Spina bifida	7	0.05	5	0.03	8	0.05	11	0.07	13	0.07	10	0.05	8	0.04
	Cleft lip; cleft lip with cleft palate	4	0.03	9	0.06	16	0.11	9	0.05	21	0.11	22	0.11	18	0.10
	Cleft palate	5	0.03	10	0.07	9	0.06	2	0.01	6	0.03	7	0.03	14	0.07
	Reduction deformity of limbs	1	0.01	3	0.02	5	0.03	6	0.04	6	0.03	7	0.03	6	0.03
	Polydactyly	4	0.03	2	0.01	7	0.05	10	0.06	10	0.05	7	0.03	6	0.03
	Syndactyly	3	0.02	3	0.02	3	0.02	3	0.02	4	0.02	6	0.03	0	—
	Exomphalos	0	—	2	0.01	4	0.03	3	0.02	2	0.01	5	0.02	0	—
	Oesophageal atresia	1	0.01	1	0.01	4	0.03	5	0.03	5	0.03	7	0.03	4	0.02
	Atresia of anal canal	1	0.01	4	0.03	5	0.03	3	0.02	6	0.03	7	0.03	3	0.20
759.8222*	Second group														
	Microcephalus	2	0.01	6	0.04	2	0.01	3	0.02	6	0.03	7	0.03	1	0.01
	Hydrocephalus	1	0.01	2	0.01	5	0.03	7	0.04	4	0.02	5	0.02	4	0.02
	Anomalies of eye	0	—	1	0.01	0	—	1	0.01	2	0.01	0	—	3	0.02
	Clubfoot	3	0.02	7	0.05	6	0.04	7	0.04	5	0.03	10	0.05	10	0.05
	Congenital dislocation of hip	2	—	1	0.01	1	0.01	1	0.01	2	0.01	3	0.01	5	0.03
	Hypospadias	0	—	3	0.02	2	0.01	1	0.01	3	0.02	2	0.01	7	0.04
	Undescended testicles	0	—	1	0.01	1	0.01	2	0.01	2	0.01	2	0.01	1	0.01
	Diaphragmatic hernia	1	0.01	0	—	2	0.01	0	—	3	0.02	0	—	4	0.02
	Anomalies of heart	5	0.03	3	0.02	7	0.05	2	0.01	5	0.03	4	0.02	8	0.40
	Anomalies of urinary system	0	—	0	—	0	—	0	—	0	—	0	—	2	0.01
	Hernias	0	—	0	—	2	0.01	0	—	0	—	0	—	1	0.01
	Anomalies of skin	0	—	0	—	0	—	0	—	0	—	0	—	0	—

	Other malformations	0	—	0	—	0	—	0	—	1	0.01	0	—	0	—
759.9	Multiple congenital anomalies, unspecified	27	0.18	20	0.13	25	0.16	38	0.24	57	0.30	5	0.02	5	0.09
550	Inguinal hernia	183	1.19	206	1.35	259	1.67	211	1.34	463	2.46	552	2.84	627	3.35
550.1*	Ing. + umb. hernia	12	0.08	12	0.08	3	0.02	5	0.03	13	0.07	18	0.09	9	0.05
551.11	Omphalocele, exomphalos	19	0.12	20	0.13	29	0.19	28	0.18	33	0.17	39	0.19	49	0.26
551.12	Umbilical hernia	81	0.53	87	0.57	56	0.36	49	0.31	73	0.39	87	0.45	104	0.56
551.3	Diaphragmatic hernia	12	0.08	23	0.15	28	0.20	41	0.26	53	0.28	37	0.18	33	0.18
551.0 551.2 551.8— 551.9	Other hernia of abdominal cavity	4	0.03	6	0.04	9	0.06	8	0.05	10	0.05	9	0.04	18	0.10
227.	Haemangioma	224	1.46	329	2.16	337	2.18	336	2.13	431	2.29	388	1.98	318	1.70
228.	Teratoma	8	0.05	13	0.08	9	0.06	16	0.10	24	0.13	27	0.14	12	0.06
	Grand total No.	3304		4356		4802		4778		6308		6904		6844	
	%	21.55		28.63		31.04		30.31		33.56		35.25		36.62	

* new subcategory established in the HCMR
** syndromes are excluded and they are within the three digit category 759

(iii) An attempt has been made to adopt some new international recommendations for the classification of congenital malformations, e.g. *anomalads* [2].

(iv) In our definition, multiple malformation means *two* or more major malformations in different organs or tissues of a person without direct relation of cause and effect. Thus, there is a possibility to exclude the confusion caused by two different parameter systems: congenital anomalies and malformed babies.

(v) Regarding multiple malformations (three digit category 759) a new classification has been developed in order to establish an easier and more efficacious evaluation.

This paper contains only the data of the HCMR, 1970—1976, without any evaluation and discussion. Its only purpose is to publish the baseline data of the HCMR for Hungarian and international use and evaluation before the HCMR will be transformed from the VIIIth Revision of ICD into the IXth Revision and before a new computer programme will be started on January 1st, 1978.

All occurrences of the different categories and subcategories of congenitally malformed babies (the so-called point-prevalences at birth) are calculated per 1000 total births. The figures for live births, stillbirths and total births in Hungary, 1970—1976, are to be found in Table I.

Table II shows only the more frequent (with occurrences over 1 : 30,000 total births) and well-defined categories and subcategories of congenital anomalies. The rare and inaccurately defined or unspecified congenital anomalies within each three digit code number are collected into joint categories.

The results of statistical utilization of malformed babies according to the month of birth; residence of parents (mother); sex ratio; rate of live births and still births; infant death; singletons and multiple births; birth weight and other parameters will be published later in detail.

These baseline figures are considered to be the final version of the HCMR, 1970—1976. The figures deviate somewhat from the earlier Hungarian publications ("Annual Report of the HCMR") due to some changes in the classifications and modifications made after the deadline.

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Recensiones

Experimental production of diseases: Liver. Edited by O. EICHLER. Heffter-Heubner Handbook of Experimental Pharmacology, Vol. 16 Part 2. XIV + 377 pages. Springer-Verlag, Berlin—Heidelberg—New York 1976. DM 240,—

Volume 16 of the huge Heffter-Heubner "Handbook" consists of a number of excellent monographs on the experimental production of diseases. The monograph at issue is one of the series. It is a very useful work since there is hardly any concise book which would offer a survey of the whole field of experimental liver injury. On the other hand, it is a sheer impossibility to solve the task on 300 odd pages in a manner which would meet the demands of researchers interested in a certain kind of hepatic lesion. The book opens with the sentence, "the literature of experimental hepatotoxicity has become so enormous as to overwhelm the effort to summarize the current state of knowledge" and the book itself is the best proof of this statement being valid for the whole contents. Not as if the book would not give a summary of the highest level of its subject and could not serve as a source of information on practically all the aspests, even the most up-to-date ones, of experimental liver research. This is especially true for the first chapter, Experimental Hepatotoxicity, by H. J. Zimmermann, which goes into such details as e.g. to devote many pages to the aflatoxins. In the next chapters, Mackay deals with the infectious and allergic diseases, with an outstanding part on viral hepatitis, then Lesch with radiation injury and Harenberg with the experimental production of gallstones.

The book will and must be welcomed by everybody who wishes to get overall information on liver injuries. It will, however, be a deception to the paediatrician, as he will find none of the data of the vast literature on the effect on the liver of the various diets and especially experimental protein deficiency, and read some questionable statements, for instance that congenital toxoplasmosis is usually fatal, etc. And research workers and clinicians will equally regret the fact that apart from its potentiating effect on CCl_4 toxicity and the frequency of cirrhosis, no mention whatever is made of alcohol.

P. V. VÉGHELYI

W. KRESSIN und M. RAUTENBACH: *Zerebrale Bewegungsstörungen im Kindesalter.* 152 Seiten mit 38 Abbildungen und 4 Tabellen. Verlag Volk und Gesundheit, Berlin 1976. M 11.—

Das Büchlein gibt eine ausgezeichnete Zusammenfassung sämtlicher Probleme, die man heutzutage über die zerebralen Bewegungsstörungen kennen muß. Diagnostik, Orthopädie, Rehabilitation, Physiotherapie sowie die Organisation der Therapie werden in dieser nützlichen Arbeit erläutert.

Der diagnostische Aspekt der Neurologie beruht auf der PEIPERschen Klassi-

fikation, die Autoren zitieren aber auch die Arbeiten von THOMA, PRECHTL und anderer Verfasser. In der Literatur findet sich eine Reihe von dokumentierten, sich auf Reflexe und Reaktionen beziehenden Beobachtungen, wie z. B. die wohlbekannten pathologischen und asymmetrischen tonischen Halsreflexe, der primäre Schreitreflex usw. Es ist also kein Wunder, daß im »Fahrplan«, der die Zeitpunkte des Erscheinens bzw. des Verschwindens der Reflexe in sich faßt, einige Widersprüche zu erkennen sind.

Die Grundlagen für die Frühdiagnostik bilden die wichtigeren Symptome; im Rahmen dieses positiven Aspektes werden die Wichtigkeit der Frühdiagnose sowie die Notwendigkeit der Frühbehandlung im Interesse der Vorbeugung der fatalen Konsequenzen der komplexen Symptomatologie nachdrücklich betont.

Da die Autoren nicht die Absicht hatten, die neurophysiologischen Details der zerebralen Bewegungsstörungen ausführlich zu erläutern, vermißt der Leser die diesbezüglichen Daten. Die klinische neurologische Entwicklungslehre beruht auf klinischen Beobachtungen; den Versuchen liegen allerdings die Grundbegriffe der Neurophysiologie zugrunde. Auf die Kenntnisse der Entwicklung der Formatio reticularis, der Funktion der extrapyramidalen Wege und der kortikalen Dominanz aufgebaut, bieten die Forscher neue Kenntnisse aus dem Bereich der Neurologie des Kindesalters.

Das Buch ist ein anschauliches Beispiel dafür, wie man das Wissenswerte kurz und bündig zusammenfassen soll.

F. KATONA

M. HERTL: *Pädiatrische Differentialdiagnose*. XXII + 750 Seiten mit 488 teilweise farbigen Abbildungen in 676 Einzeldarstellungen und 156 Tabellen. G. Thieme Verlag, Stuttgart 1977. DM 198,—

Der Autor betont, daß die Verfassung eines differentialdiagnostischen Lehrbuches nur teilweise erfolgreich sein kann, da dieses sich immer auf die Krankheiten der Organsysteme aufgebaute Lehrbücher stützen muß und letztere nicht ersetzen kann. Obwohl diese Feststellung richtig ist, erfüllt das vorliegende Buch doch restlos seine Zielsetzungen und dürfte sich sowohl als Lehrbuch wie auch ein Nachschlagewerk ausgezeichnet bewähren.

Die Einteilung ist originell und äußerst gut. Vor dem Inhaltsverzeichnis finden wir eine kurze Einleitung, aus dem der »eilige Leser« in 11 Punkte zusammengefaßt ein Bild über die Einteilung der 52 Kapitel erhält, die angefangen von den verschiedenen Zuständen und Verhaltensformen über die Veränderungen der einzelnen Körperregionen bis zu den lebensgefährdenden Zuständen alle Erscheinungen erörtern. Hiernach folgt das eigentliche Inhaltsverzeichnis, welches die Annäherung des zu lösenden Problems, vor allem aufgrund des Leitsymptoms, ermöglicht. In den danach folgenden einleitenden Worten werden unter dem Titel »Von dem Symptom bis zur Diagnose« einige grundlegende Tatsachen hervorgehoben.

Die Kapitel befassen sich an Hand der Symptome mit der gesamten Kinderheilkunde: Schmerz, Dyspnoe, Angst, Appetitstörungen, Schlafstörungen, Schwindel usw., um nur einige zu erwähnen. Die heute in den Vordergrund gerückten psychologischen Veränderungen bzw. psychischen Krankheitszeichen werden in den Abschnitten sehr zeitgemäß vielfach zuerst besprochen. Besonders zweckmäßig erscheint die Schilderung der verschiedenen Krankheitsbilder, da die wohlbekannten Krankheiten lediglich zwecks Verständnis der Zusammenhänge ganz kurz und die komplizierteren oder selteneren Erkrankungen ausführlicher, in mehreren Zusammenhängen behandelt werden. Die rasche Diagnosestellung wird durch Tabellen bedeutend gefördert, die die Krankheitsbilder, Laborbefunde und wichtige Faktoren zusammenfassen. Zur schnellen Orientierung tragen auch der gute Aufbau des Textes, die Numerierung und drucktechnische Mittel

bei, und so wird ermöglicht, daß gewisse Erscheinungen und Veränderungen an mehreren Stellen in mehreren Zusammenhängen gedeutet werden können. Sehr nützlich sind schließlich der Anhang des Buches, wo in Tabellen und Abbildungen die normalen physiologischen Werte dargestellt sind, und das ausführliche Sachregister.

Alles in allem, ist die pädiatrische Literatur mit einem die ganze Kinderheilkunde von vielen Aspekten umfassenden modernen und vortrefflichen Werk bereichert worden, das jeder Pädiater in seiner alltäglichen Arbeit verwenden kann.

K. Schmidt

Pädiatrische Intensivmedizin. Herausgegeben von P. Emmrich. XVIII + 298 Seiten mit 218 Abbildungen und 98 Tabellen. G. Thieme Verlag, Stuttgart 1977. DM 69,—

Das in der Reihe Intensivmedizin — Notfallmedizin — Anästhesiologie veröffentlichte Buch enthält die Vorträge des in Mainz 1975 gehaltenen Symposions, in 6 Hauptteilen. Der erste befaßt sich mit den Problemen des Transportes und der Organisation. Besonders interessant ist der Beitrag über den Neugeborenentransport (Meyer und Dangel). Im Rahmen des 2. Hauptthemas werden die neuen Beatmungsverfahren behandelt. In einigen Vorträgen werden die vergleichenden Untersuchungen mit verschiedenen Beatmungsapparaten, in anderen die Ergebnisse mit neu konstruierten Respiratoren mitgeteilt. Hier wird auch die Lungenblutung im Neugeborenenalter nach Ätiologie und Therapie gruppiert besprochen (Saule und Mitarb.). Bei infolge hypoxisch und azidotisch bedingter Insuffizienz der linken Kammer herbeigeführten Lungenblutung wird eine Respiratorbehandlung mit erhöhtem Ausatmungsenddruck angewandt. Weitere Vorträge sind der assistierten bzw. kontrollierten Respiratorbehandlung der Neugeborenen gewidmet, wobei die Bedeutung der ständigen und fortlaufenden Messung der Blutgaswerte und der transkutanen PO_2-Messung und der Kardiorespirographie hervorgehoben werden.

Man erhält einen guten Überblick über die kardiologischen Probleme des Säuglings- und Kindesalters. Im 5. Teil wird über die bei der pädiatrischen Intensivtherapie auftretende Sepsis, deren Entstehung und Vorbeugung berichtet. Symptomatologie, Therapie und Prognose werden auch eingehend erörtert. Im letzten Teil werden in freien Vorträgen in erster Reihe die Fragen der Beatmung und parenteralen Ernährung, die Behandlung der Hyperthermie, ferner chirurgische Themen, die Behandlung von Verbrennungen und psychologische Probleme erläutert.

Dieser in der INA-Schriftreihe erschienene Band berichtet über viele neue Fragen, besonders jene der Intensivbetreuung von Früh- und Neugeborenen, und wird für jeden Neonatologen und sich mit Intensivtherapie befassenden Arzt eine interessante und nützliche Lektüre sein.

B. Büky

P. Wunderlich: *Kinderärztliche Differentialdiagnostik.* XII + 231 Seiten mit 11 Abbildungen und 19 Tabellen. Theodor Steinkopff, Dresden 1977. M 18,—

Das Buch wendet sich an Medizinstudenten und Ärzte, die keine Fachärzte der Kinderheilkunde sind. Es besteht aus einem die allgemeinen Gesichtspunkte und einem die aus Leitsymptomen ausgehenden Differentialdiagnosen enthaltenden Teil.

Im allgemeinen Teil gibt der Verfasser einige Ratschläge zur Aufnahme der Anamnese, Technik der physikalischen Untersuchung und Altersabhängigkeit der Symptome. Die Besonderheiten des Neugeborenen werden hervorgehoben.

Der zweite Teil befaßt sich mit der differentialdiagnostischen Bedeutung der einzelnen Symptome. Die häufigsten Fie-

berursachen sind in einer Tabelle zusammengefaßt, die aber nicht als vollständig betrachtet werden kann. Schmerzen werden aufgrund ihrer Lokalisation erörtert (Kopf-, Ohren-, Nasen-, Hals-, Brustkorb-, Bauchschmerzen). Gesonderte Abschnitte schildern die mit Husten und Atemnot, Erbrechen, Durchfall und Verstopfung, Blässe, Exanthem, Ikterus, Zyanose, Schwellungen der Organe einhergehenden Krankheitsbilder. Der diagnostischen Bedeutung der Bewußtlosigkeit, Krämpfe, Lähmungen und Blutungen sind weitere Abschnitte gewidmet. Schließlich werden die möglichen Ursachen von Störungen der Gewichtszunahme, des Wachstums und der Sinnesorgane besprochen.

Ein in Dezimalsystem geordnetes Inhaltsverzeichnis, ein genaues Sachregister, mehrere Diagramme, Tabellen und Merksätze tragen zur Überblicklichkeit des Büchleins bei, so daß der Leser, trotz der äußerst knappen Form, sich rasch orientieren und über zeitgemäße Anschauungen informieren kann.

E. Cserháti

P. Gegesi Kiss: *Erfahrungen über kinderklinische Psychopathologie.* 341 Seiten. Akadémiai Kiadó, Budapest 1976.

Eines der eingehendst bearbeiteten Gebiete der Psychologie ist die Entwicklungspsychologie, innerhalb deren sich die zahlreichsten Publikationen mit den betreffenden Fragen des Kindesalters befassen. Die Erklärung hierfür dürfte jener Umstand sein, daß die Beobachtung des Kindesalters leichter ist, weil zu dieser Zeit die Kinder einander ähnlicher sind als in der späteren Jugend. Im Kleinkindesalter gestalten sich die psychischen Manifestationen wegen der Identität der biologischen und psychologischen Entwicklung ziemlich gleichartig und da die Offenbarungen individueller Variationen beschränkt sind, bietet sich die Möglichkeit zur Verallgemeinerung. Die Kinderpsychologie hat jedoch ein engeres und sehr wichtiges Gebiet, welches die allgemeine Kinderheilkunde als Stütze benötigt, und das ist die entsprechende Erklärung der psychischen Manifestationen des kranken Kindes. Gerade für die Praxis der Kinderheilkunde bietet das vorliegende Werk eine Hilfe und viel Neues. Die sich auf mehr als vier Jahrzehnte erstreckenden Erfahrungen bei einem riesigen Krankengut bilden die Grundlage dieser Arbeit, mit einem beachtenswerten Anspruch auf die womöglich vollständige Systematisierung der Erscheinungsformen der körperlichen und psychischen Abnormitäten im Säuglings- und Kleinkindesalter.

Der erste Teil des Buches behandelt das Thema in seinen allgemeinen, der zweite in den klinischen Zusammenhängen.

Im allgemeinen Teil untersucht der Autor die Zusammenhänge von Gesundheit und Krankheit, die psychischen Schädigungen durch die Außen- und Innenwelt, die Pathogene, die Probleme der kinderklinischen Psychopathologie, und dies in einem ganz individuellen Ton, mit individuellen Aperçus. In diesem Teil findet man eine Reihe von neuen, Theorie und Praxis betreffenden Kenntnissen, von denen einige, wie z. B. die Auffassung der Persönlichkeit, Einordnungsmechanismen der gefühlsmäßigen und anderen Persönlichkeitselemente usw. zur Diskussion inspirieren; letzterer Umstand soll jedoch als Verdienst verzeichnet werden, da sich hier ein lohnendes Diskussionsmaterial bietet.

Der zweite, klinische Teil kann auf das Interesse von Pädiatern, Psychologen und Pädagogen rechnen, indem er sowohl für die praktische Arbeit als auch bei der Ausbildung gut verwertbare Kenntnisse vermittelt.

L. Bartha

G. Schettler, H. Greten, G. Schlierf, D. Seidel: *Fettstoffwechsel.* Stoffwechselkrankheiten, 4. Teil. XXIV + 751 Seiten, mit 156 zum Teil farbigen Abbildungen und 61 Tabellen. Springer Verlag, Berlin—Heidelberg—New York 1976. Preis DM 370,—

Die Störungen des Lipidstoffwechsels berühren zahlreiche Bereiche der ärztlichen Tätigkeit und sind die häufigsten Risikofaktoren arteriosklerotischer Erkrankungen. Die Verfasser folgten in der Einteilung der Hyperlipoidosen dem von Fredrickson vorgeschlagenen Schema. Ein Vergleich der vorliegenden Darstellung der verschiedenen Lipoidosen mit den entsprechenden Kapiteln im Handbuch von 1955 zeigt, daß hier die Ätiologie weitgehend geklärt wurde.

Das Buch teilt sich in 5 große Kapitel. Im ersten werden die Lipide, zuerst die Triglyceride aufgrund der engen Beziehungen, welche zwischen der Hypertriglyceridämie und den Gefäßerkrankungen bestehen, besprochen. Das Kapitel über Cholesterin betont die Bedeutung der Hypercholesterinämie in den atheromatotischen Prozessen. Die folgenden vielfältigen biologischen Funktionen der Phospholipide werden ebenfalls eingehend behandelt: osmotische Regulation, potential-gekoppelte Anabol- und Katabolvorgänge, Redoxreaktionen, Energietransformationen bei Photosynthese und oxydativer Phosphorylierung, ferner Bindungsvermittlungen zwischen Proteinen und Neutrallipiden. Es wird versucht, diese Funktionen der Phospholipide aus ihren Molekulareigenschaften abzuleiten.

Das zweite Kapitel befaßt sich mit der Chemie, Physiologie und Pathophysiologie der Lipoproteine. Natürlich liegt in diesem Kapitel die Bedeutung der Elektrophorese im Vordergrund. Hinsichtlich der medizinischen Forschung war die Erkenntnis der Lipoproteinmangel-Syndrome (z. B. Tangiersche Krankheit, Alpha-Beta-Lipoproteinämie) sowie der pathologischen Lipoproteine (wie Lipoprotein X bei obstruktiver Lebererkrankung) sehr wichtig. Nach dem spezifischen Gewicht unterscheidet man Chylomikronen, Very Low Density Lipoproteine (VLDL), Low Density Lipoproteine (LDL) und High Density Lipoproteine (HDL).

Der dritte Teil befaßt sich mit den verschiedenen Formen der Hyperlipoproteinämien, — dieses Kapitel ist für den Kliniker von besonderer Bedeutung. Für den Typ I, der Hyperlipoproteinämien ist die erhöhte Plasmalipidkonzentration bezeichnend, die eine Folge der Zunahme der Chylomikronen ist. Die Krankheit wird auch als idiopathische Lipämie, familiäre Hyperchylomikronämie oder fettinduzierte Hyperlipämie bezeichnet. Ursache der Erkrankung ist die Störung der enzymatischen Spaltung der Chylomikronen. Sekundäre Formen kommen bei den verschiedenen Dysglobulinämien und Lupus erythematosus vor. Die Therapie besteht in der starken Reduzierung des Nahrungsfettes. Typ II der Hyperlipoproteinämien ist durch eine erhöhte Beta-Lipoproteinkonzentration charakterisiert. Sekundäre Formen entwickeln sich bei Patienten mit Hyperthyreose und Nephrose. In den Homozygoten kommen Cholesterinwerte über 1000 mg% vor, in den Heterozygoten findet man Werte von 300—500 mg%. Dieser Typ der Hyperlipoidämie ist bereits im Kindesalter, im Falle von familiärem Auftritt sogar schon bei Neugeborenen erkennbar. Zwecks Verhütung kardiovaskulärer Komplikationen ist die frühzeitige Behandlung durchaus begründet.

Beim Typ III handelt es sich um eine Dis-Betalipoproteinämie. Das abnormale Lipoprotein (Beta-VLDL) erstreckt sich zwischen Beta und $Alpha_2$, und wird infolge seiner Eigenartigkeit auch »Floating Beta« genannt. Es enthält mehr Cholesterin als Triglyceride. Hierbei handelt es sich um eine spezielle metabolische Störung (metabolic error) des VLDL-Katabolismus.

Die Hyperlipoproteinämie des Typs IV ist durch die Zunahme des VLDL gekennzeichnet, — der Chylomikronspiegel ist nicht erhöht. Die charakteristische Zunahme des Plasmatriglycerids ist endogenen Ursprungs. Sekundäre Formen kommen bei zahlreichen Krankheiten, z. B. im Zusammenhang mit Diabetes vor.

Der fünfte Typ ist die familiäre Hyper-Prä-Beta-Lipoproteinämie und Hyperchylomikronämie. Er ist die Kombination

der Zunahme der exogenen und endogenen Triglyceride (Chylomikronen und VLDL). Man unterscheidet eine primäre und eine sekundäre Form. Die sekundären Formen können Begleiterscheinungen von anderen Krankheiten, wie Dis-Globulinämien, Alkoholismus, Pankreatitis sein. In einem ausführlichen Kapitel werden die sekundären Hyperlipoproteinämien besprochen: Diabetes mellitus, Nierenkrankheiten, Erkrankungen der Schilddrüse, Pankreatitis, Infektionskrankheiten, abnormaler Gammaglobulin- und Lipoproteinstoffwechsel sowie Fettstoffwechselstörungen bei Schwangerschaft und bei Gebrauch von kontrazeptiven Mitteln.

Im vierten Kapitel wird die Frage der Hypolipoproteinämien, — wie z. B. die ziemlich selten auftretende Tangiersche Krankheit besprochen.

Im Buch werden die Hypo-Beta-Lipoproteinämien eingehend behandelt. Im Plasma befinden sich keine Chylomikronen, ebenso fehlen VLDL und die LDL-Lipoproteine. Diese Krankheit ist mit einer Symptomengruppe vergesellschaftet, in der gastrointestinale, neuro-muskuläre und Augensymptome mit charakteristischen hämatologischen Veränderungen (Acanthocyten) dominieren.

Der letzte Teil des Buches befaßt sich mit den Lipidosen. Hierher gehören die Niemann-Picksche Krankheit, die Gaucher-sche Krankheit, die metachromatische Leukodystrophie (sulfatide Lipidose), die Fabrysche Krankheit, die Gangliosiden wie die Tay-Sachssche Krankheit (amaurotische Idiotie) sowie die Refsumsche Krankheit (eine Störung der Phytansäure-Lagerung).

Wir empfehlen dieses beispielhafte Buch denjenigen Lesern, die umfangreiche Kenntnisse von hohem Niveau in der Frage des Fettstoffwechsels erwerben wollen. Das Buch gibt selbst über die seltensten Krankheiten ausführliche Informationen und reichliche Literaturangaben.

L. Barta

Fettemulsionen in der parenteralen Ernährung. Herausgegeben von A. Wretlind, R. Frey, K. Eyrick, H. Makowski. X + 222 Seiten mit 95 Abbildungen. Springer-Verlag, Berlin—Heidelberg—New York 1977. DM 48,—

The book contains the material of a symposion held in Stockholm, June 1976. Scandinavian, German, Swiss and British participants presented 17 papers and discussed relevant problems of parenteral nutrition. The title of the book is somewhat misleading since about half of the papers deal with total parenteral nutrition (TPN) in general and offer no or very few data on lipid infusion in particular.

Two separate lectures (Wolfram et al. and Eckhart et al.) report on linoleic acid deficiency (markedly decreased serum levels) in chronic malnutrition and in post-operative and polytraumatized patients. The essential fatty acid deficiency could be prevented in these cases by the infusion of fat (Tempel et al.).

Several authors emphasize further two advantages of lipids in TPN. Greater calorie intake can be achieved in smaller volume and the osmolality of the solution remains low as compared to the hypertonic carbohydrate mixtures. This lessens the osmotic load and allows to administer the solutions into peripheral veins instead of using central venous catheters.

The possible toxic effects and the optimum lipid composition of fat solutions have long been debated. Huth et al. describe a series of experimental studies. When fat emulsions based upon cotton seed oil were compared with those based upon soy-bean oil (Intralipid), the coagulation disturbance was less marked after the infusion of soy-bean oil emulsions.

Liljedahl et al. report about 4 patients with 80—85% burns who received 50 to 70 litres of 20% Intralipid without any signs of liver damage. In the study of Zumtobel et al. malnourished patients with liver damage of various aetiology (obstructive jaundice, hepatitis, cirrhosis, etc.) were

fed postoperatively by TPN for 10—30 days receiving 500 ml 20% Intralipid daily. Liver function tests did not deteriorate during this period.

Pohlandt's group presented data on the tolerance of intravenous fat in infants and premature babies. In three series of studies they gradually increased the dosage of neutral fat from 2 to 3 to 4 g/kg body weight/day. Intralipid was well tolerated without signs of undesired side-effects. The infusion of >3 g/kg fat increased plasma glycerol levels and fat utilization was reduced in hypoxia, acidosis and severe infection.

These papers are followed by an excellent review by A. Wretlind, and finally by a short summary of the discussions.

Most of the illustrations are clearly printed and ample references are given after each lecture. The volume offers valuable information for physicians, surgeons, paediatricians, especially for those working in intensive care units.

G. Soltész

E. Schmidt-Kolmer: *Zum Einfluß von Familie und Krippe auf die Entwicklung von Kindern in der frühen Kindheit.* »Hygiene in Kinderkollektiven«, Band 2. 325 Seiten mit 52 Abbildungen und 96 Tabellen. Verlag Volk und Gesundheit, Berlin 1977. M 23,—

An Hand eines Entwicklungsbogens, der 144 Fragen enthält, wurden in 70 Kleinkinder-Institutionen der DDR 6000 Krippenkinder zwischen 1971—73 untersucht. Die Vermessung vollzogen die Krippen-Erzieher, die die Kinder pflegten, von Lebensquartal zu Lebensquartal, über mehrere Jahre. Die Entwicklung wurde in 6 Gebiete geteilt: I. Selbstbedienung, II. Motorik, III. Spieltätigkeit, IV. kognitives Verhalten, Sprache und Denken, V. musikalische Tätigkeiten, VI. soziales Verhalten.

Die Gesichtspunkte der Aufarbeitung sind: die Altersgruppe der Kinder, Geschlecht, Familien-Situation, Kinderzahl in der Familie, Schulbildung der Eltern, Berufsbildung der Eltern, Gewicht und Länge der Kinder, Häufigkeit der Erkrankungen in dem untersuchten Vierteljahr, — in Relation zur Kapazität der Institutionen, der differenten Arbeitszeit der Institution, der Qualifikation der dort Arbeitenden. Die Daten wurden auch zueinander in Relation gebracht.

In dem umfangreichsten Kapitel (185 S.) wird die Entwicklung der Kinder analysiert und in Relation mit den oben genannten Faktoren aufgearbeitet. Ferner wurden mündlich und mittels eines Fragebogens von 64 Fragen die Eltern der Kinder von 59 Krippen befragt. Insgesamt wurden 1556 Fragebogen aufgearbeitet. Untersucht wurde das Verhalten der Eltern und deren Wirkung auf die Entwicklung der Kinder.

In der Schlußfolgerung wird nebst zahlreichen Teilresultaten festgestellt, daß die Einflüsse der Familien- und der Krippenerziehung voneinander nicht zu trennen sind. Für das Wohl des einzelnen Kindes, wie ganzer Kindergruppen, ist das harmonische Zusammenwirken guter objektiver wie subjektiver Lebens- und Erziehungsbedingungen in Familie und Krippe ausschlaggebend.

Die im Buche enthaltenen zahlenmäßigen Aufarbeitungen sind in gut übersichtlichen Tabellen und Abbildungen reichlich analysiert.

E. Pikler

A. Peters: *Bewegungsanalysen und Bewegungstherapie im Säuglings- und Kleinkindalter.* 138 Seiten. Gustav Fischer Verlag, Stuttgart—New York 1977. DM 22,—

Das mit geistreichen Zeichnungen reichlich illustrierte und mit ausgiebigem Literaturverzeichnis versehene Buch behandelt verschiedene Griffe in der heilgymnastischen Behandlung, mit deren Hilfe man aus verschiedenen Ausgangsstellungen bestimmte Bewegungsfolgen (Reflexe, Lage-

reaktionen) in verschiedenen Körperteilen einzeln oder gemeinsam auslösen kann.

Im einleitenden Abschnitt — nach einer kurzen und ein wenig sprunghaften Zusammenfassung des Wahrnehmungs-Verhaltens und der motorischen Entwickkung des Säuglings – findet man als Ausgangspunkt die Denver-Tabelle, ferner eine nach verschiedenen Autoren (Gesell, Herzka, Vojta, Müller, Hellbrügge, Pechstein) zusammengestellte Entwicklungstabelle und eine Tabelle der Lage-Reaktionen von Vojta.

Das Buch kann als nützliche Hilfe für Heilgymnastiker angesehen werden, besonders bei jenen Kindern, die mental in den Verlauf ihrer Übungen nicht einbezogen werden können. Obzwar der Untertitel »Beispiele zur Förderung der sensomotorischen Entwicklung« lautet und teilweise auch für »lediglich motorisch retardierte« Kinder empfohlen wird, ist das Buch zu diesem Zwecke nicht zu empfehlen, auch nicht für behinderte Kinder, mit denen eine Interaktion möglich ist, denn schon von den ersten Wochen an ist der Säugling nicht nur als Reflex-Objekt zu betrachten und zu behandeln. Man kann und soll bei seiner Behandlung auf seine Initiative, sein Interesse bauen. Vor allem wäre es nicht angebracht, die normale Bewegungsentwicklung des Säuglings und Kleinkindes auf diese Weise fördern zu wollen.

E. Pikler

H.-W. Kreysel: *D-Penicillamin*. 216 Seiten mit 20 Einzeldarstellungen und 49 Abbildungen. F. K. Schattauer Verlag, Stuttgart—New York 1977. DM 38.—

Die Monographie, die mit der Unterstützung der Firma Knoll A. G. (Ludwigshafen) herausgegeben wurde, enthält außer den für den praktizierenden Arzt nötigen Kenntnissen eine auch vom theoretischen Standpunkt aus wertvolle Zusammenfassung inbezug auf den Wirkungsmechanismus bzw. die multilaterale therapeutische Anwendung des auf eine insgesamt zweijahrzehntige Vergangenheit zurückblickenden D-Penicillamins. Die Autoren der einzelnen Kapitel — alle prominente Vertreter ihres Fachgebietes — erläutern aufgrund einheitlicher Stellungnahme die wesentlichen Ergebnisse der in den letzten Jahren besonders intensiven und mit zahlreichen neuen Gebieten bereicherten D-Penicillamin-Forschungen, und während sie die bereits als bewiesen betrachtbaren Daten unterstreichen, befassen sie sich nur beiläufig mit den umstrittenen Fragen. Die ausgezeichnet abgefaßte Monographie gliedert sich in drei große Teile.

Im I. Teil findet sich die ausführliche Erläuterung der Pharmakochemie, Pharmakologie, Toxikologie und der bisher bekannten wichtigsten Angriffspunkte des Medikaments: Chelatbildung, antiexsudativer Effekt, Mesenchymsuppression sowie der die humorale und zelluläre Immunantwort betreffende Einfluß. Äußerst eindrucksvoll ist das von Schumacher geschriebene Kapitel, mit seiner anschaulichen Darstellung der Entstehung der humoralen und zellulären Immunantwort sowie der genauen Bestimmung jener Punkte, wo das D-Penicillamin seine immunosuppressive Wirkung entfalten kann.

Der II. Teil enthält die kurze Beschreibung der Krankheiten, in denen das D-Penicillamin eine erfolgreiche Anwendung fand: Wilsonsche-Krankheit, Schwermetallvergiftungen, Zystinurie, chronische Polyarthritis und Hepatitis, progressive Sklerodermie, Lungenfibrose, Sclerosis multiplex und Schizophrenie.

Der III. Teil ist folgenden Themen gewidmet: Nebenwirkungen des Medikaments, molekularbiologische Untersuchungen, optimale Dosierung in den angeführten Krankheiten sowie biochemische Methoden. In Zusammenhang mit den unerwünschten Wirkungen wird betont, daß diese in überwiegender Mehrheit der Fälle bei Langzeittherapie auftreten, dosisabhängig sind, und

nach Einstellung der Medikation in kurzer Zeit verschwinden.

Alles in allem darf festgestellt werden, daß die Monographie für die sich für das D-Penicillamin interessierenden theoretischen und praktischen Ärzte leicht zugängliche, sorgfältig ausgewählte und kontrollierte Informationen sowie einen ausführlichen Überblick der Literatur bietet — obwohl ich persönlich gerne auch über die erfolgreiche Anwendung des Mittels bei neonataler Gelbsucht gelesen hätte.

L. LAKATOS

Medical Genetics. G. SZABÓ, Z. PAPP. Proceedings of the Symposium at Debrecen—Hajdúszoboszló, Hungary, April 1976. International Congress Series No. 428. 911 pages. Excerpta Medica, Amsterdam—Oxford, and Akadémiai Kiadó, Budapest 1977.

The book contains 109 papers presented as lectures or posters. The papers, according to the main topics of the Symposium, are grouped as follows: I. chromosome mapping and clinical cytogenetics; II. population genetics and congenital malformations; III. prenatal diagnosis and genetic counselling; IV. haemoglobinopathies and immunogenetics. They cover the majority of the current clinical and research problems of medical genetics.

The participants, many of them internationally known experts, surveyed practically all the pertaining fields and associated topics and presented the most recent results of research.

The volume is a considerable help in the advancement of medical genetics. It is of outstanding interest for clinicians and research workers concerned with genetics and related topics and can sincerely be recommended also to undergraduate and postgraduate students.

P. Kiss

Printed in Hungary

A kiadásért felel az Akadémiai Kiadó igazgatója — Műszaki szerkesztő: Zacsik Annamária

A kézirat nyomdába érkezett: 1978. I. 30. — Terjedelem: 8,4 (A/5) ív, 23 ábra

78.5467 Akadémiai Nyomda, Budapest — Felelős vezető: Bernát György

ACTA PAEDIATRICA

ТОМ XIX—ВЫП. 2

РЕЗЮМЕ

ФОРМИРОВАНИЕ ВЛИЯНИЯ ДРУГ НА ДРУГА СОМАТИКИ И ПСИХИКИ В ДЕТСКОМ ВОЗРАСТЕ

П. ГЕГЕШИ КИШШ

В настоящей статье автор подробно разбирает сущность понятий «соматика» и «психика» с целью четкой формулировки влияния друг на друга и зависимрсти друг от друга человеческих соматики и психики. Соматика — это обычно действительная для каждого человека, определенная морфологическая и функциональная система. Она по-своему формируется в каждом человеке в нормальных условиях согласно заданной программе в филогенезе. Психика же является индивидуально складывающейся определенной функциональной структурой. Она формируется в онтогенеза под воздействием симбиоза с окружающей средой в процессе индивидуальной внутренней переработки.

В статье подробно рассматривается безусловная и условная рефлекторная деятельность, и внутри нее — условно-рефлекторная надстройка над безусловными рефлексами.

Обсуждается, на основе какого механихма формируется человеческая психика у каждого индивидуума, и далее, в чем она проявляется после того, как уже сформировалась.

Автор знакомит с траитовкой структуры человеческой психики: дает описание систем и сущности сознательных и бессознательных функций.

Проявление принятия формы системы взаимного влияния соматики и психики и зависимости их друг от друга — и личность.

Автор статьи подробно обсуждает свое понимание личности. Выделяет «актуальную» личность, затем дает описание- структуры личности.

Закомит с положением, по которому взаимное влияние соматики и психики друг на друга вызывает в человеке современного общества социализированную гуманизацию жизненных процессов. Описывает процессы гуманизации.

В статье приводятся примеры из клиники о влиянии друг на друга соматики и психики: о сомато-психических и психосоматических процессах.

В заключение автор делает выводы отчосительно практики воспитания.

УРОВЕНЬ СЫВОРОТОЧНОГО ЖЕЛЕЗА ПРИ ОСТРОЙ ЛИМФОБЛАСТОЗНОЙ ЛЕЙКЕМИИ

Л. ЛЕГУТКО

Методом атомабсорбционной спектрометрии определяли уровень железа в сыворотке крови у 57 детей, страдающих острой формой лимфобластозной лейкемии. Уровень железа менялся в зависимости от активности болезни. Самый высокий уровень наблюдался у нелеченных детей. Вместе с нормализацией картины костного мозга снижался уровень железа в сыворотке. Снижался от также в случае органной локализации и при инфекциях в период ремиссий. Изменения уровня сывороточного железа предоставляют характерные данные в ходе лечения этого заболевания.

ДАЛЬНЕЙШЕЕ ФИЗИЧЕСКОЕ РАЗВИТИЕ НОВОРОЖДЕННЫХ, РОДИВШИХСЯ С МАЛЫМ ВЕСОМ ОТНОСИТЕЛЬНО СРОКОВ БЕРЕМЕННОСТИ

П. ТОТ, Ш. ПЕЧИ, Ж. СЕЛИД, И. ХОРВАТ, Б. ФЕРЕНЦ и К. МЕХЕШ

Авторы исследовали физическое развитие 188 детей, родившихся с низким весом относительно срока беременности, и 225

детей, родившихся с весом, соответствующим сроку беременности. Оказалось, что вес, длина тела, окружность головы и возраст окостенения детей с внутриматочным отставанием развития еще и в трехлетнем возрасте были значительно меньше, чем в контрольной группе, а также чем стандартные значения в Европе и в Венгрии.

100-ЛЕТНЯЯ ТЕНДЕНЦИЯ В ШОМОДЬСКОЙ ОБЛАСТИ

ДЬ. ВЕЛИ и П. КАДАР

Авторы настоящей статьи изучали изменения роста у мужского населения в возрасте от 18 до 20 лет в Шомодьской области на основе материалов призывных комиссий за столетний период. Они установили, что тенденция «убыстрения» роста в высоту за последние 14 лет уплостилась, ускорение приостановилось. На основании этого факта авторы делают вывод, что высота тела у популяции мужчин изучаемой области достигла оптимального уровня в настоящих условиях. Эти данные и выводы подтверждают точку зрения, по которой «акселерация» роста в высоту является, в действительности, результатом устранения тормозящих, замедляющих рост причин.

ОСТАТОК ЖЕЛТОЧНОГО ПРОТОКА: АНАЛИЗ 66 СЛУЧАЕВ

А. ПИНТЕР, Ф. СЕМЛЕДИ и И. ПИЛАСАНОВИЧ

На протяжении 20 лет мы обнаружили у 66 младенцев и детей остаток желточного протока, потребовавший хирургического вмешательства. В 20 случаях проток был открытым, в 19 случаях заболевание было вызвано дивертикулом меккеля и в 27 случаях дивертикул Меккеля был обнаружен во время операции, произведенной в связи с другим заболеванием. Бросалось в глаза превалирование мальчиков: 9 : 1. В противоположность наблюдениям других авторов, дивертикул Меккеля, требующий хирургического вмешательства, до 14-летнего возраста наблюдался с одинаковой частотой в разных возрастных группах.

Опасные для жизни случаи открытого протока были при Т-образной протрузии подвздошной кишки или при завороте тонкой кишки вокруг открытого протока. Показателями к оперативному вмешательству при вызывающем симптоме дивертикуле Меккеля были язва 12-перстной кишки и воспаление.

В результате обсложений при открытом протоке умерли три грудных ребенка. Один ребенок умер из-за осложнившегося дивертикула Меккеля.

ГЛЮТЕНОВЫЕ БЕЛКИ, ВЫДЕЛЕННЫЕ ИЗ ХЛЕБА

М. САБОЛЬЧ, Ш. ЧОРБА и М. ХАУК

Нами были изолированы глютеновые белки — глиадин и глютенин — из водного и 0,01 М уксусно-кислотного экстракта хлеба.

С помощью натрий-додецилсульфатного электрофореза на акриламидном геле мы определили молекулярные веса выделенных из хлеба гладинов (30.000, 50.000 и 35.000, 52.000 дальтонов) и глютенинов (100.000, 80.000 и 70.000 дальтонов). С одной стороны, аминокислотный состав глиадиновой и глютениновой фракций, в соответствии с литературными данными, очень похож, с другой стороны, он близок, почти одинаков, к составу аминокислот, выделенных из муки, высоко содержание в этих фракциях глютаминовой кислоты — 43,9% и 38,4% соответственно, и пролина — 17,6 и 16,5%, соответственно. Абсорбционный максимум глиадиновой фракции, изолированной из хлеба экстрагированием в уксусной кислоте, находится около 275 нм, абсорбционный спектр глютениновой фракции значительно отличается от спектра глиадининовой фракции. Изолированные нами глютеновые белки реагируют подобно антигенам с сыворотокой больных, страдающих спру.

Результаты наших экспериментов доказывают, что глютеиновые белки до такой степени устойчивы против высоких температур, применяемых при выпечке хлеба, что сохраняют первоначальные физико-химические свойства и иммунохимические особенности, по крайней мере, что касается изученных нами параметров.

СЛАБАЯ ФОРМА ЗАБОЛЕЗНИ «КЛЕНОВЫЙ СИРОП»

Я. КОВАЧ и П. КИШШ

3-летний ребенок был принят в стационар на основании обнаруженных у него умественной отсталости, умеренной мышечной гипотонии и отставания речевого развития. Результат первого анализа крови, проведенного методом ионообменной тонкослойной хроматографии, заставил заподозрить слабую форму болезны кленовый

сироп, и этот диагноз был подтвержден количественным анализом аминокислот и пробой с белковой нагрузкой. Под влиянием диеты, бедной белком (2 г/кг), с исключением лейцина, изолейцина и валина, уровень сывороточных аминокистот быстро и устойчиво кормализовался, и состояние ребенка, так же как и неврологические показатели, тоже стали нормальными.

ЭНТЕРОБИАЗ И ИНФЕКЦИЯ МОЧЕВЫХ ПУТЕЙ

ДЬ. ЙОЯРТ

Автор занимался изучением связи между энтеробиазом и инфекцией мочевых путей у девочек 6—14-летнего возраста. Яички остриц были обнаружены в соскобах аноректальной области; у каждого ребенка произвели три анализа. Среди 84 девочек, страдавших зарыжением мочевых путей, у 55 (65,4%) был энтеробиаз, в то же время из 100 девочек контрольной группы у 60 (60%). Эта разница не является статистически достоверной. Энтеробиаз и в тех случаях не встречался чаще, если инфекция мочевых путей спустя полгода возобновлялась. Не было достоверной разницы также и между группами с моносимптомным энтеробиазом и пиурией. Автор считает, что энтеробиаз не играет этиологической роли в инфекции мочевых путей у девочек.

ОСНОВНЫЕ ДАННЫЕ ВЕДЕНИЯ УЧЕТА ВРОЖДЕННЫХ ПОРОКОВ В ВЕНГЕРСКОЙ НАРОДНОЙ РЕСПУБЛИКЕ В ПЕРИОД 1970—1076 гг.

А. ЦЕЙЗЕЛ

Ведение учета врожденных пороков в Венгерской Народной Республике, сообщает основные данные 1970—1976 гг. с целью их и национального и международного использования.

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31. VIII. 1978. HU ISSN 0001-6527 Index: 26.021

ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

VOLUMEN XIX * 1978 * NO. 3

AKADÉMIAI KIADÓ, BUDAPEST

Acta paediat. Acad. Sci. hung.

ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

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1083 Budapest, Bókay János u. 53.

A szerzők közleményük honoráriumán felül költségmentesen 100 db különlenyomatot kapnak.

Megrendelés belföldre: *Akadémiai Kiadó* (1363 Budapest Pf. 24. Bankszámla: 215 11 448), a külföld számára *Kultura* (1389 Budapest 92, P.O.B. 149, Bankszámla: 218 10990).

Editorial office	Rédaction	Редакция	Redaktion

H-1083 Budapest, Bókay J. u. 53.

Annual subscription (one volume)	Abonnement par an (un volume)	Подписная цена за год (один том)	Jahresabonnement (ein Band)

$ 36.00

H-1389 Budapest 92, P.O.B. 149, KULTURA

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 167—170 (1978)

Reflex bradycardia: a grave complication of oesophageal atresia repair

by

V. F. Lukács, Martha Bognár, Maria Jámbori, J. Dénes

Apáthy Children's Hospital, Budapest

Received December 1st, 1977

Among 39 infants operated upon for oesophageal atresia in newborn age, 5 presented attacks of reflex bradycardia during meals. One patient died at the age of one and a half years. Four patients became symptom-free on atropine treatment. They are healthy and develop satisfactorily.

Since the first successful operation of oesophageal atresia in 1943 [4] a number of papers has been published on the complications of the procedure.

There are few reports on functional disturbances including reflex bradycardia and most of these discuss adult cases [2, 3, 5, 7, 8, 9]. The term reflex bradycardia or vago-vagal reflex means a slowing down of the heart rate in consequence of some kind of irritation of the vagus nerve. It mostly occurs if a space-reducing process exerts pressure on one or both vagal nerves. In most cases a sino-auricular block is seen in the ECG. The process may deteriorate into transitory asystole or even cardiac arrest. Bauer et al. in 1959 [1] were the first to report on the condition in two neonates. One had an oesophageal atresia, and the great distance had been bridged over by oesophago-gastrostomy. The intrathoracic part of the dilated stomach had compressed the vagus, and this elicited frequent bradycardiac apnoeic attacks. Small doses of atropine were given in the last three days, but this treatment was insufficient and the infant died with apnoea and bradycardia on the 34th day of his life.

The other neonate had been born with myxoedema; the attacks had stopped after the administration of atropine, and the baby made a smooth recovery under substitution therapy.

A further child reported by Kenigsberg et al. [6] had been operated upon for oesophageal atresia and then developed well until the age of 2 years. Subsequently, after swallowing coarse food he had become cyanosed and fainted. At 4 years of age the ECG had first shown the disappearance of P-waves, and then a gradual slowing down of ventricular activity, from 120/min to 60/min. A radiographic study carried out simultaneously revealed that the bradycardia set in when the barium meal had reached the site of anastomosis. The oesophagus displayed incoordinated contrac-

tions but no stenosis. Although the attacks could successfully be relieved with atropine, the child was operated upon and the right vagal nerve was found to have been compressed by the anastomosis. The trunk of the vagal nerve was resected from the recurrent nerve down to the anastomosis, and since then the child is symptom-free.

We have observed 5 cases of reflex bradycardia among 39 newborn infants operated upon for oesophageal atresia; 21 of these infants are alive and well.

Case Reports

Case 1. M. L., a male baby born from an uncomplicated pregnancy with 3.400 g body weight was admitted at the age of one day with oesophageal atresia and a tracheo-oesophageal fistula. Thoracotomy, transection of the fistula and primary anastomosis were carried out. After an uncomplicated postoperative period he was discharged. At the age of 3 months the baby after a meal developed bradycardia with deep cyanosis and had to be resuscitated. Thereafter his condition seemed to be normal but for a low serum Ca-level and a negative Ca equilibrium. To control this, chronic administration of large doses of Ca and vitamin D and dihydrotachysterol was necessary. Under such treatment he had repeatedly attacks after meals, although in milder form. Then, at the age of one year, the baby after having had thick food for dinner had a severe attack and died from massive aspiration filling the trachea and the main bronchi. No other changes were found at necropsy.

Case 2. F. N., a male baby born after uncomplicated pregnancy with 2,950 g weight, was operated upon at the age of two days for oesophageal atresia with an inferior oesophageal fistula. After thoracotomy the fistula was dissected and a primary anastomosis was created. The postoperative tracheo-bronchitis and pneumonia recovered after antibiotic treatment. Subsequently, systemic oesophageal dilatations were carried out. He was discharged with 500 g weight gain at one month of age. At the age of three months the patient had to be readmitted, since after meals apnoeic episodes had appeared and once he had to be resuscitated in a regional hospital. The performed examinations excluded a stricture of the oesophagus or recurrence of the fistula. Apnoeic episodes associated with bradycardia appeared also in our hospital. They were immediately relieved on atropine injections. Homatropine methylbromide with papaverine was prescribed for home treatment. Under this treatment the child has no attacks and thrives satisfactorily.

Case 3. N. G. born with 3,000 g was admitted on the first day of life and operated upon for oesophageal atresia with an inferior oesophago-tracheal fistula. After dissection of the fistula a primary anastomosis was carried out. After uncomplicated recovery, at the age of six weeks he produced an apnoeic episode with cyanosis and bradycardia and had to be resuscitated. During the next attack atropine was injected. This ensured complete relief. Under continuous oral homatropine therapy no more attacks were observed. At the age of four months the infant was discharged and the therapy was continued at home. When he reported for oesophageal dilatations the infant had seemed to develop well somatically and mentally and had no attacks.

Case 4. N. Z., a female baby born in the 36th week of a first pregnancy with 1,950 g weight, had been admitted at 7 hours of age for oesophageal atresia with an inferior oesophago-tracheal fistula. After the correction of acidosis, tracheal suction, etc., the fistula was ligated and an end-to-side oesophago-oesophagostomy was carried out according to Beardmore. The postoperative period was uneventful and regular oesophageal dilatations were begun at the age of four weeks. At 4 months of age she de-

veloped apnoeic attacks with bradycardia. The attacks stopped on atropine administration, but she had aspirated several times and the repated aspiration pneumonias had raised the possibility of a recurrent oesophago-tracheal fistula in the hypotrophic infant. (The fistula had not been excised.) At the age of six and a half months, recanalisation of the fistula was demonstrated with methylene blue. It was then closed with Histoacryl-N-blue adhesive via the bronchoscope. Subsequently, the baby started to develop until a month later the injected adhesive material had fallen into the bronchus of the right inferior lobe. The adhesive was removed through the bronchoscope and at 8 months of age a new thoracotomy was done, the patent fistula was ligated and transected. The postoperative period was uneventful and oesophageal dilatations were continued regularly. Under homatropine treatment she had no attacks and her mental and somatic development was satisfactory. At the age of one year she contracted a cold and vomited the drug repeatedly so that she had to be readmitted. During the night she had apnoea and bradycardia and had to be resuscitated. After the successful introduction of homatropine she has no more attacks.

Case 5. Ny. C., a 14 months old female infant, who had been operated upon for oesophageal atresia and tracheo-oesophageal fistula after birth, had been admitted from another hospital with the suspicion of recurrent fistula. In the history repeated aspirations and pneumonia were mentioned. Since several months she had attacks with apnoea, cyanosis, bradycardia and had to be resuscitated several times. On admission a ventricular septal defect was detected. The wasted, hypotrophic infant had to be fed by tube. Swallowing and methylene-blue tests showed no recanalization of the fistula, there were only a blind pouch and mild stenosis at the site of its orifice. After several dilatations the gastric tube could be removed and the infant fed orally. The apnoeic attacks associated with bradycardia manifested themselves also in our ward but after the introduction of homatropine therapy they did not return any more.

Discussion

The attacks observed in five patients are a rare complication of oesophageal repair. The symptoms appeared at the age of some months, with sudden cyanosis, apnoea, laryngospasm and bradycardia, ending with syncope, always during or after a meal. Vomiting and even aspiration were frequent but we have observed bradycardia and syncope also without vomiting. The condition was often so serious that resuscitation was necessary. The attacks lasted for several minutes and were then followed by exhaustion and sleep. The presence of an oesophageal stricture as well as of a patent oesophago-tracheal fistula was excluded by serial examinations in every single case. The serum Ca, P, alkaline phosphatase and Mg levels were regularly controlled in each patient. Although a low serum Ca level was frequent in patients operated upon for oesophageal atresia, the slow heart beat failed to normalize on normalization of the Ca level.

The attack was successfully treated with intravenous atropine and as maintenance therapy homatropine in a dose of 1 mg t.i.d. was beneficial and caused no side effects such as pupillary dilatation, flushes or constipation. Atropine inhibits vagal stimulation in a direct way, but high doses have to be given [1]. In cardiac

reflectory activity both vagal nerves play a role. Stimulation of the left vagus nerve acts on the AV node, slowing down impulse conduction. Stimulation of the right branch affects primarily the sino-auricular node and by depressing the impulses causes bradycardia and even asystole.

In the course of the surgical therapy of oesophageal atresia with tracheo-oesophageal fistula, a primary anastomosis is generally done with transection of the fistula. When the fistula is excised and the upper pouch is mobilized to perform the anastomosis, the right vagus nerve is in the operational area. Moreover, the lifted parietal pleura falls back to the reconstructed oesophagus and fixes the nerve to the dissected part. Furthermore, there are considerable postoperative adhesions between the oesophagus and the right vagus nerve, and so the nerve is tugged during swallowing. This explains why attacks of bradycardia had developed during the ingestion of coarse food like vegetables or fruits when the food had reached the site of anastomosis.

The effect of atropine was always favourable. The infants demanding repeated resuscitation became symptomless. Regular administration of homatropine is of special importance since, as it had happened in our Case 4, if the therapy is discontinued, the attack might reoccur.

Our patients, in spite of the repeated episodes, developed well both mentally and somatically. EEG changes did not appear in any of the cases. There was no need so far to liberate the vagal nerve surgically as Bauer et al. [1] had done.

The phenomenon described probably occurs more often than one would suppose from the few pertaining reports. The common episodes that develop in patients operated upon for oesophageal atresia are usually diagnosed as aspiration, dysphagia or, in serious cases, unexpected sudden death. Some of these complications seem to be episodes of reflex bradycardia.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 171—189 (1978)

The fetal alcohol syndrome: symptoms and pathogenesis

by

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Received January 7th, 1978

The symptoms of the fetal alcohol syndrome and their frequency of appearance are described based on 41 reports in the literature and on own observations. Experimental evidence is presented proving the lack of cytotoxicity, mutagenicity and teratogenicity of alcohol itself and the intensive cytotoxicity, mutagenicity and teratogenicity of acetaldehyde. Responsibility for the fetal alcohol syndrome is ascribed to acetaldehyde at maternal blood concentrations surpassing 35 μM and it is suggested that the raised acetaldehyde level is due to an inherited or acquired defect of mitochondrial aldehyde dehydrogenase. Prospective mothers displaying acetaldehyde levels exceeding 30 μM after a drink should be advised against bearing a child.

The history of alcohol consumption dates back to the earliest periods of human civilization and the connection of parental alcoholism with frailness and liability to mental deficiency of the child has been known ever since biblical times. The question has often been discussed in the last 100 years when, with the stressful consequences of urbanisation, "social" drinking has become customary. Most of the warnings, however, appeared in the lay press or in publications of temperance leagues, while the majority of medical papers was restricted to statistics and vague descriptions of ill health and susceptibility to diseases of the offspring. The first report on a distinct pattern of malformations in 127 infants born to chronically alcoholic women appeared in French periodicals in 1968 [24, 25]. It seems to have raised barely any interest until light had been shed on the subject by Jones et al. who devoted a series of studies to the syndrome [17, 18, 19, 11]. Since then, more than 60 pertinent reports have been published and now the number of cases described in the international literature exceeds 500.

Opinions are divided concerning the very factor and the mechanism responsible for the syndrome. Most authors ascribe it to a direct effect of alcohol and bring it into relation with the maternal or fetal blood alcohol

* Supported by a grant of the Hungarian Red Cross.

level. Others assume that the underlying cause is not the alcohol but some disturbance often associated with the addiction, especially calorie or protein malnutrition. In view of the satisfactory calorie intake of many alcoholic mothers, an indirect malnutrition has been suggested, due to the inhibition by alcohol of the utilization of calories required for growth. Finally, the possibility of thiamine and/or folate deficiency, nicotine abuse, or a deficiency of trace elements such as zinc or magnesium has also been raised. A further problem is why many of the heaviest addicts sometimes deliver a normal child when some social drinkers have an affected baby. In the present work, besides giving a survey of the syndrome, an attempt has been made to clarify the above questions experimentally.

The syndrome

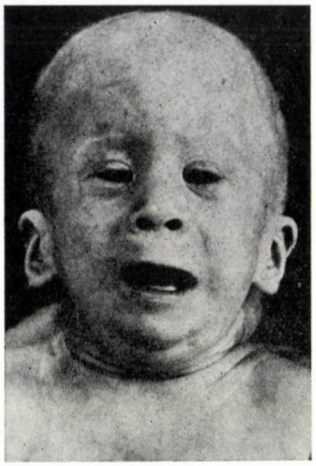
The infant

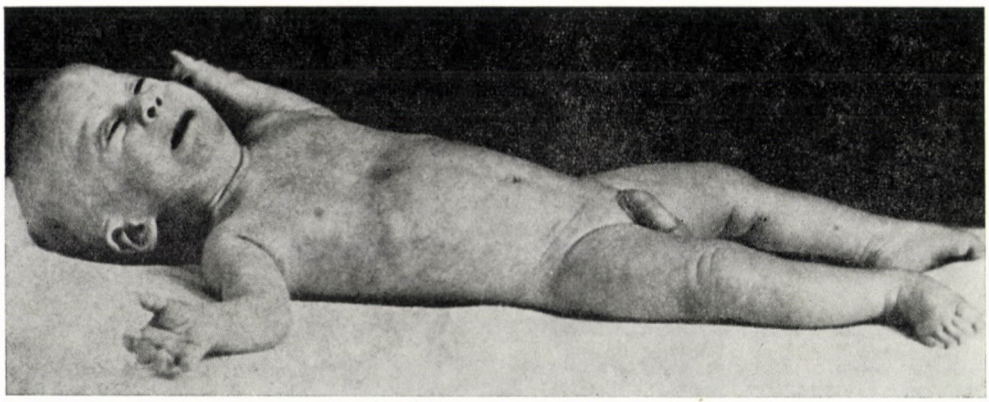
The main symptoms of the fetal alcohol syndrome are abnormalities of growth and performance and of craniofacial appearance, and anomalies of the limbs (Figs 1—5); these are often associated with heart defects and anomalous external genitalia. An attempt has been made to tabulate according to their frequency the characteristic signs reported in 41 papers (Table I). Among these, the most detailed survey is that by Majewski [27] compiled on grounds of 85 patients observed at the Tübingen (GFR) Department of Paediatrics. (The survey includes the material presented earlier by Bierich et al. [23].) Of the other teams, only 9 had a material of more than 10 patients, while 17 papers presented less than 10, and the rest dealt with single cases. Thus, the total number of patients considered in Table I, including 6 observed by us, amounts to 367. Many authors contented themselves with enumerating the main signs and failed to mention whether some symptoms were present or lacking; these have been neglected at evaluation of the frequency of the sign at issue.

The delay in intrauterine growth and mental development is an obligatory sign of the alcohol syndrome. In fact, we believe that, in spite of the characteristic facial appearance, a normal birth weight and due mental development exclude an alcoholic affection. Changes in hormonal factors also appear to do so, as hypothalamic-pituitary function is normal in these patients [39, 44].

Abortion and stillbirth are well known to be frequent with alcoholic mothers, especially with those having a long history of heavy drinking. Among their live-born offspring, females are in considerable excess; this has been suggested to reflect increased wastage of male fetuses to the effect of alcohol [38]. Preterm delivery is also frequent; according to a careful study [34] its proportion is 20% against 8% born to abstinent mothers.

The newborns with alcohol syndrome are small for dates and the lag in weight development is more expressed than that in length. Mean birth weight of 102 term infants mentioned in dif-





FIGS. 1 & 2. 3-month-old child born at term with fetal alcohol syndrome. Birth weight, 1590 g; length, 40 cm, head circumference, 28 cm. Epicanthic folds, small palpebral fissures, abnormal external ear, funnel chest, camptodactily, deep palmar creases, heart defect, mental backwardness. Mother regularly consumes alcohol since the age of 16 years and was treated with liver disease before pregnancy. Case of Prof. H. R. Wiedemann (Kiel), with kind permission of the author

ferent reports was 2210 g and mean length, less than 46 cm; both values are under the 3rd percentile. Head circumference at birth was about 2 SD below the mean. For this, multiple anomalies of brain development are responsible; common findings are leptomeningeal, glial heterotopia with agenesis of the corpus callosum and in a few cases of the brainstem and cerebellum, and internal hydrocephalus [7]. These findings fully explain the E.E.G. changes observed [13]. The baby is hyperactive, irritable, jittery. Some authors suggested that this was the result of alcohol withdrawal but as

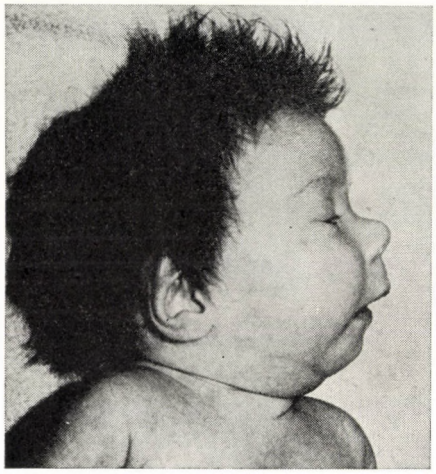


FIG. 3

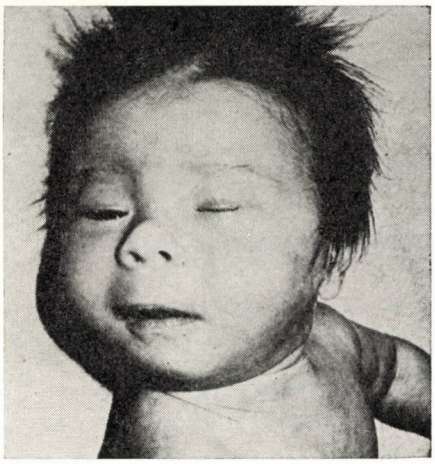


FIG. 4

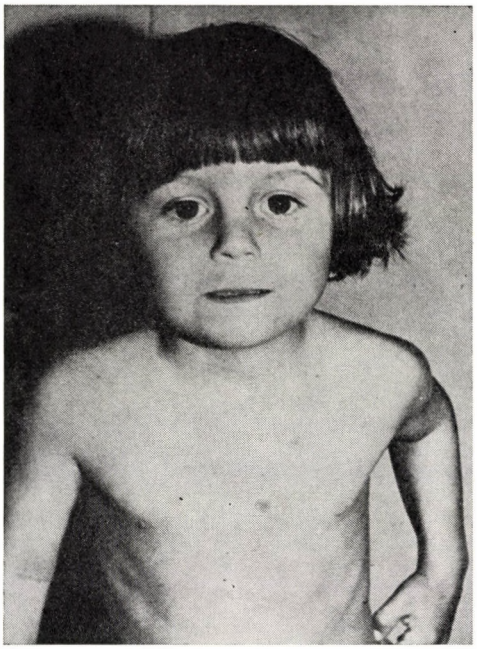


FIG. 5

FIGS. 3 & 4. 5-month-old child born at term with fetal alcohol syndrome. Weight at birth, 1970 g; at 6 weeks, 2500 g; at 5 months, 3200 g. Epicanthic folds, ptosis of eyelids, blepharophimosis, Gothic palate, heart defect, hypermotility. Mother alcohol addict since 3 years; one year before delivery, liver biopsy had revealed a fatty liver and cirrhosis. Case of Prof. J. R. Bierich (Tübingen), with kind permission of the author
FIG. 5. 4-year-old female child with fetal alcohol syndrome. Moderate epicanthic folds, thin vermilion border, retrogenia, mental backwardness. Case of Dr. F. Majewski (Tübingen), with kind permission of the author

TABLE I

Symptoms of the fetal alcohol syndrome and their percentual frequency according to 41 reports in the literature

Abnormal growth and performance	
Prenatal growth deficiency	96
Postnatal growth deficiency	96
Microcephaly	89
Mental backwardness	88
Motor dysfunction	81
Craniofacial abnormalities	
Midfacial hypoplasia	73
Thin vermilion border	69
Epicanthic folds	69
Short palpebral fissures	61
Ptotic eyelids	36
Cleft (or gothic) palate	30
Strabismus	23
Limb anomalies	
Abnormal palmar creases	69
Joint anomalies	46
Other abnormalities	
Anomalous external genitalia	43
Heart (mostly septal) defect	36
Abnormal external ear	30
Camptodactily, clinodactily, small nails	25
Funnel chest	19

it persists for years or permanently, it must be ascribed to the cerebral anomaly.

The face is typical. The epicanthal folds, the antimongoloid slant and smallness of the eyes with short palpebral fissures and ptosis of the eyelids, the short upturned nose and the thin lips lend an unmistakable appearance to these patients.

The palmar creases are usually abnormal. Different patterns have been reported. Mostly the mid-palmar crease was rudimentary, the upper one absent or, in contrast, forming a deep furrow, and the 3rd, 4th and 5th interphalangeal creases were lacking. Camptodactily and clinodactily of the 5th finger and clinodactily of some toes are common.

The genitalia display minor abnormalities such as hypertrophy of the clitoris or cryptorchidism, but several patients had hypospadias and two girls pseudohermaphroditism.

Congenital heart defects have been observed in more than one third of the cases, but some authors report on a higher incidence. The rule is an atrial or, less often, a ventricular septal defect, but patent ductus arteriosus, Fallot tetralogy and pentalogy, interruption of the aortic arch, hypoplasia or aplasia of a pulmonary artery were also observed.

Perinatal mortality of the offspring of alcoholic mothers amounted to 17% among the patients of Jones et al. [18] while in some other reports a small increase over the usual rate and in the largest material hitherto surveyed [27] no increase whatever was observed. In the survivors mortality was slightly higher than in the average population but an increased susceptibility of these infants to infections and different diseases has been emphasized.

Chromosomal studies were normal in all the patients without exception. Clinical tests yielded non-informative or negative results for blood counts, coagulation factors, electrolytes, liver function, blood protein levels, blood sugar, thyroid hormones, and growth hormone.

As to the fate of infants with the fetal alcohol syndrome, they continue to develop poorly in length and weight, and also mentally. Although several authors reported on subsequent improvement of growth and somatic and mental performance, all carefully controlled studies show that the deficiencies persist and the I.Q. even becomes lower with age.

The mother

The age of mothers of children with the fetal alcohol syndrome ranged from 21 to 41 years. Few were younger than 25 years, and the great majority was between 31 and 34 years at birth of the affected child. Parity was high in these women and few of the affected children originated from the first pregnancy. Most were third children and as a rule the previous ones were normal. Five instances of dizygotic and two of monozygotic twins with the alcohol syndrome have been reported; in at least three instances the previous siblings were healthy.

As to liver disease in the mothers, data are astonishingly scarce in the records published. Among the 51 mothers whose history is mentioned in detail, at least 28 had been treated for liver disease before their pregnancy with the affected child. In 11 of the latter mothers liver biopsy revealed a fatty liver or cirrhosis and 5 mothers died with hepatic coma.

Of maternal nutrition no details are found in any of the reports. None refers to signs of malnutrition or vitamin deficiency of any kind, while several studies emphasize that no malnutrition has been observed in these women [35].

References to disulfiram (Antabuse^{R}) treatment are even more neglected. Only a single report [3] describes two instances where the mother had

been treated with the drug, one before pregnancy and the other during the first trimester. No mention is made of an eventual alcohol consumption during that treatment. Part of the patients namely continue to have a few drops of alcohol in secret when they have experienced that under the effect of disulfiram minute amounts offer full satisfaction. The importance of this will be seen later.

Pathogenesis

The metabolism of alcohol

The alcohol ingested is rapidly absorbed from the stomach and the intestines. The great majority dissolves in the body water and is oxidized by alcohol dehydrogenase, an enzyme located in the liver, kidneys and brain. Its cofactor is nicotinamide adenine nucleotide (NAD) which in the course of the process is reduced to NADH. As a result, acetaldehyde is formed. Two other pathways also exist, a catalase + peroxide enzyme system and the microsomal ethanol oxidizing system, but these do not seem to have a role in human metabolism.

I alcohol (C_2H_5OH) ⟶ acetaldehyde (CH_3CHO) ⟶ (alcohol dehydrogenase) ⟶ (NAD ⇌ NAHD)

The acetaldehyde formed is converted to acetyl CoA which in its turn is oxidized in the citric acid cycle. The first step is catalysed by the enzyme aldehyde dehydrogenase located mainly in the liver and the brain. Part of its activity is in the cytoplasm and part in the mitochondria and the microsomes. The cofactor is again NAD. As the removal of acetaldehyde occurs much faster than its formation from alcohol, the latter reaction limits the rate of elimination.

II. acetaldehyde ⟶ (aldehyde dehydrogenase) ⟶ (NAD ⇌ NADH) ⟶ acetyl CoA

In man the main site of alcohol metabolism is the liver; extrahepatic oxidation is only a fraction of the hepatic one. The total elimination rate in healthy adults is 90 to 130 mg/kg/hr (mean, 105 mg/kg/hr), independently of the amount consumed. Alcohol oxidation seems to depend on the race, being more rapid in Caucasians than in Eskimoes or Indians [9], and to a certain extent on the overall metabolic rate. It is very slightly affected by drugs, diets, and remains normal even in liver disease. Animal studies are conflicting in this respect but in humans no significant differences in alcohol elimination were noted between normal subjects and chronic alcoholics with liver disease [28], cirrhotic patients or in those with liver necrosis [41]. In spite of these changes being the common morphological alterations caused by alcoholism, alcohol dehydrogenase activity is not depressed in the affected hepatic areas [32].

The human placenta is permeable for alcohol [15] but the embryo has no alcohol dehydrogenase. In the fetus the enzyme is very weak and becomes

fully active at 5 years of age. Therefore, alcohol elimination is slow in preterm babies [10]. Doses of 0.4 to 0.95 g/kg infused into the umbilical vein were eliminated at a rate of 64 to 86 mg/kg/hr [47] and if at birth a mother and her baby had displayed identical blood alcohol levels, a few hours later the concentration was significantly higher in the baby.

Acetaldehyde is a very active lipid soluble material which binds easily to different substances. Its metabolization proceeds rapidly so that the amount formed from alcohol or injected intravenously disappears immediately from the blood. It passes across the decidua but is metabolized by the placenta so that after the third month no acetaldehyde is found in the fetus [21].

After alcohol consumption by a normal human subject, the blood acetaldehyde level is between 21 and 30 μM. The level is higher in a number of conditions. In a careful study [23] the mean blood concentration was significantly higher in alcoholic ($42.7 \pm \pm 1.2$ μM) than in nonalcoholic subjects (26.5 ± 1.5 μM). In addition, high levels were observed in rats during pregnancy [20] and in those fed certain diets [26]. Genetic differences also exist [22], clearly proving that for the high levels of acetaldehyde some inherited or acquired defect of one or the other form, or of some hitherto undefined isozyme, of aldehyde dehydrogenase must be responsible.

Inhibition of aldehyde dehydrogenase by disulfiram, a compound widely used in the treatment of alcohol addicts, produces the highest blood acetaldehyde levels after the ingestion of alcohol. They increase at least 5-fold, but concentrations as high as 0.8 to 1 mM, 30- to 40-fold of the usual, were also noted. In our material of 17 such patients, the mean blood acetaldehyde level was 280 μM.

The period of impact

All pertinent studies emphasize that alcohol drunk in excess by expectant mothers is a powerful cause of congenital malformations without, however, stating whether this was valid for the whole period of pregnancy or only part of it. A study investigating into the question [12] states that only drinking in the period immediately before conception showed a statistically significant association with the defects, while some authors [3, 11] assume that the greatest effect inducing fetal maldevelopment is exerted in the first trimester, whereas heavy alcohol consumption near term may have a greater effect on fetal nutrition and size.

Somatic and mental development may be affected by alcohol during the whole course of pregnancy. As to the other symptoms, some embryological data allow to estimate the period when the fetus is susceptible to the consequences of alcohol and/or acetaldehyde. Thus, for microcephaly the 4th to the 8th weeks are decisive. The palpebral fissure develops from the 4th to the 15th intrauterine weeks but its length will be determined by the

12th week. At this time terminates development of the lips, but the width of the vermilion border depends on the form of the crista and this is complete by the 6th week. Ossification of the mandible begins at 6 weeks and its shape practically persists after the 12th week. For the heart defects the period between the 4th and 6th weeks is of importance, it being at this time that the septum primum becomes attached to the ventral and dorsal endocardial cushions. For the other signs too, the same weeks are significant. All this would mean that for the full-blown syndrome to develop, maternal drinking between the 3rd and 8th, and especially in the 4th to the 6th, weeks is decisive. Alcohol consumption in the third and fourth month of pregnancy may, and very probably does, affect development, but the outcome will be different from the alcohol syndrome.

As regards the effect of alcohol on the unfertilized ovum, data are lacking. It is certain that in the graafian follicle the ovum is protected against, or is able to withstand, the usual levels of alcohol and/or acetaldehyde, or else, to eliminate an eventual injury. This clearly follows from the scores of observations of healthy infants delivered after an affected one had been born. It is not known whether the same is valid for the ovum in the fallopian tube, although it very probably is protected, partly by its pellucid zone and partly by its having practically no contact with blood and body fluids. The nidating cell after losing the pellucid zone is exposed to injuries without protection, although for a short time the resulting effect might still be eliminated. Subsequently, however, the embryo must bear the impact of the mutagenic or teratogenic agents acting on it.

Maternal alcohol treatment in and after the 32nd week of pregnancy does not induce alcohol syndrome in the fetus. Such treatment resulting in blood alcohol levels up to 1.83 g/l was widespread at a time with the purpose of preventing premature labour. The offspring showed no delay in postnatal somatic or mental development [10].

Evidence in support of the above claims was offered by the case of a woman observed by us. She has been drinking regularly between 100 and 200 ml of absolute alcohol a day since the age of 23 years in 1965. In 1970 and 1972 she had delivered two normal babies, then in 1975 she had one with a characteristic alcohol syndrome. In spite of medical advice she had neither stopped drinking nor reduced the customary intake. In 1976, a year after delivering the affected child, she again became pregnant but 10 days later she was arrested and jailed. In the prison she had no possibility whatever to obtain a drop of alcohol. After 6 months she was released and immediately resumed drinking. In spite of this, at due term she gave birth to a somewhat underweight but otherwise fully normal baby. Three weeks later she was given to drink 0.5 ml/kg of alcohol; by 30 minutes her blood acetaldehyde had risen to 140 μM (Fig. 6).

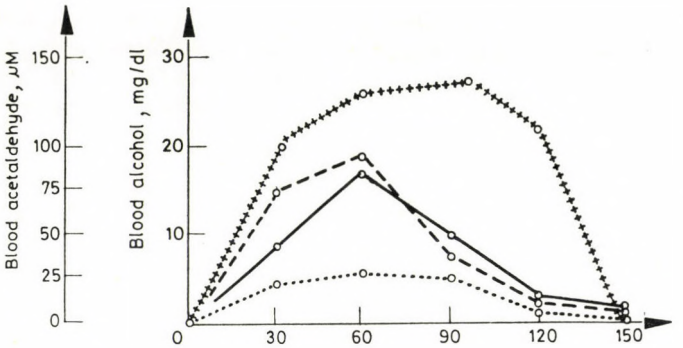


FIG. 6. Blood alcohol and acetaldehyde levels after drinking 0.4 g/kg of absolute alcohol in normal controls (mean of three subjects) and in a woman who had had a baby with fetal alcohol syndrome. ——— blood alcohol level in controls; . . . . . blood acetaldehyde level in controls; - - - - - - blood alcohol level in addict woman; + + + + blood acetaldehyde level in addict woman

The quantity consumed

Alcohol consumption by the mothers varied widely. The majority drank every day without exception, but some only on two or three occasions weakly. One woman allegedly never drank except on Saturdays when she regularly consumed one bottle of wine (1.45 ml/kg of absolute alcohol). The highest consumption reported was 4.9 ml/kg/day of absolute alcohol systematically for years, and several women confessed to having drunk about 3 ml/kg/day regularly for long periods.

Of course, these data cannot be relied upon. Few are the alcoholics who would not euphemize their addiction although just the heaviest drinkers with the longest histories often seem to be sincere, while this is rarely the case with repentant women, especially of a higher social standing and a higher education.

The same is true for the length of the drinking history. Still, few mothers said that they had been drinking for less than three years and regular alcohol consumption since childhood was no rarity. In a single case had the mother been drinking since less than a year. She drank 2 l of wine (3.3 ml/kg absolute alcohol) or more daily throughout the entire course of pregnancy. The child was born before term and displayed a typical alcohol syndrome. There is another report of a similarly short history of alcohol addiction but in this case the diagnosis was somewhat questionable.

Analysis of all serial studies failed to disclose any connexion between the occurrence and severity of the fetal syndrome and the frequency of drinking or the amount of alcohol consumed. For example, in a German report [27] the mothers of the slightly afflicted children drank a daily mean of 234 ml absolute alcohol, 100 ml more than

did the mothers of the gravest patients. All the other evaluable reports yielded similarly paradoxical results.

Experimental studies

Experiments were performed to establish the responsibility in the fetal alcohol syndrome of alcohol and/or acetaldehyde. Their effect on the mitotic cycle and DNA was studied by the sister chromatid exchange technique, mutagenicity on E. coli, and embryotoxicity and teratogenicity by investigating fetal resorption in rats.

Experimental material was obtained from 37 alcohol addicts under hospital treatment, and 8 healthy volunteers as controls.

Acetaldehyde was determined in blood samples taken under high purity argon in sample vials. After ultrasonic dispersion, 500 μl of blood was added in argon atmosphere to 500 μl of 3.2 mg/ml n-propanol in twice distilled water as internal standard. The Perkin-Elmer Model F-42 headspace gas chromatograph with hydrogen gas ionization detector was used with a 1 mV Honeywell Brown Electronic recorder. The column measured 1 mm in diameter and 500 mm in length and was packed with 80/120 mesh Chromosorb 102 (made by J. Manville). The operating conditions were, column temperature 120°C, detector temperature 160°C, injection port and needle temperature 150°C, flow rate of nitrogen high purity grade carrier gas, 30 ml/min, headspace equilibrium temperature was 40°C. Evaluation was made by a calibration curve plotted with a blood-water mixture containing 0.16 mg/ml gas chromatography grade n-propanol (C. Erba) as standard and 0.001 + 1 mM acetaldehyde (99.5% gas chromatography grade, Fluka A.G.).

Cell cycle and sister chromatid exchange (SCE)

were studied in Chinese hamster ovary (CHO) cell and human lymphocyte cultures, applying 5-bromodeoxuridine (BrdU) treatment and 33258 Hoechst and Giemsa staining (FPG) procedure [36].

(i) Alcohol added at 1 ml/dl concentration, about double the lethal human dose, had no effect whatever on CMO cells (Fig. 7).

(ii) Acetaldehyde (analytical grade, distilled twice immediately before use) added at 880 μM concentration killed 100% of CHO cells. The LD_{50} corresponded to 220 μM while 26.5 μM was ineffective (Fig. 8).

(iii) Acetaldehyde added in a dose of 400 μM to normal human lymphocytes was toxic and inhibited the multiplication of the surviving cells and had a clastogenic effect. After 72 hours the majority of cells was M_1 and of these, 12% displayed labile chro-

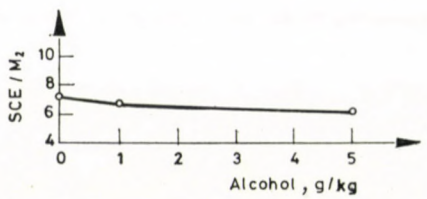


Fig. 7. Effect of alcohol on sister chromatid exchange frequency in CHO cells

mosomal aberrations. In the M_2 cells SCE was increased 4 to 6fold over the background. An acetaldehyde level of 40 μM still affected cell progression and SCE was double the control value, while lower amounts of acetaldehyde had no adverse effect (see Fig. 8).

(iv) Three alcohol addicts under chronic disulfiram treatment were made to drink about 0.2 ml/kg of alcohol in the form of wine. In some minutes when their blood acetaldehyde level had risen to above 100 μM, they developed a characteristic hypotensive episode. In the lymphocytes obtained during the episode, the distribution of M_1—M_2—M_3 cells was significantly altered in one and moderately in two patients, and SCE increased over the background in all the three. Such changes were absent in the same patients before they had drunk alcohol and in other disulfiram-treated addicts who had taken no alcohol (see Fig. 9).

(v) In 72-hour lymphocyte cultures of 7 subjects under the acute influence of alcohol, with blood levels ranging from 0.1 to 0.4%, the mitotic index was low, many of the cells were in the first metaphase, but there was no increase in SCE. In subjects with a blood alcohol level below 0.2% even the cell cycle was normal (see Fig. 10).

The above results, of which those enumerated under *(i)* and *(ii)* have been supported by a recent observation [33], seem clearly to show the harmlessness of alcohol and to prove the cytotoxicity and mutagenicity of acetaldehyde, a conclusion arrived at by us previously [45, 46].

Mutagenicity

of alcohol and acetaldehyde was then tested on Escherichia coli WP2 uvrA trp$^-$ cells incubated in hermetically stoppered test tubes at 0°C and then cultured on minimal agar supplemented with 0.25 μg/ml l-tryptophan. The number of colony-forming units was considered to reflect the frequency of mutated cells the tryptophan-synthetising capacity of which had been restored [16].

In these experiments, 1200 mg/kg of alcohol was ineffective while acetaldehyde at a concentration of 880 μM increased the spontaneous mutation frequency of the surviving cells 4.5 times at 31% lethality after 30 minutes exposition (see Table II). Variation of the exposition time between 5 and 30 minutes had no significant effect on the mutation frequency.

TABLE II

Mutagenic effect of 880 μM acetaldehyde on Escherichia coli WP2 uvrA trp$^-$ (Mean of 8 experiments each)

	Time minutes	Mutation frequency $\times 10^{-8}$
No acetaldehyde		6.3 ± 4.2
880 μM acetaldehyde	5	31.0
	10	28.0
	20	37.0
	30	28.3 ± 8.3

The difference was significant statistically (Student's t test).

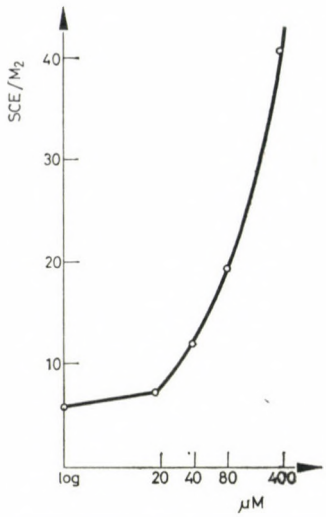


FIG. 8. Effect of acetaldehyde on sister chromatid exchange frequency in human lymphocytes. Ordinate, SCE in M_2 cells; abscissa, log acetaldehyde concentration

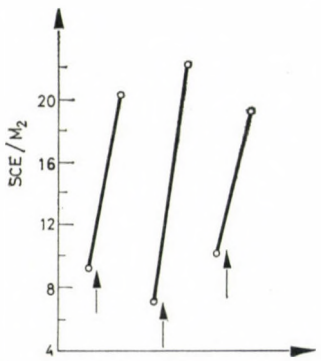


FIG. 9. Sister chromatid exchange frequency in M_2 lymphocytes of three subjects under disulfiram treatment, before and after drinking alcohol. Arrow: ingestion of 0.2 ml/kg of alcohol

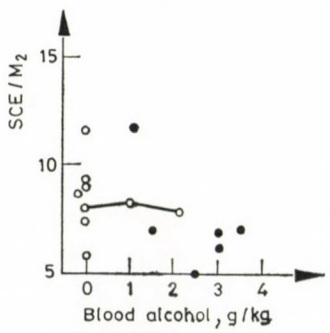


FIG. 10. Sister chromatid exchange frequency in M_1 lymphocytes of alcohol-intoxicated and control subjects. ● alcohol-intoxicated subjects; ○ control subjects. The three points connected with a line originate from the same person

Teratogenicity

was studied in virgin female Wistar/Riop rats weighing 150 to 200 g. They were caged with males of the same strain, weighing 250 to 300 g. The first day of pregnancy was determined by the presence of spermatozoa in the vaginal smear stained with 1% methylene blue. The pregnant rats were separated. On the 21st day of pregnancy, Caesarean section was performed and the fetuses were removed together with the uterine

horns. Live and dead fetuses and resorptions were counted in each horn. The offspring were weighed, one half was fixed in Bouin's solution and dissected according to a standard technique [48]. The rest was fixed in 96% alcohol and the skeleton was examined after KOH alizarin red S staining [42] and, when necessary, histological sections were prepared and examined after H + E staining.

Fetal mortality was calculated from the total implantation count while the rates of retardation and malformations were related to the live fetuses. Statistical significance was estimated by the x^2 test.

The effect of alcohol and disulfiram and their combination was tested in four groups of rats. The first group consisted of 82 untreated animals and served as control. The 6 rats in the second group were given by stomach tube 10 ml/kg of 40% ethanol daily from the 7th to the 16th days of pregnancy. The third group of 9 animals received by stomach tube 150 mg/kg of disulfiram suspended in 5 ml/kg of 1.25% methyl cellulose, on the same days. The 10 animals in the fourth group were given the same disulfiram treatment and 1.5 hours later 10 ml/kg of 40% ethanol in the same way on the same days.

The results (Table III and Fig. 11) showed, that while alcohol and disulfiram by themselves had no or a very slight effect on the rate of fetal resorption and on the weight development of living fetuses, the combined action of disulfiram and alcohol caused a strongly significant increase in fetal resorption and skeletal retardation and a strongly significant decrease in fetal weight. This combined action was ascribed to the high acetaldehyde level and was considered to prove the embryotoxic and teratogenic effect of the compound.

TABLE III

The effect of 40% alcohol, disulfiram and their combination on organogenesis in Wistar/Riop rats

	No. of pregnant females	No. of implantations	Resorptions per cent	Living fetuses	Weight per fetus, g	Skeletal retardation per cent
Controls	82	911	10.8	813	3.5	12.7
Ethanol 40%	6	74	12.2	65	3.3	14.7
Disulfiram	9	89	4.0	86	3.1	11.3
Disulfiram + Ethanol 40%	10	102	64.7*	36	2.5*	61.1*

* Difference strongly significant statistically ($p < 0.001$).

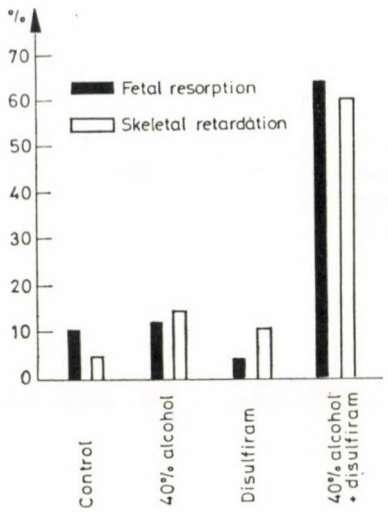


FIG 11. Teratogenicity test of alcohol, disulfiram and their combination. (Explanation see in text)

DISCUSSION

On the evidence of our experimental studies it is only the prenatal growth deficiency which may perhaps be traced back to the direct effect of alcohol on the rate of cell multiplication.

The rest of the symptoms cannot be ascribed to the alcohol itself, as not even double the lethal dose can injure the cells including their DNA. Nor can it be ascribed to the effect of acetaldehyde, provided its concentration does not exceed 30 μM, the peak level appearing in healthy people after alcohol consumption. Thus "mom's couple of drinks a day mean an abnormal baby" [31] is an excellent slogan, but as far as healthy mothers are concerned, its truth is questionable, at least in connexion with the fetal alcohol syndrome. And it is certainly questionable whether the incidence and gravity of the syndrome increase in proportion to the amount of alcohol consumed and especially to that consumed on one occasion: "women when they find out they're pregnant shouldn't celebrate with a bottle of champagne" [30]. The connexion has been assumed on empirical grounds and on the basis of some retrospective studies without calculations of statistical significance, while experiments in mice suggested that the occurrence of fetal malformations depended solely on the maternal peak blood alcohol levels [6].

The validity of this suggestion has been refuted not only by our experimental results but also by all the pertinent reports. These namely show that even the heaviest addicts often deliver unaffected children, whereas affected babies are sometimes born to mothers who drank infrequently and/or moderate quantities. The explanation lies with the mother. If she is

fully normal, her fetus will not be hurt by "binge drinking" or by a couple of drinks; the 30 ml of alcohol contained in them corresponds to 300 ml of wine and for instance in France and Italy many million pregnant women continue to take this amount with their midday and evening meals with comparative impunity. However, in some women little alcohol will suffice to damage the fetus. This will be the case if the second step of alcohol breakdown, the oxidation of acetaldehyde, is deranged, and its blood level increases above 40 μM. Such levels have been reported to be the rule in chronic alcohol addicts [23], due presumably to mitochondrial damage and a defect of specific aldehyde dehydrogenase activity caused by the acetaldehyde itself. While there is some evidence in support of the mitochondrial damage [4], data are lacking concerning the inheritance of such a defect in humans, although it is known to occur in certain rat [22] and mouse [40] strains.

The highest blood acetaldehyde levels, up to 1 mM, i.e. more than thirty times the usual, occur in subjects who drink while they are under the effect of disulfiram. In this case an amount of alcohol as little as 5 ml consumed in whatever form will suffice to exert a lethal effect on the fetus or its actually growing part. It is only natural that in this case the baby will be aborted, stillborn or born with somatic and mental defects. This was supported by our observation of a family where the heavily drinking mother after having had 6 miscarriages delivered an afflicted child; during the early weeks of this pregnancy she was on disulfiram treatment but occasionally consumed a little alcohol.

Thus, the responsibility for the fetal alcohol syndrome is ascribed to a higher than usual blood acetaldehyde level owing to a deficient functioning of some, most probably a mitochondrial, kind of maternal aldehyde dehydrogenase. Acetaldehyde, the intensive mutagenic and teratogenic property of which has been proved beyond doubt in our experiments, is believed to act by lesioning the fetus directly in the first two months of gestation and by affecting placental function during the further course of pregnancy. The direct effect would manifest itself with malformations while the placental lesion with a delay in fetal development.

Alcoholism being often associated with poor nutrition, smoking, thiamine and folate deficiency and a deficiency in trace metals such as magnesium and zinc, several authors assumed that these factors were implicated in the production of the fetal alcohol syndrome. As regards malnutrition, apart from the fact that no increased occurrence of malformations has been noted in the offspring of malnourished mothers [8], the eventual delay in growth and mental development of their children is rapidly caught up in postnatal life [43]. Neither is there any evidence of a teratogenic effect of smoking or of the other associated deficiencies, and all of the mothers mentioned in the studies displayed normal vitamin levels.

Concerning the role of alcohol addict fathers in the production of alcohol syndrome in their children, there has been no reliable evidence. A congress report suggesting this on the basis of clinical studies of 50 families and of experiments with human lymphocytes exposed to alcohol [1] has never been published, and the observation by the same author of dominant lethal mutation in male mice induced by alcohol [2] could not be reproduced by us and has recently been contradicted also by others [5, 29]. Except in that questioned study, chromosomal aberrations in male germ cells or in patients with the fetal alcohol syndrome have never been observed.

Our own studies unequivocally indicated the cytotoxic, mutagenic and teratogenic action of acetaldehyde. The higher than normal incidence of cancer in alcohol addicts has long been known; it remains to be studied whether this was the case with the fetal alcohol syndrome. To date, a single report has only been published on cancer in a 13-year-old patient with a history of fetal alcohol syndrome [14].

Since the height of the acetaldehyde level does not depend on the amount of drinks nor on their rate of elimination, it is erroneous to assume that the fetal alcohol syndrome could be prevented by setting an upper limit to the daily alcohol consumption of the mother. Once her capacity to metabolize acetaldehyde is defective, minute amounts of alcohol will already harm the child. There are two means to prevent the risk. One is a strict abstinence from any kind of alcoholic beverage during the whole course of pregnancy. This measure seems to promise an unharmed child even if the mother had had a previous one displaying the alcohol syndrome, or if her aldehyde oxidizing enzyme is not fully active. The abstinence, however, will in all probability be violated by many a woman and especially those who are regular drinkers. A more promising possibility would be a screening of perspective mothers for their blood acetaldehyde level after a drink. With a blood acetaldehyde level surpassing 30 μM, the woman must be strongly advised against bearing a child or, if she is pregnant, to have it aborted.

Acknowledgements

We are indebted to Dr. G. Korányi, for referring cases to us; to Dr. A. Druga for advice, and to Dr. J. Gáspár, for collaboration; and to Ms. Z. Lendvay, Mr. T. Cservenyák, and Mrs. V. Beer, for skilful technical assistance.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 191—198 (1978)

Ambiguous genitals and the choice of gender

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Received November 21st, 1977

In 8 children with ambiguous external genitals, sex chromosome, hormonal and histological examinations were performed. On this basis the registered sex and the surname of the child were changed from the registered male to female in 3 cases and from female to male in one case. Diagnosis and the decision about the gender are urgent tasks, since prolonged waiting may have serious consequences in psychosexual development.

The two main types of sex chromosomal anomalies, the 45,X (Turner) syndrome and the 47,XXY (Klinefelter) syndrome display well-defined clinical patterns [6, 7]. In these patients with few exceptions, the choice of gender at birth does not cause any difficulty, and later it is not necessary to alter the registered sex. On the other hand, in newborns with uncertain, ambiguous external genitals the choice of gender at birth is not a simple task. An erroneous registration leads, apart from administrative complications, to considerable disturbances in psychosexual development and in the life of the whole family. Procrastination, transitory solutions are not admissible since the examinations needed can be performed during the first days of life [3].

The present work has the aim to call attention to the diagnostic problems on the basis of 8 cases, principally from the aspect, when it seems necessary to alter the registered sex (Table I).

Case reports

Case 1. U. T; a newborn, the second child from a second pregnancy.

External genitalia: labioscrotum; massive, penis-like clitoris. The urethra opens below the apex. A probe is easily introduced into the vagina which is adequately wide and long. The labia majora contain no testicles. Rectally, a normal uterus is palpated.

Laboratory data

Female sex chromatin positive. Karyotype in peripheral lymphocyte and skin fibroblast cultures: 46,XX.

17 ketosteroid,4.8 mg/day
ketogen steroid,7.2 mg/day
serum sodium,123 mval/L
serum potassium, 7.12 mval/L
serum chlorine,92 mval/l

Diagnosis: salt-losing adrenogenital syndrome. Cortisol and DOCA substitution was successful.

Remark: The registered sex and surname of the newborn were changed to female.

Case 2. E. T., third child of the sixth pregnancy, two sisters are healthy. At birth the child was registered as female but 1 month later the registration was corrected for male.

TABLE I
Data of patients

Case No.	Registered sex (surname)	Gonadal structure	Morphology of genitalia: external	Morphology of genitalia: internal	Karyotype in cultures: lymphocyte	Karyotype in cultures: fibroblast	Diagnosis	Necessity of change of surname
1.	male	female	ambiguous	female	XX	XX	adrenogenital syndrome (salt-losing)	Yes
2.	female then male	female	ambiguous	female	XX		adrenogenital syndrome	Yes
3.	male	female	ambiguous	aplasia	XO		Turner syndrome	Yes
4.	female	—	female	—	XY	XY	agonadism	No
5.	male	male	ambiguous	male	XO/XY		hypospadias	No
6.	female	mixed	ambiguous	mixed	X/XY/XYY	X/XY/XYY	gonadoblastoma	No
7.	female	mixed	ambiguous	mixed	XY	XY	male pseudohermaphroditism	Yes
8.	female	mixed	ambiguous	male	XY	XY	testicular feminization	No

Status at the age of 4 years and 6 months: tall, slender child, making the impression of a boy. Developed pubic hair, penis-like clitoris, labioscrotum; no testicles could be palpated.

Laboratory data

Female sex chromatin positive. Karyotype,46,XX

17 ketosteroid,15.2 mg/day

ketogen steroid,27.5 mg/day

pregnanetriol,1.98 mg/day

Diagnosis: adrenogenital syndrome, not salt-losing (partial 21-hydroxylase deficiency). Cortisol substitution was effective.

Remark: new registration, now finally as female.

Case 3. J. R.: second pregnancy; 2,400 g birth weight. Registered as male. From the first pregnancy a healthy boy was born.

During the newborn period, no oedema was observed. The phenotype demonstrated no particular differences. At the age of 7 days, owing to anomalies of the external genitalia, sex chromatin examination of the buccal mucosa was performed; since the result was negative, the child was considered to be a male.

Admission at the age of 3 months: the organs are negative. Minor anomalies: larger than normal prominent ears, deep muchal hair line. Intravenous urography: normal kidneys on both sides. Miction cystography: on the right side vesicoureteral reflux; urinary bladder normal in size and shape.

External genitalia: the vaginal orifice is not visible, the probe fails to enter. Instead of labia majora a structure making the impression of a fissured scrotum can be seen (Fig. 1). Neither here, nor in the inguinal canal can testicles be palpated. At the site of the clitoris an about 2 cm large phalliform formation is found with perineal hypospadias (Fig. 2). The external genitalia correspond to pseudohermaphroditism.

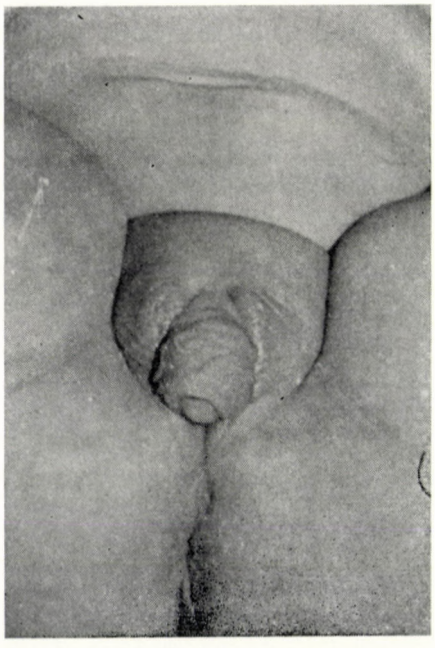

FIG. 1. Case No. 3. Penis-like clitoris and scrotal fissure in a 6-month-old child with Turner syndrome

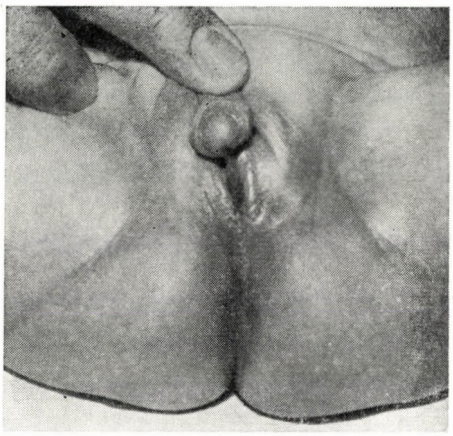

FIG. 2. Case No. 3. Penis-like clitoris with perineal hypospadias

Adrenogenital syndrome could be excluded on the basis of normal urinary 17 ketosteroid (0.3 mg/day) and pregnanetriol (traces) excretion.

Karyotype: 45,X; no suspicion of mosaicism.

Remark: based on the chromosomal examination, the diagnosis of Turner syndrome was confirmed and the registered surname and sex have been changed to female. The necessary correction and plastic surgery will be performed at later age.

Case 4. U. M., a child of female phenotype was born from the second pregnancy.

Status: dystopic sacral kidney on the left side (Fig. 3), bilateral coloboma of iris, dextroposition of the heart, pectus carinatum.

External genitalia: clitoris larger than usual (Fig. 4); the vaginal orifice is closed by a formation resembling an imperforate hymen. Rectally no uterus can be palpated; testicle-like formations are absent. The opening of the urethra is at the usual place; cystography reveals normal conditions.

Laparotomy at the age of 5 years: in the abdomen no gonad was found.

Karyotype: 46,XY in both peripheral lymphocyte and skin fibroblast cultures.

Diagnosis: total agonadism.

Remark: despite the difference between the chromosomal sex and the registered sex, it was recommended to bring up the child as a girl.

Case 5. K. I., the child was born from the second pregnancy of the 19-year-old mother. The first pregnancy ended with an artificial abortion. At birth the external genitalia were conspicuously anomalous.

Status: labioscrotum, bilateral cryptorchidism, balanic hypospadiasis.

Laboratory data:

Karyotype of the child: 45,X/46,XY

Karyotype of the mother: 46,XX/47, XXX

Remark: the anomalies of the external genitalia have been ascribed to the sex chromosomal abnormality due to the maternal mosaicism. Leaving the registered sex unchanged the child may be regarded as male.

Later the mother had two further pregnancies, which ended with spontaneous abortion in the 2nd and 3rd months, respectively. We had no possibility to examine the aborted fetuses.

Case 6. G. K., This 18-year-old girl was examined because of primary amenorrhoea (8).

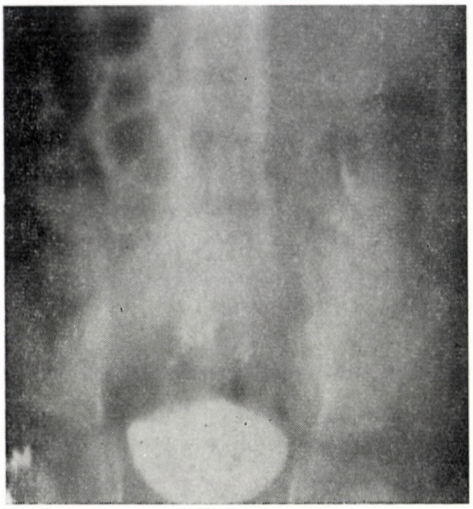

FIG. 3. Case No. 4. Dystopic left kidney in 10-month-old XY girl with total agonadism

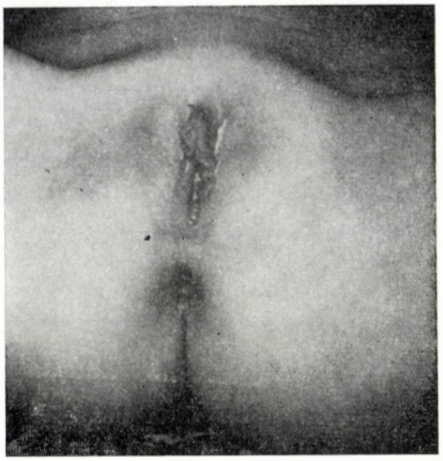

FIG. 4. Case No. 4. External genitalia in total agonadism at the age of 5 years

Status: body height 156 cm; undeveloped breasts; lacking axillary hair; pubic hair of masculine type. Hirsutism on face and extermities. Masculine appearence and character. The external genitalia are of feminine character; the clitoris is enlarged.

Laparotomy: in the right side of the pelvis a small uterus and tubae without ovaries, on the left side a bean-sized testicle-like formation were found. Histological examination of the latter revealed a gonadoblastoma.

Karyotype: 45,X/46,XY/47,XYY mosaicism in both the peripheral lymphocyte culture and in the removed gonadal tissue.

Diagnosis: gonadoblastoma. In view of the present psychosexual condition it was decided to maintain the feminine sex.

Case 7. T. Z., the 3-month-old infant, registered as a female, was operated upon in view of the external genitalia being ambiguous (Fig. 5), and the presence of a swelling (incarcerated hernia?) in the left inguinal region. In the 4 cm wide neck of the hernia, formations corresponding to an uterus and adnexa were found. The left adnexa were connected with a bean-sized gonad; the histological picture showed an undeveloped testis. No gonad was connected with the right adnexa.

Laboratory data: female sex chromatin negative. Karyotype: 46,XY in peripheral lymphocyte and skin fibroblast cultures.

Diagnosis: male pseudohermaphroditism.

Remark: the operational findings as well as the chromosome examination indicated the dominance of male sex character. The registered sex and surname were changed for male.

Case 8. B. E.; a 12-year-old girl was examined owing to unusual external genitalia. A reliable family history could not be obtained; a sibling of the mother was said to have similar genitals.

Status: well-proportioned figure, puerile breasts; axillary and pubic hair is absent. Penis-like clitoris (Fig. 6). The labia minora can be recognized; they surround the urethra at the vaginal entrance. Rectally no uterus could be palpated.

Gonadal exploration: histological examination of the testicle-like formations pal-

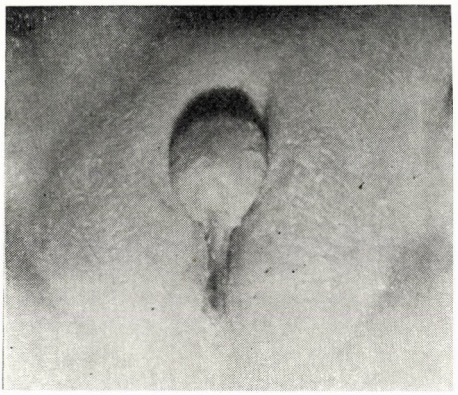

FIG. 5. Case No. 7. External genitalia of a 3-month-old child with male pseudohermaphroditism

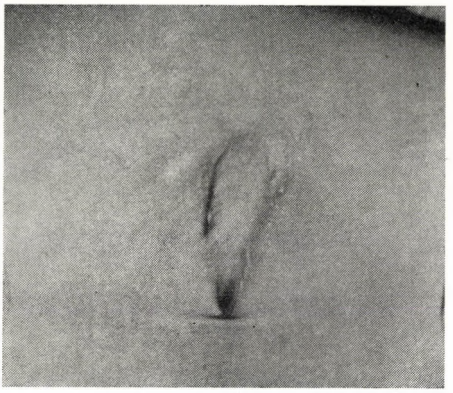

FIG. 6. Case No. 8. External genitalia of a 12-year-old child with testicular feminization

pated inguinally on both sides demonstrated rudimentary testicular tissue.

Karyotype: 46, XY, q + in both lymphocyte and fibroblast cultures.

Diagnosis: testicular feminization, somewhat supported by the supposed familial occurrence.

Remark: it was recommended to maintain the registered female sex.

DISCUSSION

According to Jones and Scott [4] the criteria of sexual gender are decided by the

1) sex chromosomes
2) gonadal structure
3) morphology of external genitalia
4) morphology of internal genitalia
5) hormonal state
6) sex of rearing
7) gender role of individual

To these should be added the registered sex, thus the chosen surname of the newborn. Luckily, there is usually a coincidence of the criteria mentioned above.

In the newborn the gender is usually established by the appearence of the external genitalia, and this will decide the gender once and for all. If, however, the external genitalia are ambiguous, the decision rests with the obstetrician and, if the decision is erroneous, a long series of damaging consequences has to be reckoned with.

In children born with ambiguous genitalia the change of the registered sex (surname) means the slightest difficulty; much more difficult is the reconstruction of the altered morphological structures, and even more so are the psychical habilitation and rehabilitation.

Most difficulties can be prevented by due examinations done as early possible. No delay is permissible, especially as in certain cases the early diagnosis is life-saving (see Case No. 1). In our experience (see Cases Nos 1, 2, 3 and 7) the necessary change of the surname causes no difficulty and the changed name signifies also the change

of sex. Just therefore the decision must be based on a careful and detailed series of examinations.

The change of name and sex in early infancy will ensure the right psychosexual development. In older children, particularly after puberty, the previous psychosexual situation and behaviour have, however, to be taken into consideration.

Human sexual behaviour is not fully dependent on the genetical code, since environmental influences such as clothes, plays, and especially the approach of the family have a considerable influence on psychosexual consciousness [9]. This is well demonstrated by the XY karyotype children raised as girls (see Cases Nos 4, 6 and 8). In other cases, owing to the anatomy of the external genitalia (Case No. 7) or due to the sex gender and psychosexual consciousness developed during a number of years, the registered sex will have to be changed [1, 2]. In the choice of gender the anatomical condition has to be considered in the first place, and the only support has to be expected from the chromosomal examination.

Finally, the problems of genetic counselling should be mentioned. The parents of the children presented in newborn and infant age would like to know the degree of risk in the next child. This too underlines the importance of early and reliable diagnosis.

Virilizing congenital adrenal hyperplasia (adrenogenital syndrome) is a recessively inherited enzyme defect. The androgen hyperproduction induces a masculinization of the female fetus so that the male character of external genitalia will occur but the internal gonads will remain female. The diagnosis rests on the urinary ketosteroid and pregnanetriol excretion [5]. If the condition is associated with salt loss, the diagnosis is life-saving. Cortisol substitution will ensure normal development in the female direction even in cases of considerable masculinization. Despite the 25 % risk of recurrence we recommend acceptance of the next child, since early diagnosis and cortisol substitution will always ensure a normal course of life.

In Turner and Klinefelter syndromes without mosaicism or in the case of XY girls or XX boys the occurrence is sporadic, therefore no recurrence has to be feared. In cases of sex chromosome mosaicism, however, chromosome analysis of the parents will only clarify the situation. In symptom-free carriers of mosaicism the risk of recurrence is high, but owing to the well-known diagnostic difficulties of mosaicism, a prenatal choromosome examination will not supply reliable support to early (prenatal) diagnosis. The only change which has to be reckoned with from the point of view of recurrence, is testicular feminization.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 199–204 (1978)

Staphylococcal scalded skin syndrome (Determatitis exfoliativa neonatorum)

von

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Eingegangen am 11. Januar 1978

Am Beispiel von zwei eigenen Fällen von Dermatitis exfoliativa neonatorum werden in einer Literaturübersicht Ätiologie, Pathogenese, Diagnostik und Therapie dieses Krankheitsbildes erläutert. Insbesondere wird auf die differentialdiagnostische Abgrenzung von anderen ähnlich verlaufenden Erkrankungen eingegangen.

Ritter von Rittershain beschrieb 1878 ein Krankheitsbild, das er »Dermatitis exfoliativa neonatorum« nannte. Er beobachtete im Laufe von 10 Jahren in einer Prager Findelanstalt 297 Fälle. Bald danach stellte man eine Beziehung dieser Erkrankung zu Staphylokokkeninfektionen fest, doch blieb dies bis in die neueste Zeit umstritten. Einen Fortschritt brachten Untersuchungen am Tiermodell (Baby-Maus) und das Auffinden eines exfoliativen Toxins bei Staphylokokkenstämmen, die von Patienten mit Impetigo und Dermatitis exfoliative isoliert worden waren. Wichtig war die Feststellung, daß es sich vorrangig um Stämme handelte, die mit Phagen der Lysogruppe II reagieren (Zusammenfassung bei [1]).

Unabhängig voneinander beschrieben 1956 Lyell und Mitarb. [10] sowie Lang und Walker das Krankheitsbild der »toxischen epidermalen Nekrolyse« (TEN) bzw. »Epidermolysis acuta toxica« [4]. Lyell und Mitarb. [10] unterschieden dabei 4 Komplexe: 1. allergisch-toxische epidermale Nekrolyse, 2. staphylogene toxische epidermale Nekrolyse, 3. sekundäre toxische epidermale Nekrolyse bei verschiedenen Grundkrankheiten und 4. idiopathische toxische epidermale Nekrolyse [5]. Wahrscheinlich können die beiden letzteren Formen der ersten oder zweiten Gruppe zugeordnet werden [5, 17].

Lange Zeit betrachteten viele die durch Staphylokokken bedingten Erkrankungen, in der angloamerikanischen Literatur unter dem Begriff »Staphylococcal scalded skin syndrome« (SSSS) zusammengefaßt, nur als infantile Verlaufsformen der TEN. Erst nach und nach kam man auf Grund klinischer und morphologischer Untersuchungen zu der Erkenntnis, daß es sich um verschiedene Krank-

heitsbilder handelt. Bei beiden kommt es zur Ablösung von Hautpartien, wobei große Wundflächen entstehen. Die eigentliche TEN wird bei Erwachsenen beobachtet. Es kann infolge Flüssigkeits-, Elektrolyt- und Eiweißverlustes tödlich enden. Die Pathogenese ist nicht klar. Häufig geht der Erkrankung die Einnahme eines oder mehrerer Arzneimittel voraus. Ein immunologischer Mechanismus wird diskutiert [4].

Das SSSS dagegen kommt hauptsächlich bei Kindern im Alter von unter 5 Jahren vor. Die Letalität ist gering. Eine Beziehung zu einer Infektion durch Staphylokokken der Phagengruppe II gilt als sicher. Man weiß heute, daß die TEN und das SSSS nicht allein durch das Alter der betroffenen Patienten voneinander differenziert werden können. Wenn auch selten, so kommt es doch auch bei Erwachsenen zum SSSS und bei Kindern zur TEN [3, 9, 10].

Eigene Fälle

Fall 1. K., Andreas. Die Geburt erfolgte 12 Wochen vor dem errechneten Termin (1710 g, 41 cm). Bis auf eine diskrete Atemnotsymptomatik war der postnatale Verlauf zunächst unauffällig. Es erfolgten die bei Frühgeborenen üblichen Maßnahmen (Neugeborenen-Intensivstation, dann Frühgeborenenstation).

Am 5. Lebenstag kam es, beginnend im Nasolabialbereich, zu einer sich innerhalb weniger Stunden entwickelnden Epidermolysis (positives Nikolsky-Phänomen). Blasen wurden nicht beobachtet. Noch am selben Tag beobachteten wir eine nahezu vollständige Ablösung der oberflächlichen Hautschichten an Händen, Füßen, Brust und Rücken. Neben anderen Erregern konnte aus Abstrichen von 5 verschiedenen Hautstellen und im Nasensekret auch Staph. aureus (Lysogruppe II, Lysisbild 71) nachgewiesen werden. Trotz Antibiotika- und symptomatischer Therapie kam es zu einem septischen Geschehen, das nicht beherrscht werden konnte. Pathologisch-anatomischer Befund: Sepsis, Dermatitis exfoliativa Ritter (histologisch).

Fall 2. P., Sven. Dieses Kind wurde zwei Tage nach dem oben beschriebenen in derselben Klinik geboren. Am 6. Lebenstag wurden erstmals mehrere eitrig belegte Hautareale sowie Hauterosionen (Nasolabialregion, Axillen, Windelbereich) beobachtet. Am folgenden Tag kam es zu groblamellösen Hautablösungen am ganzen Körper. Es erfolgte die Verlegung von der Neugeborenenstation der Entbindunsanstalt in unsere Klinik. Bei Aufnahme fanden sich zahlreiche oberflächliche Hauterosionen, Blasen und Krusten. Das Nikolsky-Phänomen war positiv. Aus Abstrichen von Nase und Nabel konnte Staph. aureus gezüchtet werden (Lysogruppe II, Lysisbild 71). Unter Antibiotika- sowie entsprechender symptomatischer Therapie besserte sich der Zustand bald und das Kind konnte nach 2 Wochen in gutem Allgemeinzustand nach Hause entlassen werden.

Diskussion

Wie bereits ausgeführt, besteht an der ätiologischen Rolle der Staphylokokken der Phagen-Gruppe II (insbesondere Stämme mit dem Lysisbild 71) kein Zweifel mehr. Dies ist insofern bemerkenswert, als die Vertreter dieser Staphylokokken-Gruppe insgesamt nur einen kleinen Anteil der bakteriologisch nachgewiesenen Staphylokokken ausmachen [9, 17]. Neuere Untersuchungen [7] weisen daraufhin, daß auch Stämme, die mit Phagen der Gruppen I und III reagieren, Impetigo und Rittersche Krankheit hervorrufen können und exfoliatives Toxin bilden.

Die Entwicklung eines Tiermodells unter Verwendung neugeborener Mäuse [12, 13] brachte neue Erkenntnisse über die Pathogenese des SSSS. Neugeborene Mäuse, denen lebende Staphylokokken der Phagengruppe II injiziert wurden, entwickelten binnen 24 Stunden eine exfoliative Dermatitis, die klinisch und histologisch nicht vom SSSS des Menschen unterschieden werden konnte. Mit Staphylokokken anderer Phagengruppen konnte diese Reaktion nicht induziert werden.

Durch die Untersuchungen dieser und anderer Autoren konnte in der folgenden Zeit eine kausale Beziehung zwischen einem extrazellulären Toxin dieser Erreger und den verschiedenen Manifestationen des SSSS hergestellt werden. Für dieses Toxin existieren mehrere Bezeichnungen: Exfoliatin, exfoliatives Toxin, epidermolytisches Toxin, Epidermolysin. Für die Induktion des SSSS bei neugeborenen Mäusen genügt es, wenn lediglich das Toxin appliziert wird. Das Toxin ist ein Protein mit einem Molekulargewicht von 24,000—33,000. Bei Stämmen, die mit Phagen der Gruppe II reagieren, ist das Toxin wärmestabil, bei anderen Stämmen wärmelabil [7].

Man nimmt an, daß das Toxin am Ort der Staphylokokken-Infektion (z. B. einer Konjunktivitis, Otitis, Angina) gebildet wird und hämatogen die Haut erreicht, um hier erst wirksam zu werden. Für diesen Mechanismus sprechen das symmetrische Auftreten des Erythems, das Fehlen von polymorphkernigen Leukozyten in den Hautveränderungen [10] und die Tatsache, daß der Inhalt intakter Hautblasen gewöhnlich steril ist. Ein Nachweis von Staphylokokken von der entzündeten Haut ist sehr wahrscheinlich auf Sekundärinfektionen der freiliegenden Wundflächen zurückzuführen.

Das Vorkommen des SSSS praktisch nur im frühen Kindesalter erklärt man sich durch die größere Kapazität der Erwachsenen, gebildetes Toxin abzubauen. Kommt es bei Erwachsenen zum SSSS, so diskutiert man neben einer Beeinträchtigung des Stoffwechsels auch eine solche der Immunabwehr [3].

Histologisch kommt es beim SSSS zu einer Ablösung im Bereich des unteren Stratum granulosum (»intraepidermale« Ablösung), wobei Entzündungszeichen fehlen [3, 4]. Das Korium liegt also nicht frei, die Basalzellschicht hat noch einen gewissen Schutz vor Infektionen sowie einem zu massiven Wasser-, Elektrolyt- und

Eiweißverlust [5]. Vielleicht ist diese »hoch« liegende Ablösungszone dafür verantwortlich, daß die Heilung relativ schnell und ohne Narbenbildung erfolgt [9].

Die heute vorliegenden Befunde sprechen dafür, daß es sich um einen extrazellulären nicht zytotoxischen Prozeß handelt. Es wurde mittels elektronenmikroskopischer Untersuchungen festgestellt, daß es zu einer Spaltung der Desmosomen zwischen den Zellen des Stratum granulosum kommt [8]. Bei der »adulten« TEN ist dagegen die Basalzellschicht der Epidermis betroffen (»subepidermale« Ablösung) [5]. Inwieweit es sich hierbei tatsächlich um einen allergischen Prozeß handelt, ist noch ungeklärt.

Das SSSS wird zunehmend häufiger beobachtet [3, 9, 10, 15]. Vor allem sind Neugeborene, Säuglinge und Kleinkinder betroffen. Nicht selten werden mehrere Fälle gleichzeitig oder hintereinander gesehen [2, 6, 15] bzw. die Kinder kommen aus denselben Entbindungskliniken [14]. Neugeborene erkranken nicht selten erst nach Entlassung aus der Klinik [16]. Familienangehörige von am SSSS erkrankten Kindern können Staphylokokken vom Typ II/71 auf Haut oder Schleimhaut beherbergen [15].

Das klinische Bild des SSSS umfaßt ein Spektrum von Erkrankungen der Haut, das von rein lokalisierten Formen (bullöse Impetigo) bis zur generalisierten Exfoliation reicht. Die Erkrankung kann mit einer Konjunktivitis, einem Infekt der oberen Luftwege, einer Angina oder Otitis beginnen. Nicht selten besteht Fieber. Nach 1—4 Tagen treten die Hautsymptome auf [3, 14, 15, 17]. Am beeindruckendsten ist die generalisierte Form der Erkrankung: fleckiges scarlatiniformes Exanthem, positives Nikolsky-Phänomen, Blasenbildung, spontane Hautablösungen. Es entsteht eine feuchtglänzende rote Fläche (das Bild erinnert an eine Verbrühung), die etwa binnen 48 Stunden trocken wird. Danach kommt es zu einer Abschuppung. 7—10 Tage nach Auftreten des Erythems ist der Prozeß, ohne Narben zu hinterlassen, abgeheilt.

Die lokalisierte Form äußert sich als bullöse Impetigo. Hautveränderung und Infektion finden (anders als bei der generalisierten Form) am gleichen Ort statt [8, 13].

Scarlatiniforme Exantheme können Ausdruck eines abortiv verlaufenden SSSS sein [13, 14]. Der Prozeß entwickelt sich hierbei nicht bis zur Blasenbildung und Exfoliation weiter.

Bei den seltenen Fällen der adulten Form des SSSS handelt es sich fast immer um eine bullöse Impetigo, also um die lokalisierte Form des SSSS, wobei in den intakten Blasen Staphylokokken nachgewiesen werden können. Typische generalisierte Verlaufsformen sind bei Erwachsenen nicht beobachtet worden.

Wahrscheinlich sind die sog. »bullösen« Varizellen dadurch bedingt, daß es zu einer Superinfektion der Varizelleneffloreszenzen durch Staphylokokken vom Typ II/71 kommt [11, 18]. Wird die Superinfektion durch andere Staphylokokken hervorgerufen, kommt es lediglich zu einer Impetigo.

Zu Beginn des Krankheitsprozesses ist eine differentialdiagnostische Abgrenzung des SSSS von anderen Hautaffektionen schwierig: Sonnenbrand, ekzematöse Dermatitis, M. Leiner Erythema exsudativum multiforme, Scharlach u. a. können ein ähnliches Bild zeigen. Im fortgeschrittenen Stadium erfolgt die Abgrenzung von anderen bullösen Hautprozessen durch die Empfindlichkeit der Haut, durch die Neigung zur Ausdehnung auf große Flächen und zur Exfoliation (intakte Blasen werden nur selten gesehen) [3].

Die Unterscheidung von »allergischer« TEN und SSSS ergibt sich in den meisten Fällen aus dem Alter der Patienten, dies gilt aber nicht absolut. Im Zweifelsfall wird eine histologische (Bestimmung des Ortes des Ablösungsprozesses in der Epidermis) bzw. zytologische Untersuchung (akantholytische Keratinozyten beim SSSS oder Entzündungszellen, zellulärer Debris und basale Keratinozyten bei nichtstaphylogener TEN) empfohlen [3]. Blasen und Erosionen der Mundschleimhaut sprechen eher für eine TEN und gegen ein SSSS [9, 15]. Die Hautveränderungen des Stevens-Johnson-Syndroms sind vorwiegend im Bereich der Körperöffnungen zu finden. Das Nikolsky-Phänomen ist negativ.

Die Unterscheidung des scarlatiniformen Exanthems als abortive Verlaufsform des SSSS vom echten Scharlachexanthem kann zunächst schwierig sein. Es fehlen aber die Rötung des Gaumens und die typische »Himbeerzunge«. Die Hautschuppen sollen wesentlich größer sein als beim Scharlach, sie entstehen bereits binnen 4 Tagen nach Auftreten des Erythems [13, 14].

Die Mehrzahl der von SSSS-Patienten isolierten Staphylokokken ist gegenüber Penizillin resistent. Daher werden heute zur Therapie penizillinasefeste Penizilline empfohlen, um die Toxinproduktion in einem möglichst frühen Stadium zu unterbinden [3, 5].

Mittels des Tiermodells konnte festgestellt werden, daß Meticillin das SSSS verhinderte, wenn es frühzeitig gegeben wurde. Erfolgte die Antibiotika-Gabe erst nach Beginn der Exfoliation, wurde der Krankheitsverlauf nicht mehr beeinflußt [12, 14]. Steroide gelten heute als kontraindiziert (Aggravation des SSSS bei neugeborenen Mäusen, Auslösung des SSSS bei Zugabe von Steroiden sogar bei adulten Mäusen). Zur Therapie des SSSS gehört selbstverständlich die Substitution des Flüssigkeits-, Elektrolyt- und Eiweißverlusts.

Die Behandlung der Hautflächen erfolgt wie bei Verbrennungen. Die Prognose ist im allgemeinen gut, jedoch kann es, insbesondere bei Neugeborenen, zum Exitus letalis kommen [3, 9].

Was unsere eigenen Fälle betrifft, fällt auf, daß beide Kinder aus derselben Entbindungsklinik kamen und fast zur gleichen Zeit erkrankten. Trotz adäquater Therapie konnte bei dem einen Kind, einem Frühgeborenen, eine septische Allgemeininfektion, deren Eintrittspforte zweifellos die Hautläsionen waren, nicht verhindert werden.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 205–209 (1978)

A recovered case of generalized BCG infection

by

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Received January 9th, 1978

A female infant was at the age of 8 months admitted with muco-cutaneous candidiasis. The applied therapy was inefficacious. Subsequent examinations pointed to a combined humoral and cellular immunopathy. At the age of 7 years the patient was readmitted with abdominal complaints. Diagnostic laparotomy revealed a tuberculous mesenterial growth. The isolated agent proved to be a BCG strain. Antituberculous therapy was beneficial, the tumour disappeared and full recovery was attained. The mycotic process remained unchanged and still needs continuous treatment.

After BCG vaccination regressive foci may develop in various organs by haematogenous dissemination [10]. These foci rarely give rise to tuberculous disease, although lupus and multiple bone infection have been observed when after BCG vaccination a decrease of resistance occurred [4, 8, 11]. A few cases of BCG osteomyelitis were also reported [3].

BCG dissemination is a rare condition; according to Wasz-Höckert and Lotte [15] 31 cases with fatal outcome were registered. Of these, 15 have been reported in detail [1, 2, 5, 7, 8, 9, 12, 13, 14, 15, 16]; their majority had a severe immuno-deficiency. In connection with partial immuno-deficiency one case has only been reported [6].

Report of a Case

L. R., a female patient, was born in 1965. The family history was irrelevant. She had had BCG vaccination at newborn age and diphtheria, whooping cough, tetanus, smallpox and polio vaccinations in due time.

At the age of 8 months, eruptions had appeared in the gluteal region, and then on the whole skin, with subsequent yellowish pigmentation, and thickening and fragmentation of the nails of the hands and feet. Candida albicans and Trychophyton rubrum had been isolated on several occasions. Later the process spread to the mucous membranes.

Antimycotic treatment with nystatin, clotrimazole, griseofulvin, and locally applied tartaric acid, iodine, salicyl brought no relief. When, in view of this, the suspicion of an immuno-deficient state had arisen, the patient at the age of 3 years was admitted to our Department. Laboratory tests revealed a combined cellular and humoral (T + B) immuno-deficiency (Table I).

The patient remained under our continuous control and was readmitted at the age of 7 years, as for a month she had had nausea, vomited repeatedly and lost 1 kg weight. At this time, besides the skin changes the poorly developed girl (15.4 kg, 104 cm), had a tight, protruding abdomen with a resistance of a child fist palpable above and to the right of the umbilicus and

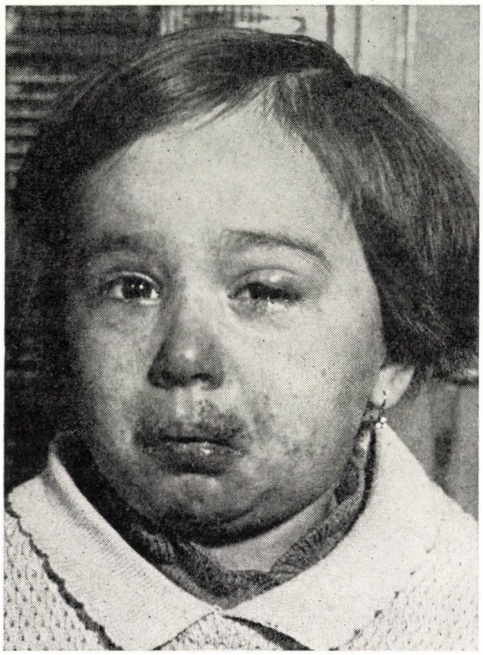


Fig. 1/1.

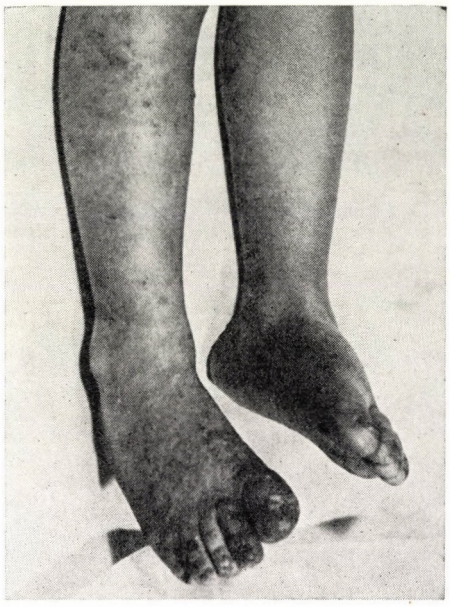
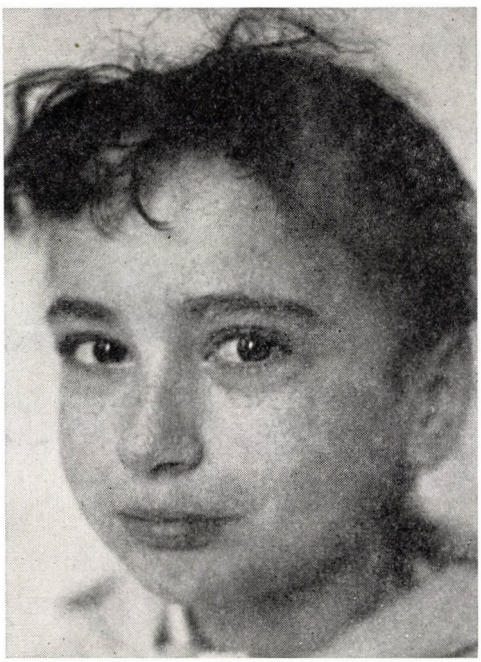


Fig. 1/3.



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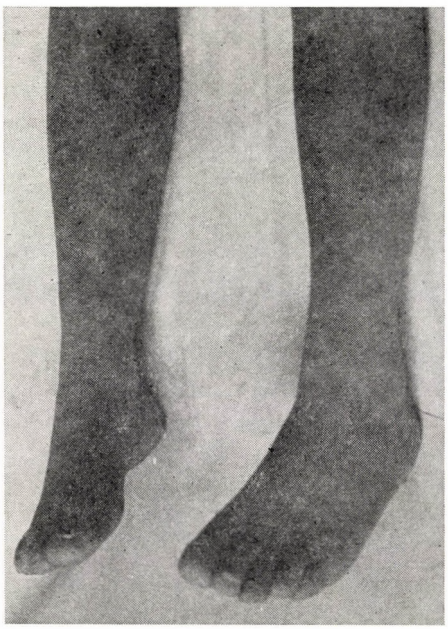
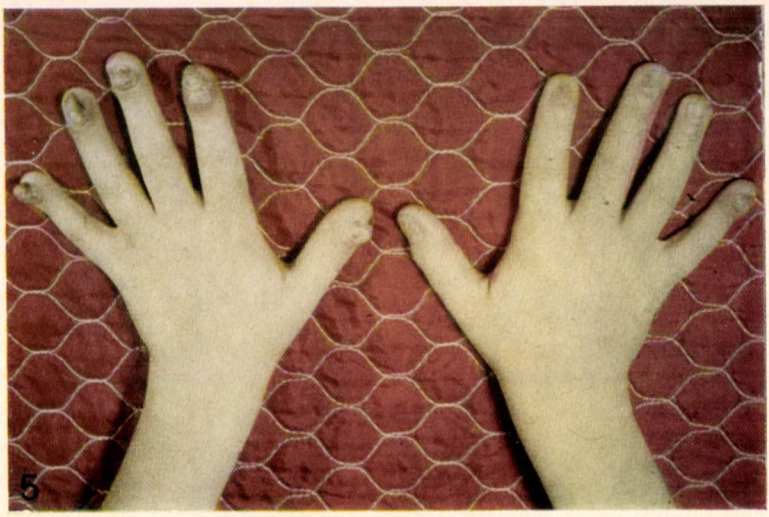


Fig. 1/4.

FIG. 1. Patient with mucocutaneous candidiasis before treatment, at the age of five years, and after prolonged treatment, at the age of 11 years



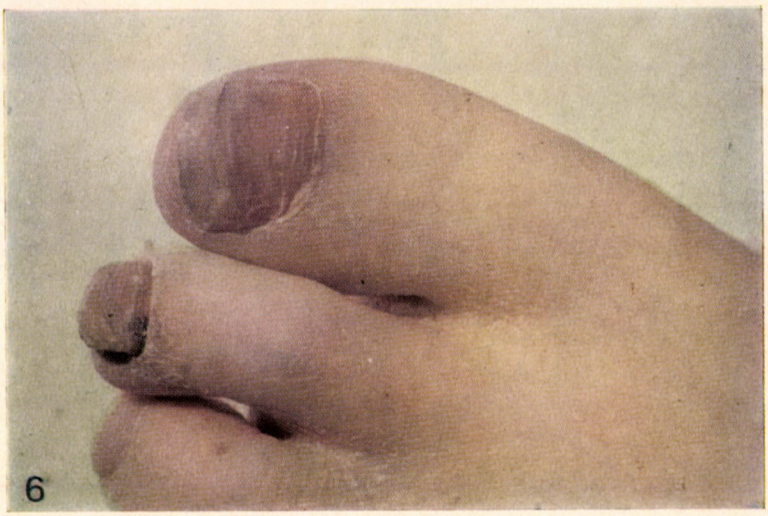


FIG. 1/5, 1/6

TABLE I

Immunological and Laboratory Data

RBC: 3,900,000; WBC: 8,000; Hb: 15.7 g/dl; ESR: 10 mm/hr. Se total protein 6.9 g/dl
Se electrophoresis: albumin 40%; alpha$_1$ globulin 7%; alpha$_2$ globulin 16%; beta globulin 12%; gamma globulin 25%
Peripheral blood: T. Ly: 68% (spontaneous rosette producing); B Ly: 12%; macrophages: 8%
Intracutaneous tests of delayed type: Tuberculin (1 : 1000): negative; Candidin (1 : 1000): negative; Trychophytin: negative; Phytohaemagglutinin (1 μg): 24 hr slightly positive, 48 hr negative
Leucocyte migration test (PPD): insignificant inhibition (migration index, 0.89), with phytohaemagglutinin: significant inhibition (migration index, 0.61)
NBT (nitro-blue-tetrazolium) reaction positive in 50% of granulocytes
Ly-transformation 60% positive

Immunoglobulins:	IgG	IgA	IgM
1969:	2084	14	121 mg/dl
1970:	2481	50	160 mg/dl
1971:	2481	59	160 mg/dl
1973:	715	80	106 mg/dl
1974:	1520	42	165 mg/dl

Antibody level (passive haemagglutination):

Staph. alpha-antitoxin:	0.25 IU/ml	Sh. flexneri 1 agglutinin:	32+++
S. typhi O. agglutinin:	8++	Sh. flexneri 2 agglutinin:	16+++
E. coli O. 26 agglutinin:	16++	Sh. flexneri 3 agglutinin:	16++
E. coli O. 55 agglutinin:	4++	Sh. flexneri 6 agglutinin:	32+++

Antibody level: decreased

a liver enlarged to two fingerbreadth. Laparotomy revealed a massive tumour located in the root of the mesentery. As it could not be removed, a wedge biopsy was made.

Histologically, the tumour proved tuberculous in origin with many acid fast rods. In repeated gastric washings and laryngeal swabs BCG bacilli were found.

Subsequently, combined antituberculous treatment was given with a total of 20 g streptomycin, 20 g INH and 16.5 g of rifampicin. Under its effect the condition improved, the patient gained 5 kg in weight and grew 4 cm in 15 months and the abdominal resistance disappeared. The skin process also improved. Now at 11 years of

TABLE II

Biochemical reactions of patient's strain in comparison with standard strains

Strains	Ziehl-Neelsen staining	Cord formation	Nicotinic acid	Nitrate reduction to nitrite	Catalase	Pathogenicity for guinea pig
BCG*	+	+	− (±)	−	+	low
Strain 23069 (Patient's strain)	+	+	−	−	+	low
Mycobacterium tuberculosis*	+	+	+	+	+	high
Mycobacterium bovis*	+	+	− (±)	−	+	high
Mycobacterium tuberculosis INH resistant	+	+	+	+	−	low

* International strains. Mycobacterial Culture Collection, Trudeau Institute, New York 1972.

age the girl goes to school and leads a normal life, her height is 127 cm and her weight, 24.5 kg.

Bacteriological examination. The samples were inoculated into 3 liquid media. After 6 weeks a small number of colonies were obtained. Morphologically they corresponded to those of pathogenic mycobacteria. They were Gram negative, acid and alcohol fast and showed typical cord formation. Their comparison with the international Mycobacterium strains is shown in Table II, the sensitivity tests in Table III.

Virulence examinations were performed in 2 guinea pigs each with quantities of 1.0 and 0.1 mg per g wet weight administered subcutaneously in the right inguinal fossa. This revealed that 0.1 mg induced no alteration during 60 days, and 1.0 mg produced local lymph node enlargement. At the same time, no INH resistant M. bovis strain was present. According to the results, the strain was one of Mycobacterium BCG.

TABLE III

Sensitivity tests
(according to Canetti)

Isoniazid	sensitive	0.2 μg/ml
Streptomycin	sensitive	4.0 μg/ml
Viomycin	sensitive	10.0 μg/ml
Ethambutol	sensitive	0.5 μg/ml
Rifampicin	sensitive	5.0 μg/ml

DISCUSSION

If complications appear after BCG vaccination the reliability of the vaccine has to be checked in the first place. In our case, 6 other newborns received the same vaccine, without any pathologic symptoms neither then, nor later. In such cases the suspicion of a BCG infection is well founded.

It is evident that in cases of severe immuno-deficiency antituberculous treatment is not efficacious. In our case, the patient responded well to the therapy and recovery has been attained, as in the only similar case reported in the literature [6]. In the latter case, the tuberculin negativity existing during the whole course of the disease pointed to a disturbance of cellular immunity. The circumstance that in our patient the complication appeared 7 years after the vaccination while in healthy individuals pathogenic BCG may persist in the organism at most for a year, shows that in immunopathic subjects this time may considerably be prolonged.

Thus, in countries where BCG vaccination of newborns is compulsory, preventive inhibitory therapy has to be taken into consideration whenever a partial immunopathy is detected after the vaccination.

ACKNOWLEDGEMENT

We are indebted to Dr. T. Révész (Second Department of Paediatrics) and to the Institute for Vaccine Production and Research for immunological examinations; as well as to Dr. J. Mohácsy (Second Institute of Pathology) for pathological examinations.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 211—219 (1978)

Urinary tract infection presenting with conjugated bilirubinaemia and the plasma amino acid pattern in young infants

by

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Received 17th January, 1978

Fasting blood glucose and plasma free amino acid levels were determined in 16 infants (average postnatal age, 44 ± 6 days) suffering from urinary tract infection associated with jaundice and cholestasis. There were no significant differences in the fasting blood glucose values of the control and jaundiced babies. The concentration of two glucogenic amino acids; alanine and lysine, decreased significantly and phenylalanine, citrulline and cystine levels were elevated, suggesting an impairment of the metabolism of these amino acids in the liver. A close positive correlation was found between bilirubin, SGPT and phenylalanine levels, suggesting a relationship between hepatic damage and the measured phenylalanine concentration. After two to four weeks of antibiotic treatment the urine became sterile bilirubinaemia disappeared and the amino acid levels returned to normal.

The most common condition associated with cholestatic jaundice in young infants is urinary tract infection rather than congenital atresia of the biliary ducts or neonatal hepatitis. The usual clinical picture is of a young infant who is failing to thrive, lethargic or irritable, and suffering from fever, jaundice, and moderate hepatomegaly [15]. Hepatocellular impairment is the main factor in the production of jaundice [2].

The major role of the liver in glucose and amino acid homeostasis has long been recognized. A serious impairment of hepatic glycogen synthesis and gluconeogenesis frequently leading to fasting hypoglycaemia has been reported in acute viral hepatitis [4]. No information is available concerning these biochemical functions in liver injury associated with urinary tract infection in young infants.

The question has been investigated by measuring fasting blood glucose and individual plasma free amino acid concentrations in such infants.

Material and Methods

Sixteen infants ranging in age from 6 to 80 days and admitted over a two year period were included in the study.

The clinical data are presented in Table I. Most babies were prematurely born, only three infants had a gestational

Supported by the Scientific Research Council, Hungarian Ministry of Health (3—23—0502—04—1/M).

age of >35 weeks. Jaundice was evident in all cases; both conjugated and unconjugated bilirubin concentrations were elevated in their plasma. The former bilirubin fraction comprised 56% of the total bilirubin level which varied from 1.6 to 25.2 mg/dl. The observed bilirubinaemia was moderate in the majority of cases. Plasma bilirubin concentration was below 2 mg/dl in 4 cases, between 2 and 5 mg/dl in 6, between 5 and 10 mg/dl in 4 cases and only two infants (both septic cases) had plasma bilirubin levels higher than 10 mg/dl. SGOT values were elevated in 8, SGPT values in 4 cases. Both SGOT and SGPT were above normal (12 IU) in 3 infants. All of the 16 infants had at least two to three urine cultures with 10^4 or more Gram negative organisms per cu. mm. Most infants were infected with E. coli, but all had sterile blood cultures. Blood urea nitrogen level was determined in 6 cases and ranged from 12 to 29 mg/dl. There were no reducing sugars in the urine and serological tests for Australia antigen, rubella, cytomegalovirus and toxoplasmosis were negative. Intravenous pyelograms and cystourethrograms were performed in half of the patients and 4 out of the 8 showed some kind of abnormality (Table I).

After 2 to 4 weeks antibiotic treatment the urine culture became sterile and both

TABLE I

Clinical data of infants with jaundice

Sex	Gest. age, wks	B. weight, g	Postnatal age, days	B. weight at examination, g	Total Bilirubin mg/dl	Conjugated Bilirubin mg/dl
M	—	1110	70	2500	2.7	1.3
M	30	1480	60	2800	2.5	1.3
F	27	1400	80	3400	1.6	0.4
F	30	1430	42	1950	2.4	1.4
M	—	1200	67	2600	2.2	1.7
F	31	1320	77	2500	3.1	2.0
F	38	3160	21	2700	9.3	7.1
F	28	1310	36	1400	7.2	4.3
M	33	2460	5	2300	25.2	6.4
M	33	2240	17	1900	5.1	3.0
F	38	3450	42	4200	14.0	11.7
M	32	1470	32	1500	7.1	5.3
F	—	1700	40	2000	1.6	1.5
M	37	2900	23	2700	3.5	1.7
M	36	1630	60	2000	1.8	1.2
F	—	1700	39	2100	1.8	1.0

fractions of bilirubin decreased gradually. Liver biopsy was performed in 6 cases at the time of peak bilirubin levels.

Histology showed a non-specific reactive hepatitis with cholestasis and some infiltration of the portal tracts with inflammatory cells.

Fasting blood glucose and plasma amino acid levels were determined from 1.0 ml of blood taken at 0900 hr. A control group of 49 premature infants with similar gestational age, birth weight, postnatal age and actual bodyweight were selected who were admitted to the unit over the same two years period when feeding regimen (formula- feeding) and care were practically the same (Table II).

Blood glucose was estimated by the o-toluidine method (4) and the plasma level of 17 individual amino acids by automated ion-exchange chromatography using Beckman Multichrom 4225 analyser. Amino acid analyses were made at the same time in both groups. Specimens of venous blood collected in heparinized tubes were promptly centrifuged and the plasma was deproteinized by addition of four volumes of 5% sulphosalicylic acid. Protein-free supernatant was immediately frozen and stored at −20°C until assayed.

For statistical analysis Student's *t*-test was used and regression equations were calculated by the method of least squares (paired analysis).

and urinary tract infection

UN, mg/dl	Fasting blood glucose, mg/dl	SGOT (IU)	SGPT (IU)	Urine culture	Liver biopsy*
—	97	10	3	E. coli 10^4	+
—	—	16	10	E. coli 10^5	+
—	56	29	15	E. coli 10^4 10^5	+
29	71	21	7	E. coli and Klebsiella 10^5	+
—	—	—	—	E. coli 10^4	+
—	—	—	—	E. coli 10^6	—
—	59	14	5	E. coli 10^5	+
—	—	42	23	E. coli 10^4	+
—	50	10	2	E. coli 10^5	—
—	83	12	8	E. coli 10^4	—
40	—	12	14	E. coli 10^5	—
12	45	62	43	E. coli 10^4	—
14	62	3	2	Klebsiella and Proteus 10^5	—
—	87	16	3	E. coli 10^5	—
14	—	25	7	E. coli 10^6	—
19	51	8	3	E. coli 10^5	—

* Nonspecific reactive hepatitis with cholestasis (see text).

TABLE II

Control and jaundiced infants
(M + SE)

	Control	Jaundice with urinary tract infection	Significance
Gestational age, weeks	33 ± 1	33 ± 2	NS
Birth weight, g	1742 ± 75	1873 ± 174	NS
Postnatal age, day	35 ± 3	44 ± 6	NS
Body weight at examination, g	2184 ± 58	2409 ± 175	NS
Mean fasting blood glucose, mg/dl	67 ± 2	67 ± 6	NS
BUN, mg/dl	10 ± 1	21 ± 5	< 0.001
n	49	16	

RESULTS

Mean fasting blood glucose concentrations were the same in the control and study groups (Table III). The mean blood urea level was significantly ($p < 0.001$) higher in the jaundiced infants, but urea levels were available for not more than 6 cases and among them only two babies showed levels markedly exceeding the upper limit of the normal (6—20 mg/dl) range.

Total and individual fasting plasma free amino acid levels are shown in Table III and Figure 1. The mean total concentrations of 17 amino acids were very similar in the two groups. Alanine and lysine levels were significantly lower, and plasma phenylalanine, cystine and citrulline were significantly higher, in the study group. Plasma tyrosine concentrations were also higher in the jaundiced group but the difference did not reach the level of significance.

Total and conjugated bilirubin levels were related to the plasma concentration of each amino acid found to be significantly lower or higher as compared to controls. A significant linear correlation was found only between total and direct reacting bilirubin levels and plasma phenylalanine concentrations (Figure 2), and there was a positive linear correlation between SGPT and plasma phenylalanine levels ($r = 0.7$, $p < < 0.05$).

The relationship between serial bilirubin and phenylalanine levels in the period of antibacterial treatment in 6 infants are shown in Figure 3. Plasma phenylalanine gradually decreased parallel with the fall of conjugated bilirubin concentration in most cases. There was no relationship between plasma phenylalanine levels and postnatal age in the control group, so a decline in plasma phenylalanine was considered a sign of improving liver function. By the time of recovery from

TABLE III

Plasma free amino acid levels in normal controls and infants with jaundice and urinary tract infection (M ± SE) (μmol/l)

	Control	Urinary tract infection and jaundice	Significance
Taurine	75 ± 18	79 ± 14	NS
Aspartate	47 ± 4	50 ± 4	NS
Citrulline	19 ± 3	45 ± 7	< 0.05
Proline	280 ± 32	248 ± 52	NS
Glycine	258 ± 17	228 ± 14	NS
Alanine	367 ± 20	261 ± 20	< 0.01
Cystine	48 ± 9	87 ± 10	< 0.01
Valine	193 ± 14	188 ± 20	NS
Methionine	28 ± 2	29 ± 4	NS
Isoleucine	60 ± 5	50 ± 6	NS
Leucine	111 ± 8	98 ± 9	NS
Tyrosine	129 ± 14	164 ± 50	NS
Phenylalanine	163 ± 22	277 ± 72	< 0.05
Lysine	251 ± 34	124 ± 11	< 0.05
Ornithine	93 ± 9	83 ± 10	NS
Histidine	73 ± 11	95 ± 10	NS
Arginine	76 ± 6	59 ± 5	NS
Total	2271 ± 30	2165 ± 118	NS
n	39	16	

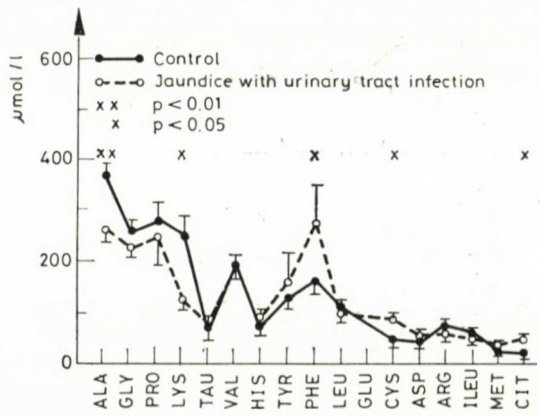

FIG. 1. Plasma aminogram in jaundice associated with urinary tract infection (M ± SE)

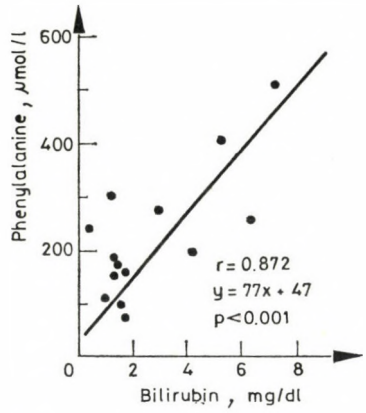

FIG. 2. Plasma conjugated bilirubin and phenylalanine levels in jaundice associated with urinary tract infection

the urinary tract infection, the rest of the amino acids also returned to normal.

The molar ratio of $\left(\frac{\text{Val}+\text{Ileu}+\text{Leu}}{\text{Tyr}+\text{Phe}}\right)$ suggested as a liver function test [16] has been calculated and is shown in Figure 4. The ratio was approximately 1.5 in the controls and was reduced to 0.92 in the study group ($p < 0.01$). The lower value of the quotient was mainly due to the higher level of aromatic amino acids included in the numerator, the plasma concentration of the branched chain amino acids remained normal.

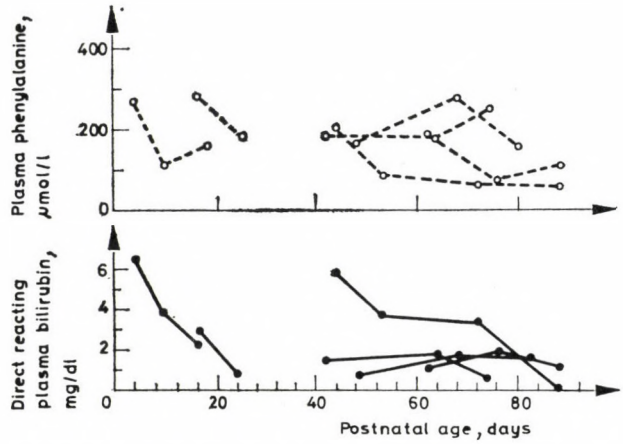

FIG. 3. Serial bilirubin and phenylalanine levels in 6 jaundiced infants with urinary tract infection

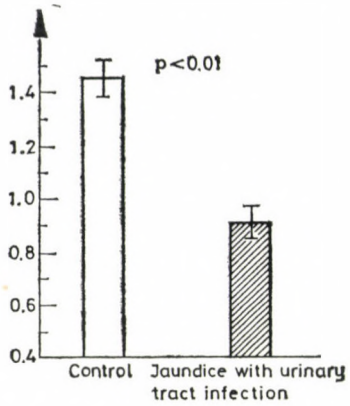

FIG. 4. $\frac{\text{Val} + \text{Ileu} + \text{Leu}}{\text{Tyr} + \text{Phe}}$ molar ratio in jaundice associated with urinary tract infection

DISCUSSION

Urinary tract infection in early infancy is frequently associated with jaundice [15]. It has been suggested that jaundice develops in these infants as a result of haemolysis [17] and toxic hepatitis [2] with intracellular and intracanalicular bile stasis. Except for the mild bilirubinaemia, the usual liver function tests are normal in this condition. Abnormal histology, on the other hand, is highly suggestive of liver impairment.

Blood glucose homeostasis, as far as it can be judged from the normal fasting blood glucose values, is maintained, but there are considerable distortions in the fasting plasma levels of some amino acids. Thus, the levels of alanine and lysine, two important glucose precursors, were reduced by 30 and 50%, respectively (Table III and Figure 1).

Since fasting blood glucose levels remained normal and no correlation was found between the degree of bilirubinaemia and the level of any of these two amino acids, it would be difficult to comment on the possible gluconeogenic significance of the hypoalaninaemia and hypolysinaemia [11].

It is a well established fact that tyrosine metabolism is abnormal in patients with liver disease. Fasting levels of tyrosine tended to be high in these patients [8]. Felig et al. [4] too found elevated fasting tyrosine levels in viral hepatitis. Recently, high tyrosine levels have been found in neonatal hepatitis [18] and in 4 preterm babies with mild cholestasis and rickets [6]. In the present study a small nonsignificant rise in tyrosine and a considerable and significant ($p < 0.05$) elevation in phenylalanine have been observed (Table III and Figure 1). Furthermore, there was a positive linear correlation between bilirubin and phenylalanine levels (Figure 2).

One must be careful when interpreting tyrosine and phenylalanine levels in young infants. Tyrosinaemia

and associated hyperphenylalaninaemia due to transient adaptive impairment of catabolism is a common neonatal condition, particularly frequent in premature babies [17, 14]. On the other hand, the protein quantity and quality of food is a major determinant of the plasma level of aromatic amino acids in that age group [3, 13]. On the basis of these considerations, infants with comparable gestational and postnatal age, as well as body weight and feeding-regimen were selected as controls.

As compared to control babies, the observed hypertyrosinaemia and hyperphenylalaninaemia were moderately, but in the case of phenylalanine clearly abnormal and can be considered as a sensitive biochemical parameter of liver impairment. This assumption is strongly supported by the observation that plasma phenylalanine levels have gradually declined during antibiotic treatment in parallel with the falling bilirubin values (Figure 3).

In adults, Soeters and Fischer [16] found a close correlation between molar ratio of the branched chain amino acids and the aromatic amino acids and the severity of liver damage associated with hepatic encephalopathy. The mean ratio was approximately 3—3.5 in the normal human adult and 0.6—1.2 in those suffering from hepatitic encephalopathy. We were able to show a fall of this ratio in a like manner in urinary tract infection associated with jaundice and cholestasis. It was surprising to see that a slight and apparently reversible liver damage noted in our patients produced a ratio similar to that observed in severe liver impairment leading to hepatic encephalopathy. It should be stressed, however, that our normal control values were also much lower than in adults, so the reduction of the ratio, significant though it may be, was far less dramatic than in hepatic encephalopathy. It also has to be kept in mind, as Soeters and Fischer had pointed out [16], that the elevation of the ratio is not at all specific for liver disease and stimuli such as sepsis, diuresis, stress, and catecholamine discharge can lead to increased plasma aromatic amino acids and decreased branched chain amino acids.

We found no apparent explanation for the elevated citrulline level. The plasma concentrations of the other (dibasic) amino acids participating in the urea cycle remained normal.

Hypercystinaemia may also be a small though significant biochemical sign of liver impairment, possibly indicating a further delay in the maturation of the enzyme(s) of the transsulphuration pathway which is particularly immature in preterm babies [5].

As regards the significance of the present findings, it can be concluded that *(1)* the distortion of the plasma aminogram indicates a moderate and reversible liver damage caused by urinary tract infection in young infants; *(2)* although the hypertyrosinaemia and hyperphenylalaninaemia observed were of moderate degree in most cases, their untoward effect on the developing nervous system cannot be excluded [9, 10]. In the most severe

cases follow-up investigations seem to be justified to distinguish it from the potentially harmful hypertyrosine and hyperphenylalaninaemias commonly seen in premature infants.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 221—224 (1978)

The 1-hour D-xylose test in the diagnosis of villous atrophy

by

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Received February 21st, 1978

The results obtained in 40 cases of intestinal mucosal biopsy and parallel 1-hour D-xylose test are presented. Of 40 patients, 15 had subtotal villous atrophy, while in 25 the villous structure was intact. Among the 15 patients with villous atrophy 10 gave D-xylose values of less than 20 mg per dl. In the control group all D-xylose values were above 20 mg per dl.

In the diagnosis of the malabsorption syndromes caused by morphological abnormalities of the intestinal mucosa, peroral intestinal biopsy has become an essential procedure in the diagnosis of villous atrophy [1, 4]. The biochemical tests have less importance in this respect. Estimation of the excretion and blood concentration of D-xylose is widely used in the diagnosis of disturbances of intestinal absorption. The 1-hour D-xylose test described in 1973 by Rolles et al. [3] is often applied as a screening test for coeliac disease. These authors claimed that a serum D-xylose level of 20 mg/dl or more, 1 hour after administration practically excluded the presence of coeliac disease. The present paper reports on studies of the diagnostic value of the 1-hour D-xylose test in subtotal villous atrophy and in cases with a normal villous architecture.

Material

Three groups of patients were examined

1st group: 25 patients referred to us for suspected malabsorption, but in whom the clinical picture, a normal intestinal structure and chemical tests excluded such a condition.

2nd group: 13 patients exhibiting typical signs of subtotal villous atrophy in the biopsy specimen. Although repeated biopsies were not carried out in each patient, they all responded favourably to a gluten-free diet.

3rd group: In 2 patients subtotal villous atrophy was found, but the underlying cause could not be revealed. They failed to respond to a gluten-free diet, or to elimination of cow's milk from the diet. Giardiasis was ruled out and repeated biopsy, demonstrating the persistance of villous atrophy, excluded the possibility of post-infectious enteritis. Nor could we find a primary immune deficiency or drug intoxication. Since both these patients were admitted with severe atrophy, their condition was most likely due to protein calorie malnutrition.

All patients were below 30 kg body weight and the tests were performed after 8 hours fasting. The patients did not receive any drugs for at least 1 week prior to testing.

Methods

Peroral intestinal biopsy was carried out using Crosby-Kugler and Watson type children's capsules. The specimen for histological examination was taken at the level of Treitz's ligament. Examinations were done with a dissecting and a light-microscope. For the latter method 5 μ thick sections were prepared and stained with haematoxylin-eosin. The condition of the intestinal mucosa was categorized on the basis of the height of the microvilli: in the case of subtotal villous atrophy (SVA) their height was below 150 μ, while in the normal case they exceeded 300 μ.

The 1-hour D-xylose test was carried out according to Rolles et al. [3]. Each patient was given 5 g D-xylose dissolved in 100 ml of water. Blood was drawn before and 1 hour after the administration of D-xylose. The chemical test was done within 4 hours following venipuncture. Samples were stored at 4°C during this interval. The method of Roe and Rice [2] was followed with the modifications of Schaad et al. [5]. When evaluating the results, values of 20 mg/dl or less were regarded as pathological, values over 20 mg/dl as normal.

Results

Results for the 2nd and 3rd groups are given in Table I. In Fig. 1 the results of each group are seen separately.

In the 1st group only one patient yielded a value of 20 mg/dl, in all the other it was well above 20 mg/dl.

In the 2nd group, the D-xylose values exceeded 20 mg/dl in 3 cases, thus reaching the normal range for the

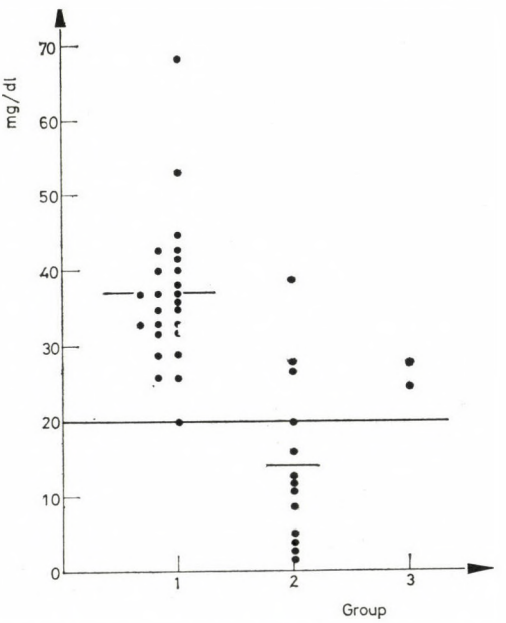

Fig. 1. 1-hour D-xylose value, mg/dl, in controls and cases of villous atrophy

TABLE I

	No. of patients	Age (year)	1-hour D-xylose value, mg/dl
Normal mucosa (1st group)	25	2.9 (0.6—8.6)	37 ± 7.4
Subtotal villous atrophy (2nd and 3rd group)	15	1.7 (0.4—6.5)	18 ± 3.8

TABLE II

	Rolles et al. [3]		Lamabadusuriya et al. [1]		Schaad et al. [5]		Present material	
	1-hour D-xylose test values							
	above	under	above	under	above	under	above	under
	20 mg/dl							
Control (normal mucosa)	75	—	19	—	not reported		25	—
Subtotal villous atrophy	1	52	6	13	—	16	5	10

test. In the 3rd group the values were over 20 mg/dl. The difference between the 1st and 2nd groups was highly significant mathematically ($P < 0.001$).

DISCUSSION

The D-xylose test values reported by different authors are collected in Table II. In the control group of patients with normal mucosal architecture the 1-hour value always exceeded 20 mg/dl. Among the 53 patients with untreated coeliac disease, Rolles et al. [3] found a single one with a value higher than 20 mg/dl. Lamabadusuriya et al. [1] found a higher value in 6 of their 19 untreated coeliac patients, while of the 16 coeliacs of Schaad et al. [5] all had values below 20 mg/dl. In addition, Lamabadusuriya et al. [1], among their 13 cases of subtotal villous atrophy and coeliac syndrome kept on a gluten-free diet, found only 3 who gave D-xylose values under 20 mg/dl.

In our own material there were 5 patients among the 15 with villous atrophy whose value was over 20 mg/dl. The results for patients with normal villous structure were in all cases in the normal zone. Thus, D-xylose values of less than 20 mg/dl present evidence of subtotal villous atrophy, but values exceeding that limit do not necessarily exclude its possibility.

The serum D-xylose level after oral administration depends on a number of factors. Among these, the quantity of xylose ingested, the osmolarity of the solution, gastric emptying, passage through the intestines, microorganisms in the small bowel, certain drugs and by all possibility the extent of villous atrophy all play a part in the process. It would be difficult and only lead to errors to take all these factors into consideration.

On the basis of our observations it may be stated that a 1-hour D-xylose test value of less than 20 mg/dl indicates villous atrophy in the small bowel, while a result above 20 mg/dl does not exclude the possibility of such a change.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 225—238 (1978)

The Hungarian congenital malformation monitoring system

by

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Received, March 1st, 1978

The Hungarian Congenital Malformation Monitor has been operating since 1973 in order to detect the temporal and regional clusters of 12 indicator congenital malformations as early as possible. This Monitor takes part in the International Clearinghouse for Birth Defects Monitoring System. Three continuously increasing trends were detected in 1973—1976. They may be connected with the more complete notifications, although the increase of limb reduction deformities are only partly explained by this factor. Transitional (quarterly) significant clusters were observed in the case of anencephaly (1974, IV), spina bifida (1974, II; and 1975, III; 1976, III), cleft lip ± cleft palate (1974, III). The possibility of three technical biases (changes in diagnosis, notification and evaluation of the given congenital malformation) has to be excluded before accepting the fact of a real epidemic. Subsequently, a case-control epidemiological study by personal interviews and with matched controls has to be performed.

Monitoring for specific congenital anomalies is an important public health task [3, 7]. It constitutes a significant part in every congenital anomaly surveillance system, since it facilitates the early detection of temporal and regional clusters. It helps to disclose their possible association with new teratogenic (or possibly mutagenic) environmental impacts, which in turn are expected to result in the introduction of preventive measures.

The Hungarian Congenital Malformation Monitor (HCMM) has been operating since January 1, 1973. Only the so-called indicator congenital malformations (ICMs) are evaluated monthly and according to regional occurrence (Table I). ICMs can easily and unequivocally be diagnosed within the first 6 days of life. (Until 1975, congenital malformations of the ear and nose, of the external genitalia, polydactyly and multiple malformations were included in the list of ICMs. In compliance with the international programme, since 1976, instead of the former, hydrocephalus, oesophageal atresia, congenital dislocation of the hip and Down syndrome are recorded.) As in Hungary nearly all deliveries take place in hospitals, obstetricians, paediatrician-neonatologists or pathologists can usually diagnose ICMs. The reporting of congenital malformations is compulsory, thus they cannot escape attention.

TABLE I

Number of births and cases of indicator congenital malformations by year and quarter of birth, 1973—1977, Hungary

Year and quarter of birth	Number of births			Number of reported cases											
	Total	Live births	Still-births	Anen-cephaly	Spina bifida	* Hydro-cephalus	Cleft palate	12—x Cleft lip	* Oeso-phag. atresia	* Rectal atresia	Hypo-spadias	Red. def. upper	Red. def. lower	* Cong. hip disloc.	* Down syn-drome
1973 — Total	157,623	156,224	1,399	137	173	138	56	196	33	48	217	19	9	975	122
I Jan.—Mar.	38,722	38,344	378	33	51	24	14	38	13	8	50	5	2	225	29
II Apr.—Jun.	40,110	39,731	379	32	45	37	15	51	6	15	49	4	3	201	28
III Jul.—Sep.	41,282	40,963	319	34	40	44	20	57	6	15	59	6	2	271	38
IV Oct.—Dec.	37,509	37,186	323	38	37	33	7	50	8	10	59	4	2	278	27
1974 — Total	187,957	186,288	1,669	197	240	144	68	199	40	34	256	58	14	1157	157
I Jan.—Mar.	42,094	41,697	397	42	51	40	14	46	10	8	65	14	3	278	34
II Apr.—Jun.	46,288	45,903	385	41	74	34	15	49	8	8	64	14	6	262	34
III Jul.—Sep.	52,135	51,682	453	49	62	36	16	49	4	9	73	13	3	299	54
IV Oct.—Dec.	47,440	47,006	434	65	53	34	23	55	18	9	54	17	2	318	35
1975 — Total	195,740	194,165	1,575	160	239	146	59	200	39	43	322	89	43	1404	156
I Jan.—Mar.	50,087	49,684	403	44	57	41	14	64	10	12	86	20	12	364	32
II Apr.—Jun.	50,350	49,940	410	37	56	34	13	46	6	7	97	23	13	356	41
III Jul.—Sep.	50,364	49,989	375	52	71	40	15	49	13	11	52	27	10	379	51
IV Oct.—Dec.	44,939	44,559	387	27	55	31	17	41	10	13	87	19	8	305	32
1976 — Total	186,916	185,408	1,551	140	184	91	78	179	42	41	383	55	23	995	137
I Jan.—Mar.	47,418	47,022	396	36	49	17	22	51	11	9	110	14	3	283	31
II Apr.—Jun.	47,856	47,448	408	31	44	25	22	37	12	13	84	24	11	225	39
III Jul.—Sep.	48,523	48,146	377	39	32	25	16	53	9	14	61	10	2	155	39
IV Oct.—Dec.	43,119	42,789	330	34	59	24	18	38	10	5	128	7	7	332	28
1977 — Total	179,152	177,574	1,578	111	161	113	50	138	35	37	357	62	7	846	139
I Jan.—Mar.	45,480	45,076	404	31	37	40	11	29	8	10	94	15	2	257	39
II Apr.—Jun.	47,048	46,629	419	20	43	33	16	40	9	6	80	22	3	250	40
III Jul.—Sep.	45,559	45,148	411	34	35	19	9	36	8	13	98	13	0	170	33
IV Oct.—Dec.	41,065	40,721	344	26	46	21	14	33	10	8	85	12	2	169	27

* Monitoring of these categories began Jan. 1, 1976. Previous years' data were obtained from the Hungarian Congenital Malformation Registry.

International collaboration is of basic importance in the monitoring of birth defects. This is why the WHO initiated a cooperation in 1972. First 8, at present 11 countries send quarterly reports on the figures of ICMs to the international centre. The collaborating countries do not use identical criteria (Table II). Moreover, some problems have arisen in certain programmes (e.g. the low number of births in the material of Israel, the lack of base-line data in France, the Swedish monitoring system is just being reorganized). In spite of the difficulties, the international monitor system ensures early information for specialists about a cluster occurring in any participating country. Thus, it can be established whether the trend is a general or a local one. The National Foundation, established from international funds, undertook to give professional and financial support to clarify the aetiology of real clusters and to issue documents on new potential teratogenic noxae. Since 1972, the National Foundation and the WHO have convened the heads of the national monitors every year, thus the national monitoring systems work in a closer co-operation and can use standardized methods.

At present, the activities of the HCMM are as follows.

(i) Monitoring of ICMs according to the principles and methods defined in the international collaborative study. The present paper reports on this activity.

(ii) The country-wide follow-up of multiple malformations conducted since 1973 in co-operation with 6 regional centres.

(iii) Monitoring for chromosomal mutations recorded in the Hungarian Chromosomal Aberrations Register [8], in the framework of the Repository of Chromosomal Variants and Anomalies in Man (The Johns Hopkins University).

Operation of the Hungarian Congenital Malformation Monitor

Reporting of congenital malformations diagnosed in the first year of life in liveborns or in stillborns has been compulsory since 1962. From January 1, 1970, onwards, the Hungarian Congenital Malformations Register (HCMR) operating at the Laboratory of Human Genetics, National Institute of Hygiene, has taken over the processing and evaluation of data. Because of increasing demands, the Hungarian Congenital Anomaly Surveillance was established and entrusted with other tasks, such as monitoring. Since January 1, 1973, the number of ICMs are entered into two tables. The first comprises the figures of ICMs according to 25 Hungarian administrative units, the second according to distribution during the 12 months of the year. Ninety days after the end of a given quarter, the cumulated data are sent to the centre of International Clearinghouse for Birth Defects Monitoring System (Table III). (Regional evaluation is done by the National Centre [9].) The Quarterly Report published by the National Foundation summarizing the recorded

TABLE II

Participating in the International Clearinghouse for Birth Defects Monitoring System

Monitoring system	Number of births (Apr.—Jun., 1977)			Maximum age at diagnosis	Criteria defining stillbirths	Data used for baselines	Program director
	Total	Livebirths	Still-births				
Canada: 4 Provinces (Alberta, British Columbia, New Brunswick, Manitoba)	25,444	25,240	204	7 days (168 hours) and reported within 45 days	20 weeks and/or 500 grams	4 quarters of 1976 plus 1st quarter 1977	Dr. Philip Banister, Director, Bureau of Surveillance Services Room 12A, L.C.D.C., Tunney's Pasture, Ottawa, Ontario K1A OL2, Canada Telephone: (613) 992-7995
Province of Ontario	32,309	32,020	289				
Czechoslovakia:	49,709	49,421	288	Hospital discharge (usually 5 days)	28 weeks and/or 1,000 grams	1961—70	Dr. Jiri Kučera, CSc. Institute for Health Statistics nabr. K. Marxe 157 147 10 Praha 4 — Podoli, ČSSR
England and Wales	137,000	*	*	Usually 36 hours	28 weeks	1972	Dr. J. A. C. Weatherall O.P.C.S. St. Catherines House, 10 Kingsway London WC2B 6JP, England Telephone: 01-242-0262
Finland	17,306	17,216	90	1 year (90% within 14 days)	180 days	1970—75 (1975 for codes 749.0, 750.2, 571.2, 752.2, 755.2, 755.3)	Mrs. Anneli Ruusinen National Board of Health Siltasaarenkatu 18 00530 Helsinki 53 Finland Telephone: 90-718511
France: Rhône-Alpes region	19,160	18,975	185	7 days	28 weeks	Not compiled	Dr. Madeleine Dessemond Department of Medical Genetics Hôpital de l'Hôtel Dieu 1, rue de l'Hôpital 69288-Lyon Cedex 1, France

Hungary	46,956	46,564	392	1 week and reported within 90 days	28 weeks	1973—76	Andrew Czeizel, M.D. National Institute of Hygiene IX. Gyáli út 2—6. 1966 Budapest, Hungary Telephone: 142-250
Israel: Kaplan Hospital Rehovot	1,186	1,174	12	Hospital discharge (usually 4 days)	28 weeks	1966—68	Prof. Marcus A. Klingberg, M.D. Head, Department of Epidemiology Israel Inst. for Biological Research P.O.B. 19, Ness-Ziona, Israel Telephone: (03) 958861
Norway	13,789	13,625	164	9 days	16 weeks	1967—71	Prof. Tor Bjerkedal Institute of Hygiene Gydas vei 8 Oslo 3, Norway Telephone: (02) 466850
South America: 20 Hospitals in 7 countries (Argentina, Brazil, Chile, Ecuador, Peru, Uruguay, Venezuela)	*	14,893	*	72 hours	Not included	Not compiled	Dr. Eduardo Castilla Laboratorio de Genetica Inst. de Biologia/Univ. de Brasilia Brasilia 70.000, DF, Brazil Telephone: 72.00.00, Ext. 2161
Sweden	*	*	*	Usually 7 days	28 weeks	1965—72	Prof. Bengt Källen Dept. of Embryology University of Lund S-223 62 Lund, Sweden Telephone: 046-11 25 50
United States:							
Metropolitan Atlanta	6,172	6,104	68	Hospital discharge (80% by the 7th day)	20 weeks and/or 500 grams	1968—75	J. William Flynt, Jr., M.D. Center for Disease Control Building 1, Room 5112 Atlanta, Georgia 30333, U.S.A. Telephone: (404) 633-3311 Ext. 3961
1200 Hospitals nationwide	195,701	193,913	1,788	Hospital discharge (usually 7 days)	20 weeks	1970—73	

* Not available.

TABLE III

Data for births occurring in 1975

Data used for calculation of baseline rates: *Hungarian Congenital Malformation Monitor 1973—1974*

Category	Base-line Rate/ 10.000	Quarter of birth: January 1 - March 31			April 1 - June 30			July 1 - September 30			October 1 - December 31		
		Expected Number	Observed Number	Rate	Expected Number	Observed Number	Rate	Expected Number	Observed Number	Rate	Expected Number	Observed Number	Rate
Total births			50087			50350			50364			44939	
Liveborn			49684			49940			49989			44552	
Stillborn			403			410			375			387	
Selected malformations:													
740 Anencephaly	9.8	49	44	0.90	49	37	0.76	49	52	1.06	44	27	0.61
741 Spina bifida	13.1	66	57	0.86	66	56	0.85	66	71	1.08	59	55	0.93
742 Hydrocephalus	7.6	39	41	1.05	38	34	0.89	38	40	1.05	34	31	0.91
749.0 Cleft palate	3.8	19	14	0.74	19	13	0.68	19	15	0.79	17	17	1.00
749.1, .2 Total cleft lip	11.8	59	64	1.08	59	46	0.78	59	49	0.83	53	41	0.77
750.2 Oesophageal atresia and stenosis	2.2	11	10	0.91	11	6	0.55	11	13	1.18	10	10	1.00
751.2 Rectal and anal atresia	2.8	14	12	0.86	14	7	0.50	14	11	0.79	12	13	1.08
752.2 Hypospadias	12.1	61	86	1.41	61	97	1.59	61	52	0.85	54	87	1.61
755.2 Reduction deformity upper limb	0.9	4	20	5.00	4	23	5.75	4	27	6.75	4	19	4.75
755.3 Reduction deformity lower limb	0.6	3	12	4.00	3	13	4.33	3	10	3.33	2	8	4.00
755.6 Congenital dislocation of hip	59.1	296	364	1.23	297	356	1.19	297	379	1.27	265	305	1.15
759.3 Down syndrome	7.3	36	32	0.86	36	41	1.14	36	51	1.41	33	32	0.97

cases is sent four times yearly to the heads of the national centres.

In the course of monitoring, the following items require special attention.

1. The principle of monitoring babies with two or more congenital malformations. Thus, it may be questionable whether newborns with anencephaly, cleft lip and dislocation of the hip should be monitored at all, since multiple malformations are not ICMs. Or anencephaly, in itself being the principal ICM should be monitored, or else all the three malformations have to be taken into consideration independently as they all represent ICMs. We follow the practice of keeping two parallel monitoring records, one for isolated ICMs and one for those occurring as part of unspecified multiple malformations. The latter facilitates the recognition of clusters of congenital malformation syndromes and associations. The sum-total of the two values is reported to the International Centre (Table IV).

2. The interval between birth and monitoring should be short in order to detect the clusters as early as possible. In compliance with the international agreement, only notifications received within 90 days after birth are taken into account. In consequence, notifications after the deadline have to be disregarded in monitoring. Table III illustrates the number of monitored ICMs as compared to the registered number of congenital malformations in the HCMR up to the last day of the year following birth. Surprisingly, anencephaly and lower limb reduction malformations are represented in higher numbers in the HCMM of 1975. The difference can be ascribed to the monitoring of ambiguously notified ICMs, and to the fact that ICMs constituting a part of unspecified multiple malformations had been taken into account in the HCMM but not in the HCMR. It is the case of later identified syndromes which are coded into the specified malformation syndrome entities. With the exception of hydrocephalus, values below 80% represent ICMs with internal localization.

3. Monitor values for the individual ICMs differ because some ICMs occurred in very low numbers, and also because much depends on the validity and reliability of the diagnosis. For instance, the diagnosis of congenital dislocation of the hip is based on Ortolani positivity, therefore babies with unstable hip joint too may be reported. It would seem justified to exclude congenital dislocation of the hip from the ICMs, and to include exomphalos. Hydrocephalus is often diagnosed erroneously in macerated stillborn babies. The diagnosis at birth of Down syndrome requires great clinical experience.

The monthly, quarterly and yearly trends of non-indicator congenital malformations registered in the HCMR are also checked. This may contribute to selecting the most suitable ICMs, and to detect possible clusters in non-ICMs. Attempts have been made to adopt the HCMR to computerized data processing and to demonstrate any clusters occurring in all congenital malformations.

TABLE IV

Quarterly number of indicator CMs

Quarter of birth	Number of births			Denomination of indices	Indicator congenital		
	Total	Live	Still		Anencephaly	Spina bifida	Hydrocephalus
Total	195,740	194,165	1575	HCMM	160	239	164
				HCMR	(156)	(243)	(200)
				%	102.6	98.4	73.0
Jan.—Mar.	50,087	49,684	403	HCMM	44	57	41
				HCMR	(44)	(56)	(56)
				%	100.0	101.8	73.2
Apr.—Jun.	50,350	49,940	410	HCMM	37	56	34
				HCMR	(42)	(54)	(47)
				%	88.1	103.7	72.3
Jul.—Sep.	50,364	49,989	375	HCMM	52	71	40
				HCMR	(42)	(61)	(46)
				%	123.8	116.4	87.0
Oct.—Dec.	44,939	44,552	387	HCMM	27	55	31
				HCMR	(28)	(72)	(51)
				%	96.4	76.4	60.8

EVALUATION OF CLUSTERS

Changes in the absolute number of ICMs are evaluated by three methods in the HCMM.

1. Based on the baseline data that is the occurrence of ICMs in the 3 previous calendar years, the expected absolute number (E) of a given ICM per 10,000 births is calculated for the given quarter. This is compared to the observed quarterly number (O) of the specific ICM by means of the O/E ratio (Table III). The quotient obtained may be considerably above 1, around 1, or considerably below 1. The problem is what to regard as considerable? At the first approach, plus and minus 0.50 and greater deviations are taken as a "warning sign". (It goes without saying that in the evaluation of deviations the number of a given ICM is also important.)

2. The preliminary evaluation described above is supplemented by the following biomathematical analyses if a "warning sign" is observed.

(i) Standard deviation can be calculated from the baseline data. If the observed quarterly value is above the expected plus 2 SD, it is taken as a "danger sign"; if above the expected value plus 3 SD it is taken as an "alarm sign".

(ii) By the help of the χ^2 test, the p value of the difference between expected and observed ICMs can be calculated.

(iii) The Cusum (cumulative sum) method [6, 10].

3. The duration of a cluster is also of importance. Changes in case numbers are analysed monthly in HCMM. In international cooperation, a significant increase for a given quarter requires conceptual commen-

in the HCMM and in the HCMR, 1975

malformations								
Cleft palate	Cleft lip ± palate	Oesophag. atresia	Rectal atresia	Hypospadias	Red. Def. Upper	Red. Def. Lower	Cong. Hip. Disloc.	Down syndrome
59	200	39	43	322	89	43	1404	156
(78)	(231)	(52)	(64)	(352)	(90)	(39)	(1529)	(168)
75.6	86.6	75.0	67.2	91.5	98.9	110.3	91.8	92.9
14	64	10	12	86	20	12	364	32
(20)	(65)	(11)	(12)	(93)	(30)	(10)	(386)	(35)
70.0	98.5	90.9	80.0	92.5	66.7	120.0	94.3	91.4
13	46	6	7	97	23	13	356	41
(18)	(55)	(9)	(10)	(98)	(18)	(11)	(379)	(46)
72.2	83.6	66.6	70.0	99.0	127.8	118.2	93.9	89.1
15	49	13	11	52	27	10	379	51
(17)	(57)	(16)	(20)	(74)	(25)	(9)	(366)	(45)
88.2	86.0	81.3	55.0	70.3	108.0	111.1	103.6	113.3
17	41	10	13	87	19	8	305	32
(23)	(54)	(16)	(19)	(87)	(22)	(9)	(398)	(42)
73.9	75.9	62.5	68.4	100.0	86.4	88.9	76.6	76.2

tary. A cluster observed for two consecutive quarters can be regarded as an "alarm situation" calling for international consultation. If perusal of relevant literature and consultation can exclude the possibility of technical biases, case-control epidemiological study has to be organized, trying to reveal the aetiological factor(s).

Some important rising trends in Hungary between 1973 and 1976

Evaluating the changing trends in ICMs, attention is mainly focussed on increased occurrence. (Nevertheless, decreased occurrence too deserves attention because of the underlying causes e.g. neglect of reporting, decrease in occurrence due to unknown causes or to the effect of introduced preventive measures.)

An increase in ICMs can be divided into two types.

1. *Continuously* increasing trend. Between 1973 and 1976, three ICMs showed such trend: congenital dislocation of the hip, congenital limb reduction malformation (CLRM) and hypospadias (Fig. 1).

Since point prevalence at birth of congenital dislocation of the hip is 2.8% in Hungary [2], it can be taken for granted that the increase was the result of the more frequent diagnoses owing to the extension of orthopaedic screening of newborns. CLRM increased to a small extent in 1974, considerably in 1975 and 1976. It seems to be a real cluster. The unbroken rising trend of hypospadias necessitates a detailed evaluation which is in progress.

2. *Transitional* clusters observed for shorter periods (Fig. 2). Such were

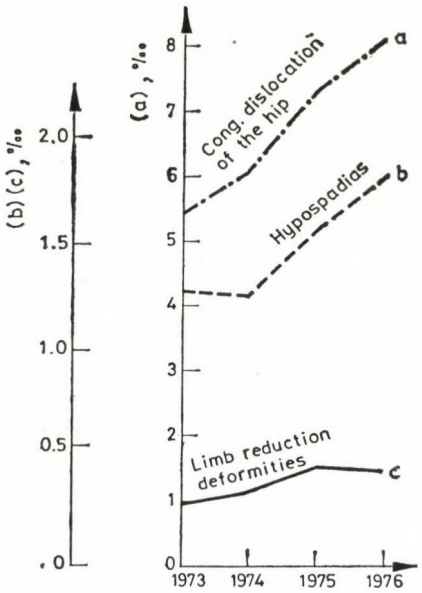

FIG. 1. A continuous increasing annual trend of three congenital malformations in the material of the Hungarian Congenital Malformation Monitor

anencephaly in the 4th quarter, 1974; spina bifida in the 2nd quarter of 1974, in the 3rd quarter of 1975 and in the 4th quarter of 1976; further cleft lip ± palate in the 3rd quarter, 1973. Biomathematical analysis proved that these increases have reached the level of a danger sign, with the exception of anencephaly in the 4th quarter, 1974, as it showed the alarm sign. Occurrence in the consecutive quarters, howewer, was not above the expected figure in these ICMs, thus no "alarm situation" developed and no epidemiological survey had to be conducted.

In accordance with the increasing yearly trends in hypospadias and CLRM, the quarterly values corresponded to a danger sign. Hypospadias reached the level of an alarm sign in the 1st and 4th quarters of 1976. In 1975, the frequency of CLRM indicated an "alarm situation". Investigations of the underlying causes will be published elsewhere [4].

Beside operating the HCMM, the frequency of all congenital malformations represented in the HCMR is regularly evaluated. Fig. 3 shows notably higher occurrence of cleft lip ± palate in 1972, of congenital pyloric stenosis in 1971, of congenital hypothyroidism in 1974. At present, no explanation can be offered for these observations.

The analysis of a periodic occurrence of congenital malformations can be useful from several other aspects, e.g. the occurrence of all and the specific types of congenital malformations have been evaluated for months

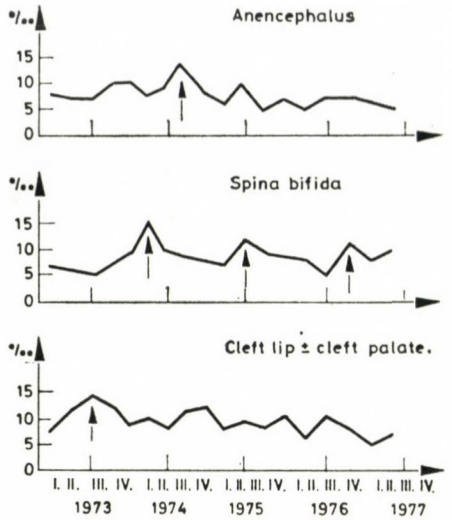

FIG. 2. Transitional clusters in the quarterly occurrence of three congenital malformations in the material of the Hungarian Congenital Malformation Monitor

following a great influenza epidemic (Fig. 4). No correlation was noted and this speaks against the teratogenic effect of *Myxovirus influenzae-A*.

ANALYSIS OF CLUSTERS

When biomathematical analysis has proved that more than a chance cluster had occurred, the possibility of three technical biasing factors has to be excluded before accepting the fact of a real epidemic.

1. Changes in the diagnosis of the given congenital malformation.

(i) New examination procedures (e.g. PKU or orthopaedic screeing can considerably increase the fre-

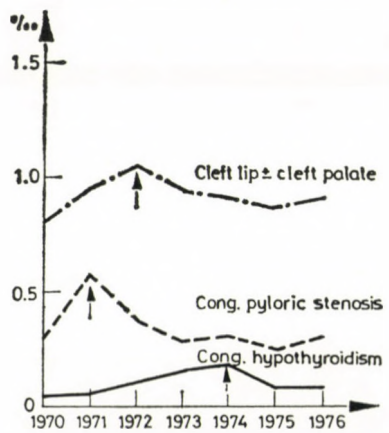

FIG. 3. Higher annual occurrence of three congenital anomalies in the material of the Hungarian Congenital Malformation Register

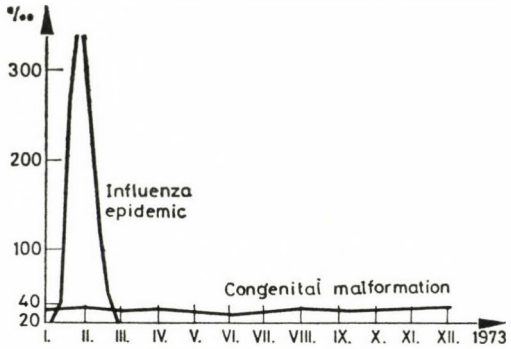

FIG. 4. There wars no correlation between the occurrence of congenital malformations and the influenza epidemic in 1973

quency of diagnosed cases. In internal malformations there will be a parallel increase with the increase in the frequency of necropsies.

(ii) Changes in diagnostic attitudes. Reporting of minor variations or of borderline cases will primarily elevate the number of mild malformations.

(iii) More accurate definition or classification of a given congenital malformation can increase its participation usually at the expense of another malformation.

All the three biasing factors could be excluded in the case of CLRM [4].

2. More complete notifying.

(i) Data of the HCMR show that in 1975 the occurrence of all reported congenital malformations increased by 18.4% as compared to the period 1971—1974. In contrast, the increase in the occurrence of CLRM amounted to 48.3%, more than two-fold of all congenital malformations.

(ii) A comparison of international data. The point-prevalence at birth of CLRMs varies for example between broad limits (0.25—0.82 per 1000 total births). This is mainly due to differences in notification [5]. Significant increases were, however, observed in other countries too, so e.g. in Canada [1].

An estimated 30% increase in CLRM cases but by no means the whole, could be attributed to improved completeness of notification.

3. Changes in the evaluation and recording of notified cases. It was excluded in CLRMs.

An estimate of 0.3—0.4 point prevalence per 1000 total birth of CLRM seems to be the real figure in Hungary. The 1971—1974 findings correspond to this value. However, in 1975 and 1976 the occurrence was somewhat less but significantly increased.

POLICY IN REAL CLUSTERS

If a significant cluster is observed exceeding the limits allowed by chance for over six months, i.e. facing an "alarm situation", actions should be introduced to detect possible aetiological factors. It is generally recom-

mended to carry out a retrospective case-control epidemiological study with personal interviews and matched controls. The stages of an epidemiological study are as follows.

(i) *Careful preparation.* It involves the perusal of the literature and preliminary consultations with experts. It is of major importance that different nosologic (aetiologic) types of the given malformations be treated separately.

(ii) *Selection of controls.* The mode of selecting matched controls depends on the character of the given malformation. The date of birth (at least the same week), the place of birth (at least the same district or city) and sex are essential criteria. In principle, matched control cases have to be identical in every but one parameter: the occurrence of the congenital malformation under study. Overdone matching may, however, hinder the tracing of adequate controls and useful information may be lost. For instance, if identity of the social status of the parents is set as a criterion, it will be impossible to examine the effect and importance of this very factor on malformation prevalence.

(iii) *The epidemiological study.* It is a drawback of retrospective case-control surveys that the parents of the index patients and especially the mothers speculate too much about the alleged or real causes why the child was affected by the malformation. As a consequence, the mother can give more accurate answers but also subjectively exaggerated ones. In contrast, the mothers of the matched controls meditate less upon their previous pregnancies, thus give less detailed answers. The distorting effect of this factor can be illustrated by the frequency at which the taking of common harmless drugs is listed. To eliminate this disturbing effect, the following can be recommended.

(a) Personal interview with the parents of the index patients and the controls. Preferably, one and the same person should interview both groups, using identical methods.

(b) Checking and supplementation of interview information by the "prospective" data recorded in the course of prenatal care.

(c) Special emphasis on the critical period when the given malformation develops. Concentrating the questions to this period may considerably improve the value of information.

If an aetiological correlation has been revealed, a prospective survey has to be organized, and it is preferable to extend the survey to other countries.

The monitoring of congenital malformations done in international collaboration is one of the most important means in detecting new and old aetiological factors. It contributes to the limitation of their effects and in turn to the decreased occurrence of certain congenital malformations.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 239–243 (1978)

The changing face of paediatric surgery

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Received January 11th, 1978

The position and security of a child in society is generally taken as a reflection of the stage of development of that society. Treatment of the sick child, especially of the surgically sick child, was an aspect of the development of medical services that had to take low priority until quite recent years. Progress in surgery has always been closely related to war surgery; the return of the wounded soldier to battle is, after all, logistically important and, furthermore, even the most ardent defender of his homeland will go to war with more confidence in the knowledge that a surgeon awaits to heal his wounds should he become a casualty. The civilian population historically had to content themselves with the peacetime spin-off of wartime advances and the children came last.

Although some children's hospitals claim existence for five hundred years or more, these were not hospitals designed for curing disease but for the care of abandoned children and in some cases for the care of the severely handicapped. Hospitals for the surgical correction of diseases in children were unthinkable in the pre-Listerian era, an era when any surgeon who had the courage to publish his results had to admit to an overall post-operative mortality rate of something over 90 percent. It was not until the introduction of antiseptic methods, closely followed by asepsis that the ratio of those surviving and those dying following surgical procedures was reversed, and it was then that children could be included amongst those to benefit from the new advances in surgery and children's hospitals began to be opened all over the western world. This period of active surgical advancement and the opening of children's hospitals occurred only 100 years ago.

For the first 50 years of the existence of our present children's hospitals the surgical admissions always accounted for more than half the total admissions as they do now. Those admissions were very largely for the treatment of acute and chronic infection, especially tuberculosis of bones and joints; those congenital anomalies which were treated were those that threatened function not those that

threatened life. Improvements in social conditions and in drug therapy, particularly in the 1930's, first reduced the incidence of tuberculosis and later reduced the demands for surgical treatment of pyogenic infections and it was in the late 1930's that the paediatric surgeon was beginning to face up to the problems of the treatment of congenital abnormalities which were incompatible with life.

Neonatal Surgery

It is likely that the development of techniques for the surgical management of congenital abnormalities in the newly born also owes a great deal to war surgery. In the 1940's further improvements in social conditions, together with the emergence of new antibiotics so reduced the infant mortality rate attributable to prematurity and infections that the hard core of deaths from congenital abnormalities was exposed. The paediatricians faced with this group of patients whose congenital abnormalities were life threatening looked for surgical assistance to correct those abnormalities; and experience gained in the battle fields in resuscitation and the treatment of shock, as well as in anaesthesia, opened new fields for major surgery in the first few days of life. Experience gained in the management of these neonates and the introduction of valved drainage systems for the control of hydrocephalus led also to an aggressive attack on open myelomeningocele during the neonatal period in many centres. Certainly in the United Kingdom it was this new surge of material producing about 100 cases for admission to a neonatal surgical unit for each million population that resulted in the development of a number of regional neonatal surgical centres with the consequent appointment of paediatric surgeons who would care not only for those neonatal surgical cases but for the surgery of older children.

The 1950's and 1960's were years of advancement and consolidation in the care of congenital abnormalities starting very largely in the neonatal period. New operations and techniques of management were developed which led to a marked reduction in mortality rates and an improvement in the quality of life of the survivors. In many instances, for example in oesophageal atresia, diaphragmatic hernia and intestinal atresias, babies born with a condition incompatible with life survived to live perfectly normal lives.

In other conditions, notably myelomeningocele, survival rates were increased but so was the number of severely handicapped survivors. Indeed, as results improved, so did early diagnosis of congenital abnormality and an increasing number of children often of very low birth weight with multiple abnormalities, were referred for surgery; in these children correction of the primary abnormality is often possible but there is serious postoperative morbidity attributable to the complications of low birth weight or to the associated anomalies.

In the United Kingdom in particular, and in some other countries the

long term survivors with myelomeningocele with severe handicap have caused a number of referring paediatricians to refrain from referring all such children for surgery believing that the end results do not justify the strain on hospital resources and family care.

Over the past five years attempts at selection of those children likely to benefit from aggressive treatment have resulted in a 50% reduction in the number of myelomeningoceles admitted during the neonatal period. During the same period there has been a very considerable drop in the birth rate in most European countries and this fall of 25% or more has probably reduced the incidence of congenital abnormalities disproportionately since the fall in the birth rate is particularly marked in women under 20 and over 32 years of age, the women in whom there is a slightly increased incidence of congenital abnormalities. The overall result in Liverpool has been a reduction of the admissions to the Neonatal Surgical Unit in Liverpool from 259 in 1971 to 165 in 1976.

It was neonatal surgery which accounted for the increased recognition of paediatric surgery and any decrease in it must cause some concern, particularly with regard to material available for training. However, provided the Regional Neonatal Surgical Unit serves a population of two million or more, there are still likely to be at least 100 admissions each year and concentration of effort on these children should improve results. New techniques in open heart surgery in the very small child are likely to lead to an increase in the amount of open heart surgery in the neonate. Paediatric surgeons undertaking the care of the newborn, must increasingly be prepared to undertake total care; there is no place for dealing with only one part of a child's multiple anomalies. For instance, if a child with oesophageal atresia is known to have a severe ventricular septal defect then the oesophageal atresia should not be repaired unless it is intended that the ventricular septal defect will also be repaired if necessary in the first few days of life. The increasing contributions of intensive care, especially ventilatory care, will continue to improve the survival of very small children and, hopefully, to improve the quality of life in the survivors, and very close association between the surgeon, the anaesthetist and the neonatologist become increasingly important.

Surgery of Malignant Disease

The establishment of national and international groups for the study of tumours in children has resulted in the pooling of information and some remarkable improvements in survival rates in spite of the fact that malignant tumours are rare: indeed, not only are tumours rare but the varieties are few and it has thus been possible to concentrate on specific types. Improvements in radiotherapy and the use of cytotoxic drugs have altered the function of the surgeon; combined

treatment is essential and the days of massive destructive surgery are probably past with far more attention paid to the quality of life of the long-term survivor. However, the surgeon still has an important part to play. Few would argue that complete excision was not the treatment of choice in a tumour that was confined to its primary site; and when the disease is more widespread, staging will usually depend on the surgeon and reduction of tumour bulk or removal of residual tumour after other forms of therapy may often be indicated.

System Specialties

Traditionally, the part played by the system specialist varies from centre to centre. Otorhinolaryngology and ophthalmology in children are almost universally practised by adult specialists. Orthopaedic surgery in children is a major problem and, if not practised by a paediatric surgeon, it is often practised by an orthopaedic surgeon who devotes the majority of his time to the treatment of children. Plastic surgeons often overlap with paediatric surgeons in the care of cleft lip and palate and many other soft tissue anomalies. Urology is an area of competition in many centres; urologists tend to believe that urological conditions in childhood persist into adult life and therefore the child should be cared for by the adult system specialist. But urological conditions in childhood pose many problems different from those in adults and, in general, advances in paediatric urology have come from paediatric urologists; the clinical material in the larger paediatric surgical centres will provide sufficient work for at least one surgeon to concentrate on urology and it is to be hoped that the number of paediatric urologists will increase in the next decade.

Trauma

If 60% of the admissions to a paediatric surgery unit can be attributed to congenital abnormalities of some variety, then another 30% can be attributed to trauma, and in spite of the work of many committees on the prevention of accidents this total is unlikely to change appreciably in the coming years.

The work load of a paediatric surgeon therefore will not appreciably diminish until the effect of reduction in the birth rate makes itself apparent in the reduction of the total child population; and it is rather doubtful if this situation will ever occur, since the reduced birth rate is more likely to reduce population increase rather than produce an actual decrease.

In the United Kingdom the hospitals account for 67% of the National Health Service budget: but children who account for 25 of the total population take up only 17% of hospital beds and no more than half of these children are undergoing surgery. These children therefore account for only a very small part of the total hospital population. Yet 90% of hospital admissions in paediatric surgery are

emergencies. The responsibility of the paediatric surgeon is much greater than the size of his specialty; his patients cannot speak for themselves but he must obtain for them the highest priority; in no other specialty can one look for 75 year survivals.

The paediatric surgeon must also deliver to his patients the highest standards of surgery and justify his specialty by the excellence of his service. In a small specialty international co-operation is of the utmost importance and paediatric surgeons can modestly claim to have achieved a very high level in the exchange of experience between nations. The first large national association was The British Association of Paediatric Surgeons and at its foundation almost 25 years ago, one third of its members were from overseas; today, of a total membership of over 400, over 300 members are from a total of 60 countries abroad. It is at the international congresses organised by the B.A.P.S. and other associations that problems in paediatric surgery are identified and hopefully that research projects are developed to solve them; world wide communications are facilitated by the World Federation of Associations of Paediatric Surgeons which now has 34 member societies from all continents.

The specialty which is small nationally thus becomes much larger internationally; its strength lies in co-operation not only with paediatric surgical colleagues but also with other surgeons and with all those concerned in the care of children. The development of paediatric system specialists in the larger centres, especially in cardiac surgery and urology, and a closer relationship with paediatricians in such special fields as neonatology and oncology are areas in which advancements can be expected in the next few years.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 245—252 (1978)

Notwendige Operationen in der Neonatalperiode

von

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Eingegangen am 15. Januar 1978

Angeborene Fehlbildungen haben etwa 5—7% aller Kinder, einige von ihnen sind ohne operative Korrektur mit dem Leben nicht vereinbar. Bei den Fehlbildungen des Zentralnervensystems ist der operative Verschluß von Myelomeningozelen unmittelbar nach der Geburt notwendig, um eine aszendierende Meningitis mit Pyozephalus zu verhüten. Bei der Ösophagusatresie ist ein Überleben ohne Operation nicht möglich. Durch die extrapleurale Technik hat sich die Prognose wesentlich verbessert. Eigene Ergebnisse werden mitgeteilt. Fehlbildungen des Zwerchfelles, der Bauchwand und der angeborene Ileus erfordern ebenfalls operative Eingriffe bei Neugeborenen. Ausführlich wird die Differentialdiagnose des akuten Abdomens bei Neugeborenen dargestellt. Angeborene Fehlbildungen der ableitenden Harnwege verlangen nur in wenigen Fällen eine operative Korrektur bei Neugeborenen. Nur eine enge interdisziplinäre Zusammenarbeit zwischen Kinderchirurg, Neonatologen und Anästhesist führt zu Erfolgen in der Neugeborenen-Chirurgie. Wo diese Voraussetzungen fehlen, sollten heute Neugeborene nicht mehr operiert werden.

Eine stürmische Entwicklung vollzog sich in den letzten Jahrzehnten im Fachgebiet »Kinderchirurgie« insbesondere auf dem Gebiet der Neugeborenenchirurgie. Der operativtechnische Eingriff ist jedoch nur ein Teil des komplexen Behandlungsplanes. Die operative Korrektur zahlreicher, mit dem Leben unvereinbarer Fehlbildungen wäre nicht möglich gewesen, ohne die Entwicklung der modernen Anästhesie und ihrer gezielten Anwendungsmöglichkeiten bei Neugeborenen. Der darin erfahrene und speziell ausgebildete Anästhesist hat einen entscheidenden Anteil an den Operationsergebnissen. Frühzeitige Diagnose durch geschulte Neonatologen und Pädiater, neue Erkenntnisse über optimale prä-, intra- und postoperative Behandlung, moderne technische Voraussetzungen zur Überwachung, Operation und Pflege sowie ein darin speziell ausgebildetes Personal sind weitere Voraussetzungen für eine erfolgreiche chirurgische Behandlung der Neugeborenen. Sehr bald stellte sich heraus, daß die besten Ergebnisse in den Kliniken und Abteilungen zu erreichen waren, an denen diese Voraussetzungen gegeben sind. An anderen Stellen sollte heute die Neugeborenenchirurgie nicht mehr betrieben werden.

Welche Operationen sind bei Neugeborenen notwendig?

Innere Verletzungen unter der Geburt, z. B. Leber- und Milzruptur, werden sehr selten beobachtet (unter 1% aller operativen Eingriffe bei Neugeborenen). Hierbei ist eine Laparotomie sehr dringlich und lebensrettend.

Die meisten Operationen sind bei *angeborenen Fehlbildungen* erforderlich. Ein großer Teil ist ohne chirurgische Therapie nicht lebensfähig. Es besteht in diesen Fällen auch eine Dringlichkeit der Operation.

Immer aber ist eine angemessene Zeit zur notwendigen Vorbereitung dieser Neugeborenen erforderlich, um unter optimalen Bedingungen zu operieren und mögliche intra- und postoperative Komplikationen zu verringern. Man spricht daher auch vom »Prinzip der Dringlichkeit mit aufgeschobener Operation« [3].

Über die *Häufigkeit* von Fehlbildungen findet man im Schrifttum sehr unterschiedliche Angaben. Der Gesamtprozentsatz wird mit 5—7% aller Kinder angegeben. Bei der Geburt sind 1,5—3% bereits erkennbar, die restlichen Prozent werden im Kindes- und selten im Erwachsenenalter offenbar. Die Ursache für die unterschiedlichen Angaben liegt darin, daß der Begriff Fehlbildung nicht einheitlich verwandt wird, daß Untersuchungsgut und -Methodik sehr unterschiedlich sind und in den meisten Ländern keine Meldepflicht besteht. Auch wir in der DDR können an Hand des dokumentationsgerechten Krankenblattes nur Behandlungsfälle registrieren, die Feststellung der absoluten Zahlen ist schwierig.

Im Auftrage der WHO wurde eine internationale statistische Klassifikation der Krankheiten, Verletzungen und Todesursachen erarbeitet. Die 8. Revision ist z. Z. auch in der DDR eingeführt. In der Klasse 14 (Nr. 740—759) sind die Fehlbildungen verzeichnet.

Folgende *Fehlbildungen des Zentralnervensystems* verlangen bereits beim Neugeborenen eine chirurgische Therapie: Bei den Myelomeningozelen ist der operative Verschluß sehr dringlich, weil auf der freiliegenden Myelonplatte der offene Zentralkanal mündet, über welchem sich sehr rasch eine aszendierende Meningitis mit nachfolgendem Pyozephalus entwickeln kann. Die Rückverlagerung der Myelonplatte mit Rekonstruktion des Duralsackes, Türflügelplastik und Hautdeckung wird daher schon wenige Stunden nach der Geburt vorgenommen. Die Operation erfolgt in Intubationsnarkose und Bauchlage. 1—3 von Tausend Neugeborenen werden mit einer Myelodysplasie, am häufigsten in Form der Myelomeningozele geboren. Bei einer jährlichen Geburtenzahl in der DDR von 150 000—200 000 ist mit einem Neuzugang pro Jahr von etwa 300 bis 400 derartigen Kindern zu rechnen.

Ein angeborener Hydrozephalus mit Hirndruckzeichen verlangt evtl. schon in der Neugeborenenperiode eine Ableitungsoperation. Durch Verwendung druckentlastender subkutan verlagerter Ventile läßt sich heute in 90% der Fälle ein progredientes Kopfwachstum

aufhalten. Um die gefürchteten Thrombosen, Embolien und Sepsisfälle nach ventrikulo-kardialen Ableitungsoperationen zu verhüten, bevorzugen wir heute die ventrikulo-peritoneale Drainageoperation mit Ventil.

Von den *intrathorakalen Fehlbildungen* ist die operative Korrektur der Ösophagusatresie dringlich und lebensrettend. Die Ligatur der Ösophagotrachealfistel und die Anastomose der Ösophagusteile erfolgt heute nicht mehr nach Thorakotomie und Eröffnung der Pleurahöhle, sondern retropleural nach Abschieben der parietalen Pleura. Durch Anwendung dieses technisch etwas schwierigeren Verfahrens gelang es, die postoperative Pneumonierate wesentlich zu senken.

Die Leistungsfähigkeit einer kinderchirurgischen Fachabteilung wurde immer gemessen an den Erfolgen in der operativen Behandlung der Ösophagusatresien. Wir sind in Greifswald nur eine kleine Abteilung und haben in den letzten 7 1/2 Jahren 23 Ösophagusatresien mit der extrapleuralen Technik operiert, davon 17 mit Erfolg. Das Ergebnis war nicht abhängig vom Geburtsgewicht, sondern von den Begleitfehlbildungen. Alle Neugeborenen ohne assoziierte Fehlbildungen haben überlebt und auch noch ein Teil mit Begleitfehlbildungen. So konnten wir ein Frühgeborenes von 1,400 g operieren, welches eine Ösophagusatresie mit unterer Ösophagotrachealfistel, eine Duodenalatresie und eine Omphalozele hatte. Alle Fehlbildungen wurden in einer Sitzung operativ korrigiert. Dieses Beispiel soll zeigen, welche Möglichkeiten der Kinderchirurg heute in enger kooperativer Zusammenarbeit mit dem Anästhesisten und Pädiater hat. Von der Ösophagusersatzplastik mit Kolon ist man bei Fehlen eines Teiles des thorakalen Ösophagus heute abgekommen. Vielmehr legt man nach Rehbein retropleural zwischen den genäherten Anteilen einen Faden, um den sich ein verbindender Kanal bildet, den man dann aufbougieren kann.

Von den *Fehlbildungen am Zwerchfell* ist am schwerwiegendsten der Zwerchfelldefekt mit Prolaps der Bauchorgane in den Thorax. Zahlreiche Synonyma sind für diese Fehlbildung in der Literatur gebräuchlich (s. Tab. I). Die operative Reposition

TABELLE I

Im Schrifttum gebräuchliche Synonyma für angeborene Zwerchfelldefekte

Kongenitale Zwerchfell-Lücke
Zwerchfell-Hernie
Bochdaleksche Hernie
Kongenitale postero-laterale Zwerchfell-Lücke
Persistierender pleuro-peritonealer Kanal
Pleuro-peritoneales Foramen
Kongenitaler Zwerchfell-Defekt
Pleuro-peritonealer Hiatus
Intrathorakaler Darmprolaps

der Bauchorgane mit Verschluß des Zwerchfelldefektes erfolgt von abdominal nach Querschnitt oder Rippenbogenrandschnitt. Für den Anästhesisten ergeben sich bei dieser Fehlbildung Schwierigkeiten in der optimalen Beatmung vor, während und nach der Operation, da gleichzeitig eine ausgeprägte Lungenhypoplasie auf der betroffenen Seite, die Gefahr eines Spontanpneumothorax beiderseits und eines postoperativen Zwerchfellhochstandes bestehen. Ähnlich sind die Verhältnisse bei den angeborenen Lungenzysten, welche eine respiratorische Insuffizienz verursachen und schon beim Neugeborenen eine Lobektomie erforderlich machen.

Die notwendigen Operationen bei Neugeborenen an der Bauchwand sind in Tab. II zusammengestellt. Die Nabelschnurbrüche werden, wenn irgend möglich, operativ behandelt. Die Pinselung mit 2%iger Mercurochromlösung und konservative Verfahren sind heute wegen der nachgewiesenen Quecksilber-Intoxikation verlassen. Bei kleinen Nabelschnurbrüchen rekonstruiert man sofort die Bauchdecke. Bei größeren Omphalozelen geht man nach Gross zweizeitig vor, indem man beim Neugeborenen zunächst nur die lateral mobilisierte Haut über dem Prolaps verschließt und die Rekonstruktion der Bauchdecke im 4.—5. Lebensjahr ausführt. Bei der Gastroschisis sind operative Reposition und Rekonstruktion der Bauchwand ebenfalls dringlich, zumal unter der Geburt eine Infektion der prolabierten Bauchorgane erfolgt. Besteht ein zu großes Mißverhältnis zwischen Bauchorgane und Fassungsvermögen der Bauchhöhle, kann man auch einen Plastikbeutel auf den Defekt aufnähen, aus welchem die Bauchorgane schrittweise in die Bauchhöhle zurückverlagert werden.

Irreponible und inkarzerierte Leistenhernien mit nachfolgendem mechanischen Ileus beobachtet man schon bei Neugeborenen, desgleichen die Hodentorsion. In beiden Fällen ist eine Operation dringlich.

Sehr vielfältig sind die Ursachen des angeborenen Ileus und des erworbenen Ileus, der beim Neugeborenen eine Laparotomie erforderlich macht (Tab. III). Besonders wichtig ist hierbei eine optimale Operationsvorbereitung, sehr von Nachteil für den intra- und postoperativen Verlauf eine überstürzte Operation unter ungünstigen Bedingungen. Unter den Darmatresien sind die Duodenalatresien am häufigsten. Die möglichen Operations-

Tabelle II

Notwendige Operationen im Neugeborenenalter an der Bauchwand bei:

Omphalozele
Gastroschisis
Irreponible Leistenhernie
Hodentorsion
Bauchwandphlegmone nach Nabelinfektion

Tabelle III

Ursachen des angeborenen und erworbenen Ileus beim Neugeborenen

Angeborener Ileus	
a) innere Verschlüsse	Darm-Atresie und -Stenose
	Mekoniumileus
	Mekoniumpfropfsyndrom
	Megakolon
b) äußere Verschlüsse	Pankreas anulare
	Fehlbildung der V. portae
	Drehungsanomalien des Darmes
Erworbener Ileus	Mesenteriallücken
	Innere Hernien
	Darminvagination

verfahren sind Membranexzisionen und die Anlage einer Duodeno-Duodenostomie, eine Duodeno-Jejunostomie jedoch nur in seltenen Fällen.

Bei den Dünndarmatresien ist man davon abgekommen, die Passage durch eine seit-zu-seit Anastomose wieder herzustellen. In den dabei entstehenden Blindsäcken spielen sich chronische Entzündungen mit Ulzerationen und Blutungen ab. Die Wiederherstellung der Darmkontinuität durch eine end-zu-end Anastomose ist wegen des erheblichen Kaliberunterschiedes erst nach Resektion des blindsackförmigen erweiterten oralen Darmstückes und bei bestimmter Technik möglich. Entweder wird gegenüber dem Mesenterium das aborale Darmstück längsinzidiert und somit angeschrägt oder vom proximalen Darmstück ein Keil reseziert. Bei oralwärts gelegenen Jejunalatresien kann man die Doppelschlauchtechnik nach Rehbein anwenden. Große Erfahrungen sind bei der operativen Therapie der verschiedenartigen ano-rektalen Fehlbildungen notwendig, um ein günstiges Ergebnis mit Kontinenz zu erreichen. Beim unkomplizierten Mekoniumileus ist es möglich, durch einen Gastrografin^{R}- oder Visotrast^{R}-Einlauf die Mekoniumentleerung in Gang zu bringen. Bei Erfolglosigkeit oder kompliziertem Mekoniumileus hat sich die Resektion des verstopften Ileum mit temporärer Ileostomie des aboralen Abschnittes und gleichzeitiger Fußpunktanastomose end-zu-seit bewährt, wobei das orale Stück in der Modifikation nach Rickham schräg von oben eingenäht wird.

Bei einer äußeren Duodenalstenose durch ein Pankreas anulare erfolgt eine Duodeno-Duodenostomie. Fehldrehungen und Lageanomalien des Darmes führen ebenfalls zum angeborenen Ileus und verlangen eine operative Korrektur, desgleichen die inneren Hernien, Mekoniumperitonitis und die Komplikationen einer bei Neugeborenen noch seltenen Enterokolitis und Perforationsperitonitis.

Sehr schwierig und manchmal oft nur bei großen persönlichen Erfahrungen möglich kann für den Kinderchirurgen die Stellung der Operationsindikation und die Differentialdiagnose zu den sog. extraabdominalen Ursachen des akuten Abdomens (Tab. IV) sein.

Erhält die Mutter unter der Geburt hohe Dosen von Opiaten, kann das Neugeborene eine abdominale Symptomatik mit Erbrechen zeigen. Die Krankheitszeichen bessern sich jedoch sehr rasch. Auffällig ist, daß die Kinder diabetischer Mütter häufig eine Ileussymptomatik mit galligem Erbrechen bieten. Die näheren Zusammenhänge, die zu diesen Erscheinungen führen, sind noch ungeklärt. Pathologische Befunde im Zuckerstoffwechsel dieser Neugeborenen sind nicht zu erheben. Die klinische Symptomatik bildet sich innerhalb einiger Tage zurück. Am ehesten wäre differentialdiagnostisch die Verwechslung mit einem Megacolon congenitum möglich und eine fehlerhafte Laparotomie für das Neugeborene eine große Gefahr.

Schwere Pneumonien beim Neugeborenen entwickeln sich entweder nach Aspiration von Fruchtwasser, besonders von infiziertem Fruchtwasser nach vorzeitigem Blasensprung, sowie deszendierend nach Intubation. Ein im Gefolge auftretender paralytischer Ileus kann mit seiner klinischen Symptomatik im Vordergrund stehen und darf nicht Anlaß zu einer Laparotomie sein.

Auch nach perinataler Hirnblutung, bei Enzephalomeningitis und Sepsis ist ein paralytischer Ileus möglich. Eine Sepsis entwickelt sich am häufigsten vom Nabel aus. Eine toxische Enteritis kann das Bild eines akuten Abdomens in der Neugeborenenzeit bieten, jedoch bei Auftreten von

Tabelle IV

Extraabdominale Ursachen des akuten Abdomens beim Neugeborenen

Opiatintoxikation der Mutter unter der Geburt
Kind einer diabetischen Mutter
Pneumonie
Sepsis
Hirnblutung
Enzephalomeningitis
Toxische Enteritis
Hochgradige Hydronephrose
Blasenhalsstenose
Hydrometrokolpos
Nebennierenrindeninsuffizienz
Elektrolytentgleisung
Hyperbilirubinämie
Grey-Syndrom

Komplikationen (Darmperforation, Darmgangrän, Konglomerattumor mit mechanischem Ileus) auch eine operative Therapie erfordern. Bei einem großen tastbaren Tumor im Unterbauch des Neugeborenen mit den klinischen Zeichen eines akuten Abdomens wäre eine Laparotomie in den meisten Fällen fehlerhaft. Handelt es sich bei dem Tumor um eine gefüllte, sehr wandhypertrophe Harnblase bei Blasenhalsstenose, beseitigt die Einlage eines Blasenkatheters schlagartig das akute Zustandsbild. Einen derben Tumor über der Symphyse tastet man auch beim Hydrometrokolpos. Das Krankheitsbild entwickelt sich infolge Atresien des Hymens und Verschlußmembranen in der Vagina, wobei zusätzlich die mütterlichen Östrogene die kindlichen Zervixdrüsen zur Sekretion veranlaßt haben. Der durch angestautes Sekret verursachte Tumor kann gleichzeitig die Urethra komprimieren und zur Harnrückstauung führen. Bei der Inspektion des Genitale sieht man in der Vulva die vorgewölbte Membran, deren Inzision zum Abfluß des Sekretes und zur Beseitigung des Tumors und der abdominalen Symptomatik führt. Die Zeichen eines akuten Abdomens mit hochgradigem Erbrechen beobachtet man auch beim adrenogenitalen Syndrom. Nach Korrektur der Elektrolytentgleisung und entsprechender fortgesetzter Substitutionstherapie verschwindet die Symptomatik. Inspektion des Genitale und Kenntnis über die Elektrolytwerte im Blut führen zur tatsächlichen Diagnose und verhindern Verwechslungen.

Aufgetriebene Abdomen, Erbrechen, graublasse Zyanose und unregelmäßige Atmung beobachtet man ebenso bei Neugeborenen oder Frühgeborenen unter Chloramphenikoltherapie (sog. Grey-Syndrom). Die Ursache hierfür beruht in einer ungenügenden Kopplungsmöglichkeit des freien Chloramphenikols an Glukuronsäure bei noch ungenügender Leberfunktion des Neugeborenen und dadurch bedingter fehlender Ausscheidung und Kumulation.

Die Kenntnis der aufgezeigten »extraabdominalen Ursachen« des akuten Abdomen beim Neugeborenen ist notwendig, um Fehldeutungen des Krankheitsbildes und fehlerhafte Operationsindikationen zu vermeiden. Auch wenn die abdominale Symptomatik im Vordergrund zu stehen scheint, führt eine sorgfältige Diagnostik zur Aufdeckung der wahren Ursachen und bewahrt die Neugeborenen vor Schaden.

Nur wenige *Fehlbildungen der ableitenden Harnwege* verlangen schon beim Neugeborenen eine operative Korrektur (monströse Hydronephrosen, Blasenhalsstenosen, Urethraverschlüsse, Meatusstenosen). Das gleiche trifft für die *Fehlbildungen an den Extremitäten* zu.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (3), pp. 253–262 (1978)

Altersspezifische Besonderheiten der Nebennierentumoren beim Kind

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Eingegangen am 1. Februar, 1978

Es werden die differentialdiagnostischen Unterscheidungsmerkmale der Nebennierentumoren zwischen Kindern und Erwachsenen besprochen. Anhand der Literatur und des eigenen Krankengutes konnte gezeigt werden, daß Nebennierentumoren im Kindesalter in bezug auf Häufigkeit, Lokalisation, Krankheitsbild und diagnostische Maßnahmen größtenteils andere Probleme als beim Erwachsenen bieten. Die Ähnlichkeit mit spezifischen pädiatrischen Krankheitsbildern kann zu Trugschlüssen führen. Diagnostische Maßnahmen sind nicht selten sehr schwierig. Hingegen bestehen keine wesentlichen Unterschiede bezüglich des therapeutischen Vorgehens.

Nur die im Kindesalter seltenen Tumoren von Rinde und Mark, den beiden Bestandteilen der Nebenniere, sollen an dieser Stelle besprochen werden, weil die verhältnismäßig häufigen, dem ektodermalen Bestandteil der Nebenniere entstammenden Sympatikusgeschwülste eine andere Problematik bieten. An der Kinderklinik und Kinderchirurgie der Mainzer Universität wurden in den letzten 10 Jahren 40 derartige Tumoren, jedoch nur 6 Tumoren der Nebennierenrinde und des Nebennierenmarkes beobachtet.

So konnten beispielsweise auch Hayles und Mitarb. [13] bis 1962 erst 222 hormonaktive Nebennierenrindentumoren bei Kindern registrieren. AGS-Symptomatik war in 2/3 der Fälle, Cushing-Symptomatik in 1/3 der Fälle vorherrschend. Von diesen Patienten überlebten nur 23 Kinder 2 Jahre lang. Hayles u. Mitarb. [13] konnten allerdings aus der Mayo-Klinik über 12 weitere Fälle berichten, von denen nur 1 Kind starb und bereits seit 1942 keines mehr.

Im Kindesalter sind die Kleinkinder am häufigsten betroffen und zwar Mädchen dreimal so häufig wie Knaben.

Nahezu alle Nebennierenrindentumoren sind hormonaktiv, wobei ein Cushingbild im Vordergrund steht, das häufig mit Virilisierung bei Mädchen und isosexueller Pseudopubertas praecox beim Knaben einhergeht. Einem reinen Cushing und reiner Virilisierung begegnet man ebenso selten wie Feminisierung, Hyperaldosteronismus und Hypoglykämie [23]. Funktionslose Tumoren kommen kaum vor.

Morbus Cushing

Im Gegensatz zum Erwachsenen, bei dem die Rindenhyperplasie im Vordergrund der Cushingursachen steht, handelt es sich im Kindesalter nahezu ausschließlich um Tumoren. 70 bis 80% des Morbus Cushing bei Kindern sind tumorbedingt, meist handelt es sich um Karzinome. Nur 10 bis 25% Tumoren bilden die Cushingursache bei Erwachsenen [10, 21]. In der Mayo-Klinik wurden von 103 Tumoren bei Mädchen, 94 Karzinome der Nebennierenrinde, von 64 Knaben 37 mit Nebennierenrindenkarzinomen beobachtet. Liegt eine Mischform mit Virilisation vor, dann handelt es sich nahezu immer um ein Karzinom. Auch spricht ein Cushing-Syndrom vor dem 10. Lebensjahr nahezu immer für einen Tumor, da die Hyperplasie erst nach Ausreifung der Nebennierenrinde entstehen soll. Allerdings läßt sich die tumorbedingte Virilisation auch schon bei Kindern unter 1 Jahr beobachten [3]. Es wird sogar über angeborene Rindenkarzinome berichtet. Selten sind auch paraneoplastische Cushing-Syndrome [20], bisher wurden im Kindesalter nur 33 derartige Fälle beobachtet [5].

Die für das Kindesalter spezifische Cushing-Symptomatik wurde in der nachfolgenden tabellarischen Übersicht zusammengestellt:

Charakteristische Cushing-Symptome im Kindesalter

Fettdepots an den Extremitäten.	Osteoporose → pathologische Fraktur.
Muskelatrophie an den Extremitäten (Muskelzylinderindex).	Hemmung des Längenwachstums.
Thymusatrophie.	Hemmung der Knochenreifung.

Die häufigen Mischformen mit Virilisierung können die Symptome verwischen, wobei besonders eine schnellere Knochenreifung und Muskelmassenzunahme zu Fehldeutungen führt [6]. Als Beispiel sei ein typischer Fall aus dem eigenen Krankengut dargestellt:

Bei einem 11 1/2-jährigen Mädchen mit nebennierenrindenkarzinombedingten typischen Cushing-Symptomen war bei der Aufnahme bereits ein großer Tumor in der linken Flanke zu tasten (Abb. 1a und b), der sich jedoch operativ makroskopisch völlig entfernen ließ. Die histologische Untersuchung erbrachte mit der Kapselinfiltration und Polymorphie den typischen Befund eines Nebennierenrindenkarzinoms. Wegen der guten Operabilität des Tumors ging postoperativ auch die Cushingveränderung (Abb. 2a und b) schnell zurück. Eindrucksvoll ist hier der Verlauf der Hormonbefunde (Abb. 3). Nach der Operation waren die Werte sofort stark abgefallen. Das Rezidiv war jedoch ein halbes Jahr später bereits klinisch sichtbar, noch bevor die Hormonwerte wieder langsam anzusteigen began-

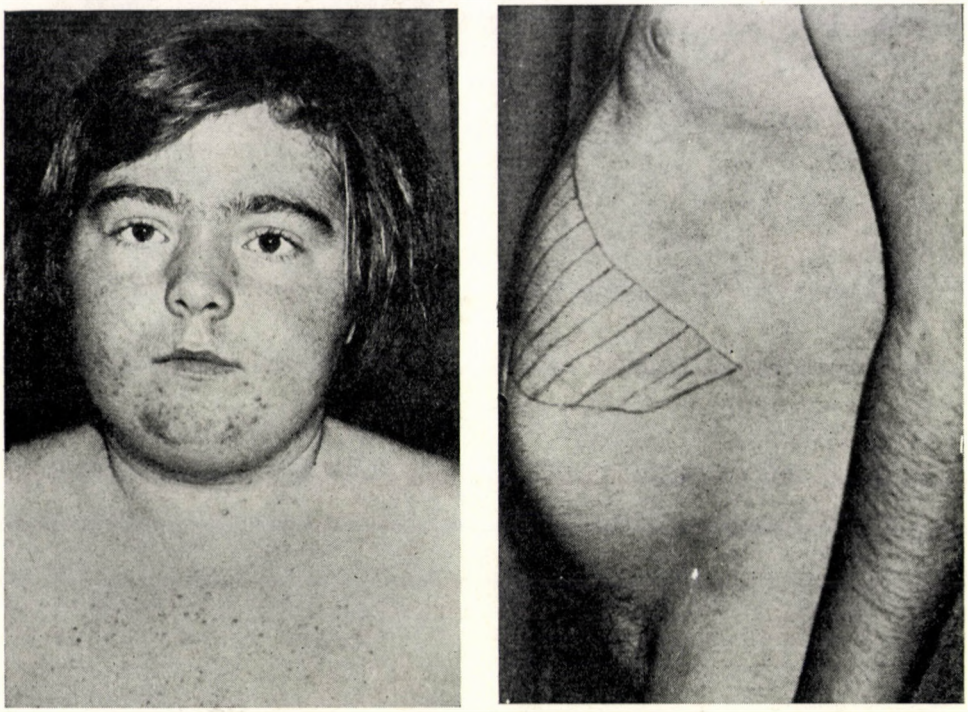

Abb. 1. Sp., C weiblich, 12 Jahre: Nebennierenrindencarcinom. a) typischer Cushing-Habitus: Mondgesicht, Akne; b) großer Tumor linke Flanke und Bauchseite

nen, um dann unter op-DDD erneut zum Normwert abzusinken. Das Cushingbild hatte sich neu entwickelt und blieb bestehen. Szintigraphisch und angiographisch wurde eine große Lebermetastase nachgewiesen; das Kind verstarb 12 Monate post operationem.

Ähnlich den Wilms-Tumoren und primären Leberkarzinomen sind Nebennierenrindenkarzinome häufig vergesellschaftet mit Fehlbildungen und Tumoren [8, 11]:

Angeborene Hemihypertrophie
Hirntumoren oder -Anomalien
Harnwegsfehlbildungen kontralaterale Nebennierenagenesie
Hamartome

Diagnostisch kommt der steroidchemischen Untersuchung besondere Bedeutung zu [14], welche die Domäne des pädiatrischen Endokrinologen ist. Allerdings müssen Nebennierenrindentumoren im Kindesalter nicht immer zu leicht erfaßbaren Veränderungen des Steroidstoffwechsels führen, so daß sie häufig aufwendigere diagnostische Maßnahmen erfordern. So wird heute zunehmend auch bei kleinen Kindern die Arteriographie eingesetzt; ebenso die selektive Splenographie mit selektiver Hormonanalyse, insbesondere beim Verdacht auf Marktumoren. Die Nebennierenszintigraphie mit ^{131}Jod-Cholesterin sollte bei Frauen vor dem 35. Lebensjahr

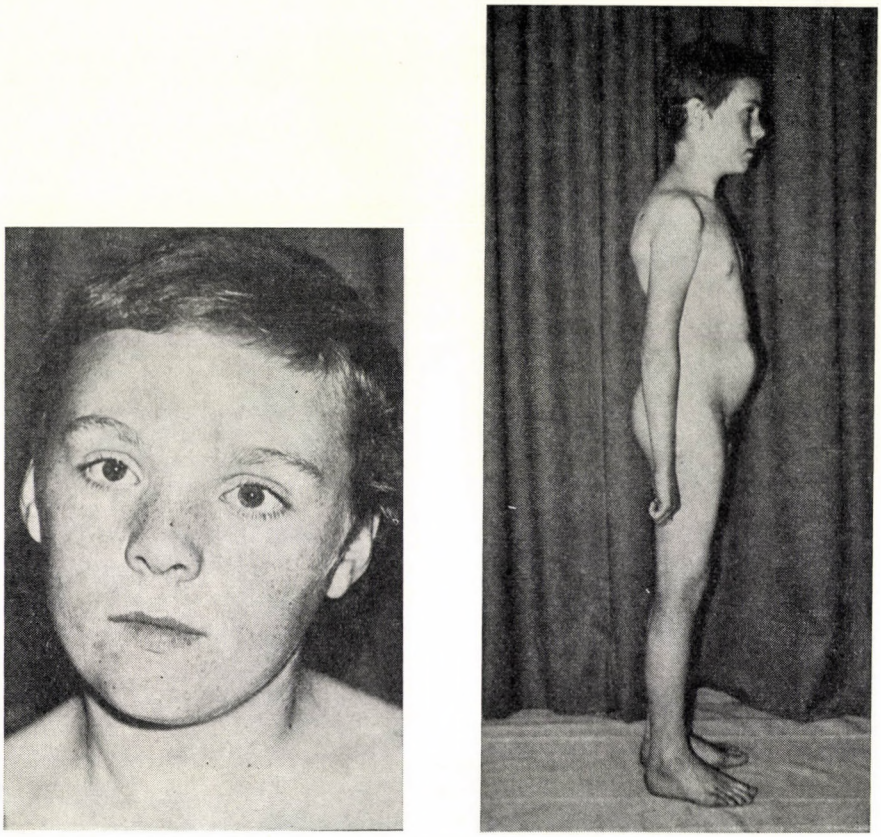

Abb. 2. Fall wie Abb. 1. 5 Monate post operationem. a + b) völliger Rückgang der Cushing-Symptomatik

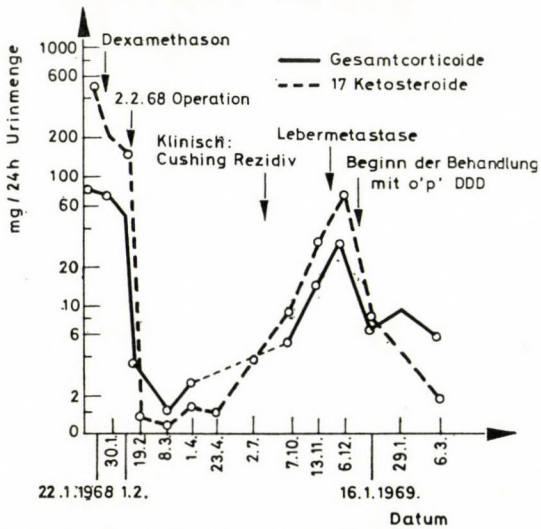

Abb. 3. Fall wie Abb. 1 + 2. Verlauf der Gesamtcorticoid- und 17-Ketosteroid-Werte

und bei Kindern wegen der zu starken Strahlenbelastung unterbleiben [1]. In der postoperativen Phase setzt ein typisches Aufholwachstum ein [7], allerdings ist das Knochenalter bei Therapiebeginn ausschlaggebend. Fängt die Therapie erst nach Pubertätseintritt an (Knochenalter bei Mädchen über 11 Jahre, bei Knaben über 13 Jahre), so ist ein verbleibender Minderwuchs unvermeidlich, da die mit der Pubertät einsetzende vermehrte Androgenproduktion die Knochenreifung beschleunigt.

Adrenogenitales Syndrom

Geht die nebennierenrindentumorbedingte Veränderung mit Virilisierung einher, dann ist der Befund so auffällig, daß er kaum übersehen werden kann. Da die meisten AGS-Formen jedoch angeboren sind, bestehen gewisse differentialdiagnostische Schwierigkeiten bei reinen virilisierenden Nebennierenrindentumoren. Die nachfolgende Übersicht stellt die Differentialdiagnose der AGS-Symptomatik dar:

Differentialdiagnose der AGS-Symptomatik

AGS-Form	Angeboren	Tumorbedingt
Intersex	+	0
Familienanamnese	+	0
Kombination mit Cushing	0	+
17-Ketosteroide (Norm: 0,5 mg/D)	bis 70 mg/d	200 mg/d und mehr; bei Ca bis über 1500 mg/d
Ketosteroidausscheidung bei Cortison-Hemmtest	Normalisierung	keine Änderung

Häufig entwickelt sich der Tumor erst im Kleinkindesalter, es sind aber auch reine AGS-Tumoren im 1. Lebensjahr bekannt geworden. Das Verhältnis Karzinom zu Adenom beträgt 3 : 1. So können auch reine AGS-Tumoren ebenso wie reine Cushing-Tumoren Karzinome sein [3]. Ganz selten ist die AGS-Symptomatik mit einer feminisierenden Komponente [16] kombiniert, wie der nachfolgende Fall zeigt:

Bei einem 1 1/2-jährigen Jungen mit typischer AGS-Symptomatik, Akzeleration und Entwicklung sekundärer Geschlechtsmerkmale fand sich eine beginnende Schambehaarung und Mammahyperplasie (Abb. 4a und b). Die Angiographie (Abb. 5) ergab einen kleinapfelgroßen Tumor links über der Niere. Die Gesamtcorticoide und 17-Ketosteroide waren gering erhöht. Die Operation bestätigte den angiographischen Befund, wobei ein gut abgrenzbarer eingekapselter Tumor entfernt wurde, der histologisch unerwartet den Befund eines Nebennierenrindenadenoms mit Isomorphie zeigt. Bei dieser Rarität eines AGS-Adenoms mit feminisierender Komponente beim Knaben ist die Prognose immer mit Zurückhaltung zu beurteilen. Dieser Junge überlebt aber jetzt bereits 7 Jahre.

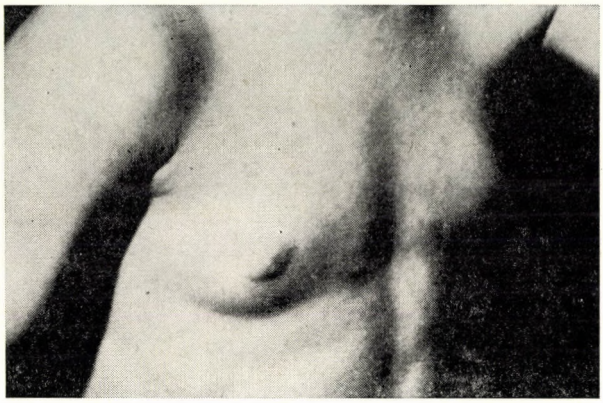

Abb. 4. H., V männlich, 1 1/2 Jahre: AGS-Adenom mit Feminisierung. a) Mammahyperplasie; b) beginnende Schambehaarung

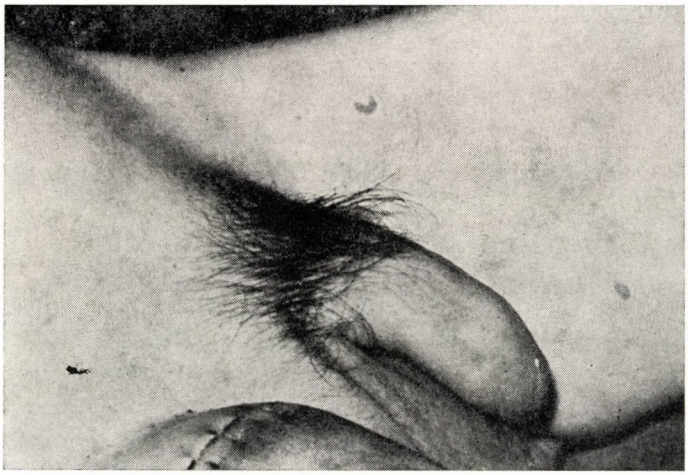

Abb. 5. Fall wie Abb. 4. Angiographie: linksseitiger kleinapfelgroßer Tumor über der Niere

Wichtig ist in jedem Fall mit AGS-Symptomatik eine sichere differentialdiagnostische Abklärung, da einerseits das angeborene AGS keine Operationsindikation darstellt, andererseits aber die malignen Nebennierenrindentumoren zu frühzeitiger Metastasierung — besonders in Leber und Lunge — neigen und somit immer dringlich operiert werden müssen.

Conn-Syndrom

Der Hyperaldosteronismus ist bei Kindern außerordentlich selten [17]. Bis 1975 wurden nur 6 Kinder be-

schrieben, darunter waren 5 Mädchen. Im Unterschied zum Erwachsenen war die Seitenlokalisation 4-mal rechts; die Operation führte bei allen 6 Kindern zur restitutio ad integrum, während im Erwachsenenalter eine Letalität von 5% bleibt. Mit einer Besserung kann nur in 70%, aber in 25% mit einer völligen Wiederherstellung gerechnet werden [18].

Adrenale Zysten

Auch Nebennierenzysten betreffen selten Kinder [25]; bis 1966 konnten unter 237 Fällen nur 16 Kinder beobachtet werden. Diese Zysten sind meist asymptomatisch und ein Zufallsbefund bei der Autopsie. Sie treten in 70% der Fälle rechtsseitig auf. Gelegentlich kommt es zur Nebennierenrindeninsuffizienz; dann aber sind die Zysten meist so groß, daß eine Verdrängung der Nachbarorgane beobachtet werden kann. Im Gegensatz zum Erwachsenenalter ist die Ursache der Zystenbildung meist eine Nebennierenblutung in der Perinatalzeit, die häufig wegen ihrer Symptomlosigkeit unentdeckt bleibt.

Postadrenalektomie — Hypophysenadenom (Nelson-Syndrom)

Zur Hypophysenadenomentwicklung nach Nebennierenentfernung kommt es beim Erwachsenen, jedoch seltener bei Kindern. Young u. Mitarb. [27] konnten allerdings bis 1976 9 Fälle zusammenstellen. Sie vermuten, daß im Gegensatz zum Erwachsenen (10%) in 30% der Fälle im Kindesalter, bei denen wegen eines Hyperplasie-Cushings die Nebennieren entfernt wurden, mit einem solchen Hypophysenadenom zu rechnen ist. Diese Fälle sind oft nicht erfaßbar, da sich das Adenom häufig erst im Erwachsenenalter zeigt.

Phäochromozytom

Nur 5 bis 10% aller Phäochromozytome kommen im Kindesalter vor. Seringe u. Mitarb. [22] konnten bis 1968 153 Fällen sammeln. Die Hauptunterschiede wurden in der nachfolgenden Tabelle zusammengestellt:

Phäochromozytom

Hauptunterschiede	Kinder	Erwachsene
Verhältnis männlich : weiblich	70 : 30	30 : 70
Hypertonie konstant	90%	50%
anfallsartig	10%	50%
multiple Tumoren	30%	10%
maligne Entartung	3%	10%

Daraus geht hervor, daß das männliche Geschlecht im Gegensatz zum Erwachsenenalter bei Kindern doppelt so häufig betroffen ist wie das weibliche.

Die nächste Übersicht zeigt die Unterschiede zwischen Kindern und Erwachsenen bezüglich der Lokalisation:

Lokalisation des Phäochromozytoms

	Kinder	Erwachsene
Einseitig	55%	85%
Doppelseitig	20—70%	7%
Intraadrenal	70%	90%
Extraadrenal	30%	10%

Das Phäochromozytom ist ebenso wie die Pubertätshypertonie, der Morbus Cushing und die Aortenisthmusstenose im Kindesalter nur selten Ursache einer Hypertonie: diese ist nämlich meist nierenbedingt. Häufiger sind Kopfschmerzen, Erbrechen, bei der Hälfte der Kinder Sehbeschwerden mit Augenhintergrundveränderungen, oft findet man auch Polydipsie und Polyurie [26]. Leicht wird das Phäochromozytom mit anderen Krankheitsbildern verwechselt, zumal der Hochdruck sehr schnell zu Herzfehlern, Enzephalopathie und schließlich zum Tode führt.

Die kindlichen Phäochromozytome sind meist sehr klein und selten so differenziert, daß sie Adrenalin produzieren [9]. Urin und Tumorgewebe enthalten also vorwiegend Noradrenalin.

Abgesehen von den laborchemischen Untersuchungsmethoden lassen sich die bekannten lokalisationsdiagnostischen und therapeutischen Maßnahmen bei Kindern schwieriger als bei Erwachsenen durchführen. Sicher genügen heute die einfache Röntgenaufnahme des Thorax und ein Urogramm nicht mehr. Am wichtigsten ist die Aortographie; da meist ältere Kinder betroffen sind, bestehen in der Regel keine technischen Schwierigkeiten. An zweiter Stelle rangiert die selektive Venographie mit etagenweiser Blutentnahme zur Seitenlokalisation [18, 19]. Diese Diagnostik ist viel wichtiger als beim Erwachsenen, weil mehr Phäochromozytome in dieser Altersgruppe multiple, doppelseitig und extraadrenal vorkommen. So muß auch die operative Exploration des chromagenen intraabdominellen Gewebes außerordentlich sorgfältig durchgeführt werden. Auch erhebliche Gefäßveränderungen bilden sich in der postoperativen Phase beim Kind glücklicherweise nahezu immer völlig zurück. Die Entartungsrate ist niedrig. Jeune u. Mitarb. [15] fanden unter 130 Phäochromozytomen nur 3 bösartige. Interessant ist ein Fall eines seinerzeit 9jährigen Mädchens, das ohne medikamentöse Therapie nach Entfernung des Primärtumors noch

immer — bereits 12 Jahre lang — mit Lungenmetastasen lebt [24].

In 10% der Fälle wird familiäres Vorkommen beobachtet. Auch tritt eine Häufung bei Zwillingen auf. Interessant ist auch das Vorkommen von Phäochromozytomen im Rahmen der multiplen endokrinen Adenomatosen (MEA). Beim Typ MEA II a ist es vergesellschaftet mit medullärem Karzinom der Schilddrüse und häufig mit Hyperplasie der Nebenschilddrüse. Beim Typ MEA II b besteht eine Kombination mit Mukosaneuromen der Zunge und Lippen, medullärem Schilddrüsenkarzinom, marfanoidem Habitus, aber normalen Nebenschilddrüsen [12]. Neuerdings wird diskutiert, daß die bilaterale Nebennierenmarkhyperplasie der Vorläufer von bilateralen Phäochromozytomen sein kann [4], so wie die C-Zell-Hyperplasie Karzinomvorläufer ist, insbesondere bei familiärer Belastung.

Unbehandelt kann die Krankheit bereits im Kindesalter sehr bald unter kardiovaskulären und zerebralen Symptomen (nicht selten sogar unerkannt oder fehlgedeutet) zum Tode führen. Die Letalität lag vor 20 Jahren noch bei 70 bis 80%; heute ist die Sterblichkeitsrate, insbesondere durch die Einführung der alpha- und beta-Rezeptoren-Blocker, bei Kindern auf unter 10% gesunken.

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Recensiones

B. SCHAUMANN and M. ALTER: *Dermatoglyphics in medical disorders.* 258 pages with 74 figures and 51 tables. Springer Verlag, Berlin—Heidelberg—New York 1976. Price DM 54.90

Classical works on the ontogenesis, genetics and characteristics of dermatoglyphics, as were those of Kolman, Johnson and Galton in the last century or those of Bonnevie, Cummins, Cummins and Midlo 50 or 30 years ago, have remained exciting readings for human geneticists, biologists, anthropologists or medical research workers of different specialities, but practitioners would certainly not be interested in them. This short, excellently didactic monograph presents a comprehensive review of studies carried out mainly by medical investigators in the last three decades. It is again the geneticist or biologist who can profit from it and not the practising physician despite that the authors promise that the book will be useful "in his day-to-day work". Research workers must be grateful for obtaining such a complete bibliography of the recent publications on dermatoglyphic findings in different congenital malformation syndromes, but the practitioner will be disappointed.

In the late thirties, when Cummins described the main dermatoglyphic characteristics in a patient with Down syndrome, dermatoglyphics should really have been of practical use in the diagnosis of this frequent congenital malformation syndrome. Analysis of dermatoglyphics became popular later, at the start of the cytogenetic era, when chromosome analysis was carried out in few laboratories only. Those who had no possibility to apply cytogenetic methods in routine diagnostic work were looking forward to substituting cytogenetic investigations by this simple, inexpensive method. One hoped that analysis of dermatoglyphics, the "poor man's karyotype", could help to differentiate free trisomy from translocation, or to identify mosaic individuals. Afterwards it was, however, chromosome analysis and not dermatoglyphics that had come into general use. The immense quantity of data collected during the last twenty years shows that an unusual dermatoglyphic feature by itself means not more than any other aspecific dysmorphic sign.

One could enumerate many examples demonstrating the lack of pathognomonic importance of unusual dermatoglyphics. I quote a single one from page 109: "The Sidney line was the most frequently seen palmar crease aberration in a series of children with delayed development, learning difficulties or minor behavioural problems". Besides, the Sidney crease could be observed with increasing frequency in Down syndrome, congenital rubella and leukaemia.

A modern trend in the field of congenital malformations is to establish a system strictly according to the aetiopathogenesis. I do not think that for the

practising physician the knowledge of dermatoglyphics would contribute to this effort. More important is to understand congenital malformations at the deepest level by the help of the methods of biochemistry, cytogenetics and molecular biology. All in all, if not for the practitioner, the monograph will be an excellent source of information for the geneticist.

M. Osztovics

Developmental biology and pathology. Edited by A. Gropp and K. Benirschke (Current Topics in Pathology, Vol. 62), IX + 216 pages with 86 figures. Springer Verlag, Berlin—Heidelberg—New York. 1976. Price DM 96.—

A summary of the papers presented at a symposium on the "Control of early embryogenesis and factors responsible for failure of embryonic development" in Travemünde in May 1—4, 1974 is published in this book.

The introduction by C. R. Austin deals briefly with problems of fertilization and first cleavages resulting from oocyte and sperm defects. D. Szöllösi's paper on "Oocyte maturation and paternal contribution to the embryo in mammals" presents experiments that were performed in the mouse, rat and rabbit. 26 well selected EM pictures demonstrate the different stages of oocyte maturation and sperm elements in the fertilized eggs. — Maternal storage in the mammalian oocyte (Engel and Franke) is introduced by results on amphibians followed by comparative works on mammals. The authors suggest that only a quantitative difference exists among the oocytes of invertebrates, lower vertebrates, and mammals in respect of the maternally derived cytoplasmic storage substances, including mRNA. — During the last 15 years many papers have dealt with the genetic activation of early mammalian embryos. Ch. J. Epstein as a prominent specialist of the subject gives a good survey on it. — Two theories have been known about the determination of trophoblasts and embryonic knot. H. W. Denker reviews the pros and cons of both theories. The question remains open which type of determination is more suitable for the in vivo rather than in vitro developmental mechanisms.

The next chapter discusses the pharmacological and hormonal influences in early embryogenesis. — Cecilia Lutwak-Mann reports on the response of the preimplantation embryos to exogenous factors and she hopes that fertilization of human gametes and early development in vitro will become a routine laboratory procedure in the not too distant future. — H. Spielmann reviews the toxic effects induced in the preimplantation embryo after treatment with cytostatics in vivo and in vitro. The most interesting part of this paper is the description of different transplantation experiments in mouse and rat when the embryos were treated in vivo and in vitro (in culture) before transplantation. — H. M. Beier writes about normal uterine secretion proteins and about various deviations of the protein pattern under various hormonal influences, especially considering the "pill" problem.

The fourth part of the book is dealing with problems of teratology. — L. Saxén et al. summarize the advantages and disadvantages of organ culture techniques in teratological studies. Their experiments demonstrate the usefulness of methods which help to obtain results that would not be possible in studies in vivo. — On the specific teratogenic activity of heavy metals (Pb, Cd, As, Cu, In) V. H. Ferm gives a good summary and he emphasizes the existence of new possibilities (radioautography, EM histochemistry, and electron probe analysis) for the study of the ontogeny of these malformations.

The last chapter reports on connections between cytogenetic abnormalities from the aspects embryolethality and malformations. — O. Bomsel-Helmreich discusses the questions and significance of experimental heteroploidy in mammals. — A. Gropp et al. discuss autosomal monosomy

and trisomy causing developmental failure in mouse embryos. — Finally, J. G. Boué and A. Boué' report on the significance of chromosomal anomalies in early spontaneous abortion. Among the 1498 abortuses chromosome anomalies occurred in 921 cases and most of these developed during gametogenesis and fertilization and were not transmitted by any of the parents.

Summing up, the book contains well selected, actual papers on the subjects of both normal and abnormal gametogenesis, fertilization, and early embryogenesis, and the genetic aspects of development in mammals and man. The work is recommended to all those interested in fertility problems, embryology, teratology and cytogenetics in mammals.

A. Druga

Pathology of the gastrointestinal tract. Editor: B. C. Morson. (Current Topics in Pathology, Vol. 63). VI + 356 pages with 155 figures. Springer Verlag, Berlin—Heidelberg—New York 1976. Price DM 96.—

This quite outstanding monograph is the work of 11 authors from many parts of the world, all of them internationally known authorities in their field. They have written a book which is equally interesting to pathologists and clinicians including paediatricians. There are nine chapters, discussing early gastric cancer, coeliac disease, gastric polyps, polyps and cancer of the large bowel, mucin histochemistry, ulcerative colitis, the GI endocrine cells, immunological aspects, and tumour-associated antigens. In Thompson's excellent chapter on coeliac disease an outstanding review of the complications is presented, especially from the aspect of malignancies. The chapter on mucin describes in detail the technical procedures and the possibilities of their use in differentiating between some pathological entities. A wholly up-to-date part of the book deals with the immunopathological relations and the tumour antigens, two fields where quite a number of problems awaits clarification.

The book will be welcomed by all those concerned with GI diseases and especially with their morphological characteristics.

I. Kósnai

Breast feeding and the mother; Ciba Foundation symposium 45 (new series). VIII + 280 pages. Elsevier — Excerpta Medica — North Holland, Amsterdam 1976. Price Dfl. 54.—

This symposium was held in 1976 under the chairmanship of June Lloyd who explained in her introduction that in the two previous symposia connected with breast feeding the emphasis has been on the baby and now it should be on the mother. To point out some of the many interesting topics, Smotherman et al. found that lactating rats exposed to stress showed a reduction of pituitary-adrenal activity; maximum suppression coincided with the period of maximum lactation. Schams reported on the effect of bromocriptine and thyroliberin on the release of prolactin. Tyson et al. studied the connexion of prolactin and gonadotropin with puerperal lactational infertility. Elsie Widdowson reported many interesting points concerning the physiology of lactation and the relation of the latter with nutrition, showing among others that during lactation the liver increases in size owing to an increase in the number and size of its cells. Patrice Jelliffe too dealt with the subject of maternal nutrition and lactation and in the discussion of her paper it was shown that under poor living conditions the quality of milk does not deteriorate but the stress of urbanization causes its volume to decrease.

The papers to follow were concerned with the psychology of the mother, of her accepting or rejecting the idea of breast-feeding, the early mother–infant contact,

the cross-cultural aspects of breast-feeding, the midwife's attitude to the mother's response to breast-feeding, on the teaching of lactation and on its community and socio-political considerations, this last paper by D. B. Jelliffe. In both the discussions following the individual papers and the general discussion usual at every Ciba meeting, we may read a number of extremely interesting pertaining data from all over the world, concerning savage tribes as well as highly urbanized societies. The book is a must for every psychologist treating young women and every paediatrician. It will make interesting reading even for lay people, especially including future mothers.

F. PETER and A. K. GEIGER

Herzchirurgie. Herausgegeben von E. DERRA, W. BIRCKS. In 2 Bänden, LIII + 1288 Seiten mit 570 Abbildungen. Springer-Verlag, Berlin—Heidelberg—New York 1976. Preis DM 1180.—

Das von E. Derra herausgegebene 3-bändige Handbuch der Thoraxchirurgie, dessen zweiter Band die damals aktuellen Kenntnisse der Herzchirurgie in einem Umfang von 1200 Seiten zusammenfaßte, erschien im Jahre 1959. Das Gebiet hat sich dann in den folgenden Jahrzehnten stürmisch entfaltet; als die bedeutendsten Meilensteine dieser Entwicklung wären die Einführung der Lungen-Herzpumpe, die Klappenimplantation, die Ausbildung der Herzchirurgie des Säuglingsalters, die Herztransplantation, die neuartigen Gesichtspunkte in der Coronarienchirurgie und hinsichtlich der postoperativen Behandlung hervorzuheben. Diese rasche Entwicklung machte die neue Auflage des 2. Bandes des Handbuches in einer zeitgemäßen Überarbeitung notwendig. Die Aufgabe wurde von 47 international bekannten Autoren verschiedener Länder in der Redaktion von Derra und Bircks verwirklicht.

Band I besteht aus 6 großen Kapiteln, von denen das erste den funktionelle Anatomie des Herzens, den extrakorporalen Kreislauf, den Stoffwechsel des Herzens, den induzierten Herzstillstand, die Kontrolle und Therapie der frühen postoperativen Periode und das EKG nach Herzoperationen erläutert. Kapitel 2 befaßt sich mit den theoretischen und praktischen Fragen der Herztransplantation, Kapitel 3 mit der Ektopie, Kapitel 4 mit den angeborenen und erworbenen Veränderungen der herznahen großen Gefäße (Aortenbogen, Isthmusstenose, Ductus arteriosus persistens, aortopulmonale Fenestration, Aneurysmen der thorakalen Aorta, die Veränderungen der A. pulmonalis, Lungenembolie). Im Kapitel 5 finden sich die Krankheiten des Perikards, im 6 die verschiedenen Formen des ASD und des VSD (die traumatischen, postinfarktorischen VSD inbegriffen) sowie die postoperativen Komplikationen.

Band II umfaßt 7 große Kapitel über die Veränderungen der Klappen, die komplexen Fehlbildungen, die angeborenen und erworbenen Koronarveränderungen (auch die Diagnostik der Koronarsklerose und deren chirurgische Behandlung), ferner die Divertikula des Septums, die Störungen der Reizleitung, die Geschwülste des Herzens und Perikards und schließlich die traumatischen Veränderungen des Herzens und des Herzbeutels.

Aufbau und Konzeption des Buches sind hervorragend und widerspiegeln die Notwendigkeit der Teamarbeit, ohne die eine entsprechende herzchirurgische Tätigkeit und befriedigende Resultate heute nicht vorstellbar sind. Dieser Konzeption gemäß befinden sich unter den Mitarbeitern außer Herzchirurgen auch Internisten, Kinderärzte, Anatomen, Pathologen, Radiologen und Anaesthesiologen. Die ganz ausgezeichnete Qualität des Bildmaterials muß hervorgehoben werden. Das Handbuch ist unentbehrlich für alle, die sich mit der konservativen und chirurgischen Therapie und der postoperativen Betreuung von Herzkrankheiten befassen.

J. KAMARÁS

Lehrbuch der Anaesthesiologie, Reanimation und Intensivtherapie. Herausgeber: H. Benzer, R. Frey, W. Hügin, O. Mayrhofer. 4., völlig neubearbeitete Auflage. XX + 809 Seiten mit 375 Abbildungen. Springer-Verlag, Berlin—Heidelberg—New York 1977. Preis: DM 168,—

Diese völlig neubearbeitete vierte Auflage des wohlbekannten Lehrbuches ist die kollektive Arbeit hervorragender, anerkannter Fachärzte, die Konzeption ist jedoch einheitlich.

Der erste Teil ist der Anästhesiologie gewidmet. Die Themen der einzelnen Kapitel sind: Biotechnische Meßmethoden — Funktionsprinzip der zur kontinuierlichen Beobachtung der Patienten dienenden Apparate — Sicherheitsfragen des Operationssaales — Ursachen und Präventionsmöglichkeiten von Brandfällen, Explosionen bzw. elektrischen Unfällen sowie nötige Schutzgeräte. Mit den Problemen der Desinfektion und Sterilisierung befaßt sich ein separates Kapitel. Die in der Anästhesiologie gebräuchliche Dokumentation wird am Beispiel eines Muster-Protokolls dargestellt.

Im physiologischen Abschnitt finden die vom Standpunkt der Anästhesiologie wichtigen Aspekte der Atmung, des Kreislaufs, des Nervensystems, des Säure-Basen-Gleichgewichtes, des Wasserhaushaltes, des Stoffwechsels sowie der Blutgerinnung eine ausführliche Besprechung. Der pharmakologische Abschnitt behandelt folgende Fragen: Verteilung der Medikamente im Organismus — Eigenschaften der zur Prämedikation verwendeten Pharmaka — die zur lokalen, Inhalations- und intravenösen Anästhesie gebräuchlichen Medikamente und Muskelrelaxantien. Im Zusammenhang mit den praktischen Aufgaben der Narkose werden die Bedeutung der präoperativen Visite, der Kontaktaufnahme mit dem Patienten und der anästhesiologischen Anamnese betont.

Das folgende Kapitel befaßt sich mit der Atemfunktionsdiagnostik. Nach Erörterung der Fragen der endotrachealen Intubation, der intravenösen Narkose, der Lokalanästhesie sowie der spinalen und periduralen Narkose folgt — unter Berücksichtigung der praktischen Gesichtspunkte — der dritte, die speziellen anästhesiologischen Probleme der in den der topographisch-anatomischen Aufteilung entsprechenden einzelnen Regionen durchgeführten Eingriffe umfassende Abschnitt. In diesem Rahmen werden die speziellen anästhesiologischen Beziehungen der thorakalen, abdominalen, gynäkologischen, geburtshilflichen, ophthalmologischen und otologischen Eingriffe besprochen.

Die Bestimmung des Begriffs der Reanimation, ihre Bedeutung, die Wiederbelebungsverfahren und ihre praktische Anwendung, Pathophysiologie, Symptomatik sowie Therapie des Schocks bilden das Thema des nächsten Kapitels. Ein besonderer Abschnitt behandelt die Probleme der Intensivpflege: Infusionstherapie, parenterale Ernährung, Behandlung des kardiorespiratorischen Systems, antibakterielle und Chemotherapie. Das anschließende Kapitel liefert nützliche Kenntnisse über die in der postoperativen Phase gebräuchlichen Atem-Kreislauf- und Schmerzlinderungstherapie, Behandlung von Stoffwechselstörungen und über die Krankenpflege in der Wachstation.

Das letzte, kurze Kapitel befaßt sich mit der Ausbildung der Anästhesiologen, den juristischen Problemen der Narkose sowie mit den Personal- und Organisationsfragen der anästhesiologischen Abteilungen.

Dieses fundamentale Werk ist den praktizierenden Anästhesiologen und den in Ausbildung stehenden jungen Ärzten unentbehrlich. Es darf aber berechtigt auch auf das Interesse von Chirurgen, Neurologen und Internisten rechnen.

G. Tornáry

Diagnostic Radiology in Paediatrics. Edited by J. Apley, I. R. S. Gordon, F. G. M. Ross. Butterworths, London—Boston—Sidney—Wellington — Durban — Toronto 1977. Price £ 29.50

This book offers practical and up-to-date information on diagnostic radiology in a concise form. It is divided in 9 chapters. The first discusses the skeletal dysplasias whose aetiology is mostly unknown. Chapter 2 deals with tumours and tumour-like lesions classified as bone-forming, cartilage-forming, giant cell tumours, marrow and and vascular tumours. The most interesting ones are compiled under the subtitle, other forms of tumours. Chapter 3 contains the skeletal lesions, inflammatory, blood and metabolic diseases, traumatic injuries and miscellaneous diseases. The fact is emphasized that in young infants early and subtle signs are best demonstrated on films exposed without intensifying screen and with a fine spot focus, without considerably increasing the radiation damage. Caffey's cortical hyperostosis is treated among the inflammatory conditions and Scheuermann disease among the miscellaneous diseases, reflecting their uncertain or disputed aetiology. Chapter 4 is concerned with the cardiovascular system. It is introduced by a very good and complete account of the methods used. Ultrasonic investigation is recommended as a fully harmless non-invasive method. Sophisticated diagnostic tools such as angiography, catheterization, etc., should follow only after considering and evaluating plain films. A wide range of congenital and acquired diseases is presented to illustrate the subject. The next chapter presents the radiology of the respiratory system. To obtain films suitable for correct diagnosis, equipments of highest accomplishment are needed. Even the most modern portable apparatus works with inherent errors, thus babies should be transported in up-to-date incubators without causing distress to the X-ray department, as films obtained there will only be fully reliable and the process causes less radiation injury than in the ward. Thymus, congenital anomalies, neonatal diseases, airway obstruction (a delicate subject in the early period of life) cysts and tumours are dealt with in this chapter.

Chapter 6 discusses the gastro-intestinal tract, describing, apart from X-rays, the ultrasonic techniques, angiography and scintigraphy. Chapter 7 deals with the radiological diagnosis of urinary tract diseases. The urographic techniques are described in much detail, their practical knowledge being indispensable in obtaining films of adequate quality. The methods of genitography and gynaecography are also included. Special attention is devoted to the congenital anomalies, obstructive uropathies and to traffic injuries. Chapter 8 is devoted to the nervous system. Old and new techniques are all outlined, first of all computer tomography and EMI-scan. In the last chapter we find data concerning the development, nutrition and malnutrition of bones. Those who are interested in growth, development, proportions and maturity of children, will find here useful information.

The book with its wealth of good illustrations and its concise text will be a real help to radiologists and paediatricians. The references although up-to-date are rather scanty and restricted mostly to English-speaking authors, disregarding even the most distinguished contributions from other countries. This is regrettable because we are missing names such as that of Bergerhoff who has done so much in the field of cranial interpretation. It is an advantage that some sound criticism is offered, for instance, concerning the examination method of Andrén and Rosen.

CH. M. GEFFERTH

F. LAMPERT: *Krebs im Kindesalter*. Leitfaden der pädiatrischen Onkologie. 4., neu bearbeitete und erweiterte Auflage. XII + 160 Seiten mit 67 Abbildungen. Urban & Schwarzenberg, München—Wien—Baltimore 1977. DM 36,—

Die Tatsache, daß 1971 in der Bundesrepublik mehr als 1000 Kinder an Krebs starben, zeigt klar, daß sich der Kinderarzt

in den kommenden Jahren mit dem Problem der malignen Tumoren intensiv befassen muß. Jedes zweite an einem malignen Tumor leidende Kind hat jedoch Aussichten zum Überleben, zu dem vor allem die Frühdiagnose und die Verbesserung der immunologischen Verfahren beitragen müssen.

In dem vorliegenden Buch gibt der Verfasser einen allgemeinen Überblick der ganzen pädiatrischen Onkologie. Aufgrund eigener Erfahrungen wurden die therapeutischen Pläne so zusammengestellt, daß sie neben der entsprechenden Wirksamkeit auch die leichte Adaptation in die klinische Praxis sichern.

Verschiedene Kapitel wurden in der neuen Auflage mit neuen Abbildungen und Tabellen versehen, einige Kapitel, wie das der Knochentumoren, wurde neugeschrieben, andere neu aufgenommen.

Im allgemeinen Teil behandelt der Autor die Bedeutung der Verbesserung der Diagnostik, die Rolle der Therapiezentren und der ambulanten Behandlung. Ausführlich werden die möglichen ätiologischen und auslösenden Faktoren (onkogene Viren, ionisierende Strahlen, chemische Noxen) erläutert, und auf die zukünftige Entwicklung der molekularbiologischen Beziehungen der genetischen Forschung hingewiesen. Ferner werden die Wirkung der Cytostatika und chemischen Substanzen, deren Nebenwirkungen und die Bedeutung der Stadieneinteilung besprochen.

Im speziellen Teil werden die häufigsten kindlichen Krebsformen angeführt und auf die von der der Erwachsenen abweichenden Lokalisation und Manifestation hingewiesen: im Kindeslater handelt es sich vorwiegend um Erkrankungen des Knochenmarks, des Lymphsystems, Zentralnervensystems und der Niere.

Das Buch bietet nicht nur dem Spezialisten, sondern auch dem allgemeinen Arzt eine wertvolle Hilfe zur Vorbeugung und frühen Erkennung dieser Krankheiten.

Z. Erdős

W. H. Hitzig: *Plasmaproteine, Pathophysiologie und Klinik.* 2., neubearbeitete Auflage. X + 230 Seiten mit 34 Abbildungen und 41 Tabellen. Springer-Verlag, Berlin—Heidelberg—New York 1977. DM 24,—

Die in der Reihe »Kliniktaschenbücher« veröffentlichte vorliegende Arbeit ist die überarbeitete Auflage des unter dem Titel »Plasmaproteine in der klinischen Medizin« publizierten früheren Werkes des Autors. Der modifizierte Titel deckt eine vollständige Neufassung, da die neue Auflage vor allem die pathophysiologischen Beziehungen eingehend bespricht; etwa ein Drittel des Buches befaßt sich mit diesen Fragen.

Einleitend werden die physikochemische Struktur der Proteine, die Methoden der Proteinanalyse und die praktische Bewertung der einzelnen Untersuchungsverfahren erörtert, so daß der in den biochemischen Fragen weniger gewandte Leser sich zum Verständnis des weiteren Materials die nötigsten Grundkenntnisse aneignen kann. Hiernach wird die praktische Durchführung spezieller Plasmaproteinuntersuchungen geschildert, wobei auch jene pathophysiologischen und technischen Ursachen angedeutet werden, die zu Bestimmungsfehlern führen können. Dann folgt ein Kapitel, das den Eigenschaften der klinisch bedeutsamen Plasmaproteine in der folgenden Gliederung gewidmet ist: phasenspezifische Proteine, Transportproteine, Immunglobuline, zum Komplementsystem gehörende Proteine, Enzyme, Enzyminhibitoren, Gerinnungsfaktoren, Lipoproteine und Proteine mit noch unbekannter Funktion. Weitere Kapitel befassen sich mit den pathologischen Befunden: Störungen der Proteinsynthese, reaktive Anomalien, Plasmaproteine in anderen Körperflüssigkeiten (Urin, Exsudate, Sekrete, Liquor, Lymphe, Augenkammerwasser).

In dem Literaturverzeichnis wurden vor allem jene weiterführenden Übersichtsarbeiten zitiert, in denen die Originalliteratur

zu finden ist. Die Abbildungen sind sehr übersichtlich, und die Tabellen bieten äußerst viele Angaben.

E. Cserháti

Keller—Wiskott Lehrbuch der Kinderheilkunde. Herausgegeben von A. Wiskott, K. Betke und W. Künzer. 4., neubearbeitete Auflage. XX + 1004 Seiten mit 550 Abbildungen in 710 Einzeldarstellungen. Georg Thieme Verlag, Stuttgart 1977. DM 110,—

Die erste Auflage dieses klassischen Lehrbuches erschien 1961. Die vorliegende 4. Auflage wurde dem Leser mit neuen Redakteuren, Autoren und den heutigen Kenntnissen gemäß erweiterten und umgearbeiteten Inhalt in die Hand gegeben.

Die den Stoffwechsel, die Immunologie, das Nervensystem und die Infektionskrankheiten behandelnden Teile sind beträchtlich erweitert worden, und neue Kapitel sind den Augenkrankheiten und malignen Tumoren gewidmet. Die einzelnen Kapitel umfassen in entsprechenden Proportionen alle Zweige der Säuglings- und Kinderheilkunde: Physiopathologie der perinatalen Periode, Ernährung und ihre Störungen, maligne Tumoren, Unfallverletzungen, Infektionskrankheiten, Schutzimpfungen, Arzneivergiftungen usw. Die charakteristischen Erkrankungen der verschiedenen Organe und Organsysteme werden ausführlich erläutert. Die Krankheiten des Blutes, und Blutbildungssystems, des Herz- und Gefäßsystems, der Verdauungsorgane, Atemwege und des urogenitalen Systems sind mit besonderer Betonung dargestellt.

Es war wohl keine leichte Aufgabe, das große Material in einheitlicher Konzeption und Konstruktion aufzuarbeiten, dies ist den Herausgebern jedoch musterhaft gelungen. Das Werk wendet sich natürlich an die Pädiater, infolge der äußerst klaren und knappen Besprechungsart wird es sich jedoch auch für Medizinstudenten und allgemeine Ärzte als ein nützliches Hilfsmittel erweisen.

Á. Székely

Die Langzeitbetreuung des chronisch kranken Kindes. Zusammengestellt von K. Lorenz. 242 Seiten mit 23 Abbildungen und 40 Tafeln. Georg Thieme Verlag, Leipzig 1977. M 23,—

Der in der Reihe »Moderne Pädiatrie« erschienene Band ist das Werk eines aus 15 Mitarbeitern bestehenden Autorenkollektivs. Die Wahl des Themas war aktuell: durch den Rückgang der Morbidität vieler akuten Krankheiten soll die Aufmerksamkeit der Kinderärzte in entscheidendem Maße auf die Betreuung der chronischen Patienten gerichtet werden. Diese Frage wirft zahlreiche medizinische, soziale und organisatorische Probleme auf, von denen ein Teil in der DDR bereits gelöst worden sind, so daß die Arbeit nicht individuelle Ansichten, sondern die Ergebnisse langfristiger gemeinschaftlicher Tätigkeit spiegelt.

Die 13 Kapitel des Buches befassen sich mit der Behandlung des chronischen Kranken in folgender Reihenfolge: chronische und rezidivierende Bronchialerkrankungen, Erkrankungen der Nieren und Harnwege, Herzfehler, zerebrale Anfallsleiden, angeborene Stoffwechselstörungen, Malabsorptionssyndrome, Mukoviszidose, endokrine Erkrankungen, maligne Erkrankungen, Diabetes mellitus, rheumatische Erkrankungen, Verhaltens- und Anpassungsstörungen und schließlich die klinisch-genetische Familienberatung. Im Rahmen dieser Kapitel werden Symptomatik, Komplikationen und Prognose der einzelnen Krankheitsbilder geschildert und die Grundprinzipien der Langzeitbetreuung, der Verlauf der Medikation, deren Nebenwirkungen erörtert. Die angedeuteten therapeutischen Maßnahmen sind zeitgemäß; so werden z. B. als Antibiotikum statt dem von Bronchopneumologen so oft angewandte Chloramphenicol, die Trimethoprim-Sulfonamidpräparate bzw. Ampicillin empfohlen.

Es wird auch der organisatorische Aufbau der Betreuung, von den Bereichsärzten bis zu den hochspezialisierten Zentren, angegeben. Die genaue Erfassung des Krankenmaterials (diagnostische Kriterien, An-

meldungspflicht), die Aufgaben der einzelnen Fachorgane, die Ambulanzkarte, Kontrolluntersuchungen, Kooperation mit anderen Fachgebieten, Hinweise zur Lebensführung, Diät, Sport, Schulung und Rehabilitation werden ausführlich besprochen.

Der Wert der Arbeit wird durch die einheitliche Anschauung und das jedem Kapitel hinzugefügte Schrifttum bereichert. Sie ist als ein für Klinik und Praxis nützliches Buch zu empfehlen.

I. Romhányi

Kinderheilkunde. Herausgegeben von G.-A. von Harnack. XIV + 394 Seiten mit 193 Abbildungen. Springer Verlag, Berlin—Heidelberg—New York 1977. DM 39,—

Die vorliegende vierte, neubearbeitete Auflage vermag die hohe Reputation dieses Werkes noch weiter zu steigern. Alle Kapitel wurden zeitgemäß überarbeitet und ergänzt, überholte Kenntnisse oder Entbehrliches gestrichen.

Das Buch bespricht in 21 Kapiteln die gesamte Kinderheilkunde mit der Konzeption, dies kurz und in einem gedrungenen doch leicht verständlichen Stil, ohne Simplifikation jeder Art zu verwirklichen. Es werden alle wichtigen und häufigen Erkrankungen und Veränderungen erläutert und die Zusammenhänge entsprechend angedeutet. Den genetischen und exogenen vorgeburtlichen Schäden wurde diesmal auch ein Kapitel gewidmet.

Der Aufbau des Bandes ist äußerst klar, und die Lesbarkeit wird durch den neuen zweispaltigen Druck noch verbessert.

Zusammenfassend soll betont werden, das es der Zielsetzung entsprechend gelungen ist, eine übersichtliche Wissensvermittlung auf knappem Raum, also im wahren Sinne einen Leitfaden zur guten Orientierung in dem komplexen Gebiet der Pädiatrie zu bieten.

K. Schmidt

Kelly, P. T.: *Dealing with dilemma: a manual for genetic counselors*. XIII + 143 pages. Springer Verlag, Berlin—Heidelberg—New York 1977. Price DM 17.10

The three criteria of adequate genetic counselling are according to the author, 1) knowledge of diagnostics; 2) knowledge of genetics; and 3) communication. The role of the first and second factor is evident, but it is almost equally important that the necessary information should be well absorbed, understood and assimilated by the counsellees, as the author, an expert in the teaching of genetic counselling, calls the patients.

In this small, almost pocket-size, well edited volume, 9 chapters deal in a consequent and logical order with the course of genetic counselling. The reader can find a well-scheduled plan for the shaping of each session from the first admission to the final follow-up. In the last chapter we find the most frequent questions and answers asked and answered by the counsellors as well as by the counsellees.

The author's personal experience is well reflected by excerpts from her sessions, and they ensure practical benefit for those who are engaged in genetic counselling. Sometimes, however, there is a superfluous overlapping of the quotations.

The book fills a gap that exists in the field of genetic counselling in that it helps to overcome the barriers of communication which frequently impede understanding during the sessions. That is the first and only aim as well as the merit of the compendium.

In two appendices a sketch of the detailed planning of counselling sessions as well as a very short genetic glossary help in the enquiry. The book ends with a short selected bibliography dealing only with the questions of genetic counselling.

P. Kiss

W. THAL, W. LEUPOLD und P. WUNDERLICH: *Asthma bronchiale im Kindesalter*. 142 Seiten mit 23 Abbildungen und 8 Tabellen. Georg Thieme Verlag, Leipzig 1977. M 21,—

In der vorliegenden Monographie wird die heutige Lage des kindlichen Asthma bronchiale von drei erfahrenen Kinderpneumologen behandelt.

Im ersten Teil wird die Erkrankung nach der in der DDR derzeit gebräuchlichen Form definiert, laut der es sich um eine teilweise oder ganz reversible Atemnot auf dem Boden einer erhöhten Reizbarkeit der Bronchien handelt und die Atemnot in der Regel anfallsweise auftritt oder sich anfallsweise verstärkt. Es werden extrinsic oder intrinsic Asthma oder eine Mischform unterschieden. Die Häufigkeit der Krankheit wird in der DDR auf 0,5% geschätzt. Hinsichtlich des Erkrankungsbeginnes wird die Bronchitis asthmatica des Säuglingsalters hervorgehoben und die Entstehung des echten Asthmas um das vierte Lebensjahr gesetzt. Die Pathogenese der Krankheit wird mit Hilfe einer didaktischen Abbildung aufgrund der zeitgemäßen Theorie besprochen.

In dem sich mit der Diagnostik befassenden Teil wird die Symptomatik und Differentialdiagnostik des Asthma und Status asthmaticus erörtert. Vom 4—5. Lebensjahr an wird eine obstruktive Bronchitis von der asthmatischen Bronchitis unterschieden; bei letzterer handelt es sich um von Atemnot begleitete typische Asthmaanfälle. Die richtige Diagnose wird mit Hilfe verschiedener Proben (IgE, RAST, Hauttests, spezifische und aspezifische Allergenprovokation, Blutgasanalyse, Röntgen usw.) unterstützt, ferner mit psychologischen Untersuchungen ergänzt.

Bei der Therapie bieten sich heute eine Reihe von Möglichkeiten, doch mit der Gefahr der Polypragmasie. Die Vorbeugung eines Anfalles kann durch die Vermeidung des verantwortlichen Antigens, durch Hyposensibilisierung und mit entsprechender Medikation (Cromoglycat) gefördert werden. Zur Lösung des Anfalles werden Theophyllin oder Betamimetika empfohlen. Kortikosteroidgaben sind lediglich bei Status asthmaticus oder äußerst schweren Fällen von Asthma für ganz kurze Kuren indiziert. Bei der Betreuung der Asthmatiker sind die Teilnahme an Sport und die Berufswahl entsprechend zu erwägen.

Das Büchlein soll dem praktizierenden Kinderarzt als nützlicher Wegweiser empfohlen werden.

G. PÓDER

F. HADŽISELIMOVIĆ: *Cryptorchidism*. 72 pages with 43 figures. Springer Verlag, Berlin—Heidelberg—New York 1977. Price DM 27.—

This little monograph contains two parts. The first deals with the ultrastructure of normal testicular development, amply illustrated by diagrams and electron micrographs. The second part discusses the primary and secondary changes of undescended testicles. That they become permanently damaged and the resulting high rate of infertility, have been known since long. Twenty years ago, puberty was considered to be the best time for orchiopexy and 10 years ago still the age of 5 to 6 years, before beginning school, was thought appropriate for performing surgery. Seven years ago, new data yielded by testicular biopsies examined first under the light microscope and more recently by the electron microscope have, however, made it evident that cryptorchidism must be treated earlier, with gonadotropin in the first year and surgically in the second year. This conclusion was drawn first by Hösli and Hedinger in 1971 and two years later by the author of the present book. After ultrastructural studies of 154 biopsies and on the basis of experiments in newborn mice, the author reported that primary changes were visible in cryptorchid testicles as early as one week after birth and secondary changes in the second year. He concluded further that reduced gonadotropin stimulation is one of the main factors in the

aetiology of cryptorchidism and presented animal experiments in support of the hypothesis that cryptorchidism results from an insufficiency of the hypothalamo-hypophysogonadal system. Therefore, the program of therapy allowing to preserve fertility should be as follows.

1) Gonadotropin therapy should be started in infancy in the case of both unilateral and bilateral cryptorchidism;

2) if the hormone therapy is unsuccessful, surgery is indicated at the age of two years;

3) in every case of testicular maldescent in newborns, the parents must be made aware of the importance of check-ups and of the necessity of early treatment of the condition.

J. DÉNES

PERINATAL MEDICINE

Volume I–II.

Edited by E. Kerpel-Fronius, P. Véghelyi, J. Rosta

Knowledge concerning the physiology, pathophysiology and clinics of the perinatal period has greatly accumulated in the last two decades. This progress has resulted in a spectacular decrease in perinatal mortality and incidence of birth injury. This important collection was written by 49 authors, physiologists, genetics, obstetricians and pediatricians. Twenty chapters discuss problems concerning the pregnant mother and the fetus, such as prenatal care, normal and complicated pregnancy, the development of the fetus, the influence of genetic and environmental factors, intrauterine and intrapartum diagnostics. Perinatal medicine is surveyed in great detail in 41 chapters including its physiological, pathophysiological and clinical aspects. The small-for-date infants are considered in their complexity.

In English — The two volumes together approx. 1600 pages — Cloth

ISBN 963 05 1413 3

AKADÉMIAI KIADÓ
Publishing House of the Hungarian Academy of Sciences
Budapest

Printed in Hungary

A kiadásért felel az Akadémiai Kiadó igazgatója — Műszaki szerkesztő: Zacsik Annamária

A kézirat nyomdába érkezett: 1978. VI. 13. — Terjedelem: 9,8 (A/5) ív 39 ábra (1 színes melléklet)

78.5993 Akadémiai Nyomda, Budapest — Felelős vezető: Bernát György

ACTA PAEDIATRICA

ТОМ XIX—ВЫП. 3

РЕЗЮМЕ

РЕФЛЕКТОРНАЯ БРАДИКАРДИЯ: ТЯЖЕЛОЕ ОСЛОЖНЕНИЕ ПОСЛЕ ОПЕРАЦИИ ПО ПОВОДУ АТРЕЗИИ ПИЩЕВОДА

В. Ф. ЛУКАЧ, М. БОГНАР, М. ЯМБОРИ, Й. ДЭНЕШ

Авторы описывают в настоящей статьи случаи особенных осложнений после операций по поводу атрезии пищевода у новорожденных детей. Среди подвергнувшихся этой операции 39 новорожденных 21 ребенок жив и нормально развивается (53,8%). В 5 случаях была отмечена рефлекторная брадивардия. Первый ребенок — патология еще не была распознана — умер в возрасте полутора лет. У четырех больных под влиянием лечения атропином исчезли симптомы, дети здоровы, хорошо развиваются. Хирургического вмешательства не потребовалось.

ФЕТАЛЬНЫЙ АЛКОГОЛЬНЫЙ СИНДРОМ: СИМПТОМЫ И ПАТОГЕНЕЗ

П. В. ВЕГХЕЙИ, М. ОСТОВИЧ, Г. КАРДОШ, Л. ЛЕЙСТНЕР, Э. САСОВСКИ, Ш. ИГАЛИ и Ю. ИМРЕИ

Мы определяли симптомы фетального алкогольного синдрома и частоту отдельных симптомов на основе 41 сообщения, опубликованного в специальной литературе, а также собственных наблюдений. Для выяснения патогенеза этого синдрома мы выполнили опыты, которые определенно доказали отсутствие у алкоголя цитокситоческого, мутагенного и терагенного действий, и наличие сильного цитотоксического, мутагенного и тератогенного эффектов у ацетальдегида. На основании результатов этих опытов, мы считает ответственным за фетальный алкогольный синдром уровень ацетальдегида в материнской крови, превышающий 35 μM,, который, повидимому, связан с унаследованным или приобретенным отсутствием митохондриальной альдегид-дегидрогеназы. Если будущая мать выпивает, и если после потребления алкоголя уровень ацетальдегида поднимается выше 30 μM, то мы должны высказаться против рождения ребенка.

РЕШЕНИЕ ВОПРОСА О ПОЛОВОЙ ПРИНАДЛЕЖНОСТИ РЕБЕНКА В СЛУЧАЕ СПОРНЫХ НАРУЖНЫХ ГЕНИТАЛИЙ

П. КИШШ, М. ОСТОВИЧ и П. СЕНИ

У восьми детей, пол которых было невозможно определить на основании наружных гениталий, исследовались половые хромосомы и были произведены гормональные и гистологические исследования. На основании результатов исследований в метрических свидетельствах трех детей сменили пол, в двух случаях мужское имя заменили на женское и в одном случае — женское на мужское. Половую принадлежность ребенка необходимо устанавливать сразу после его рождения, так как ошибка или промедление вызывают тяжелые нарушения в психосексуальном развитии ребенка и в жизни всей семьи.

ЭКСФОЛИАТИВНЫЙ ДЕРМАТИТ НОВОРОЖДЕННЫХ (ВЫЗВАННЫЙ СТАФИЛОКОККОМ КОЖНЫЙ СИНДРОМ)

В. ХАНДРИК, Т. ЛИТЦ, Л. БЕРГМАНН и В. ВИТТЕ

На основании своих собственных двух наблюдений авторы настоящей статьи знакомят с литературой, этиологией, патогенезом, диагностикой и терапией эксфолиативного дерматита новорожденных. В статье подробно обсуждается вопрос дифференциальной диагностики этого заболевания.

СЛУЧАЙ ИЗЛЕЧЕНИЯ ГЕНЕРАЛИЗОВАННОЙ ИНФЕКЦИИ BCG

З. ЭРДЕШ, Э. ЧЕРХАТИ и И. САБО

Восьмимесячная девочка была принята на лечение с диагнозом *mucocutan candidiasis* но примененная терапия оказалась неэффективной. Дальнейшие анализы обнаружили комбинированную гуморальную и целлюлярную иммунопатию. В возрасте 7 лет девочка снова поступила в больницу, на этот раз с жалобами на живот. Пробная лапаротомия показала мезентериальный туберкулез. Высеянный возбудитель оказался штаммом BCG. Противотуберкулезные препараты были эффективными, очаг исчез, но микозное заболевание по-прежнему осталось и требует постоянного лечения.

ИНФЕКЦИЯ МОЧЕВЫВОДЯЩИХ ПУТЕЙ И КОНЪЮГИРОВАННАЯ БИЛИРУБИНЕМИЯ У ГРУДНЫХ ДЕТЕЙ: ИЗМЕНЕНИЕ СОДЕРЖАНИЯ СВОБОДНЫХ АМИНОКИСЛОТ В ПЛАЗМЕ

ДЬ. ШОЛТЕС, ДЬ. МЕШТЬАН и Т. ДИЖЕРИ

Авторы определяли уровень сахара крови натощак и содержание свободных жирных кислот в плазме у грудных детей, страдающих инфекцией мочевыводящих путей и присоединившейся к ней холостатической желтухой. Уровень сахара крови остался нормальным, плазменный уровень двух важных аминокислот глюкогена (аланина и лизина) статистически достоверно снизился, содержание фенилаланина, цитриллина и цистина статистически достоверно увеличился, что указывало на нарушение внутрипеченочного обмена аминокислот. О наличии причинной связи между повреждением печени и гиперфенилаланинемией можно было сделать вывод на основании тесной корреляции уровней билирубина, SGPT и фенилаланина. После 2—4-х недельного курса лечения антибиотиками моча стала стерильной, исчезла билирубинемия и нормализовалось содержание аминокислот в плазме.

ЗНАЧЕНИЕ №1-ЧАСОВОГО ТЕСТА НА Д-КСИЛОЗУ ДЛЯ УСТАНОВЛЕНИЯ АТРОФИИ ВОРСИНОК

И. КОШНАИ, М. В. ТИХИ и П. БУЧКИ

Авторы провели сравнительное исследование на основе материала 40 биопсий тонкого кишечника и 1-часового теста на Д-ксилозу. У 15 больных наблюдалась субтотальная атрофия ворсинок, в 25 случаях слизистая тонкого кишечника была нормальной. 15 из 25 больных с субстальной атрофией ворсинок значение 1-часового теста на Д-ксилозу было выше 20 мг%. В контрольной группе все значения Д-ксилозы превышали 20 мг%.

ДЕЯТЕЛЬНОСТЬ МОНИТОРА ВРОЖДЕННЫХ АНОМАЛИЙ В ВЕНГРИИ

Э. ЦЕЙЗЕЛ

Венгерский Монитор Врожденных Аномалий действует с 1 января 1973 г. Его целью является скорейшее выявление возможных повышений частот во времени и по районам индикаторных врожденных аномалий. Венгерский Монитор являются частью организованного ВОЗом сотрудничества, распространяющегося в настоящее время на 11 стран. До настоящего времени понадобилось установить состояние опасности в 1975 году при повышении редукционных аномалий конечностей. Это повышение лишь в малой мере объяснялось техническими искажениями регистрации. При повышении частоты случаев необходимо организовывать ретроспективные эпидемиологические исследования, проводимые на основе личных распросов, по отношению к согласованным с ними контрольным случуям. В настоящее время мониторирование врожденных аномалий может считаться одним из наиважнейших средств для раннего выявления тератогенных и мутагенных вредных воздействий.

ИЗМЕНЧИВОЕ ЛИЦО ДЕТСКОЙ ХИРУРГИИ

Д. ЛИСТЕР, ЛИВЕРПУЛЬ

Автор знакомит с изменениями и прогрессом в детской хирургии, которые произошли за последние 40 лет. Отдельно рассматривает результаты, достигнутые в детской хирургии, в хирургии злокачественных опухолей у детей, в детской травматологии и специальных областях детской хирургии.

ОПЕРАЦИИ, КОТОРЫЕ НЕОБХОДИМО ПРОИЗВОДИТЬ В ДЕТСКОМ ВОЗРАСТЕ

В. ТИШЕР, ГРЕЙФСВАЛЬД

5% детей появляется на свет с врожденными пороками развития. Некоторые из этих проков несовместимы с жизнью. Среди

дефектов развития центральной нервной системы закрытие миеломенингоцеле должно производиться сразу же после рождения ребенка, чтобы предотвратить развитие восходящего менингита и пиоцефалита. Атрезию пищевода тоже необходимо оперировать сразу, чтобы ребенок остался в живых. Экстраплевральная техника этой операции сильно улучшила ее прогноз.

Нарушения развития диафрагма, брюшной стенки, а также илеус тоже требуют немедленного оперативного вмешательства. В связи с этим автор подробно разбирает дифференциальный диагноз «острого живота» у новорожденных. Дефекты мочевыводящей системы лишь редко оперируют в новорожденном возрасте.

В хирургии новорожденных совершенно необходимо самое тесное сотрудничество детского хирурга, неонатолога и анестезиолога. Новорожденных детей можно оперировать лишь в таком учреждении, где эти условия имеются.

ВОЗРАСТНЫЕ ОСОБЕННОСТИ ОПУХОЛЕЙ НАДПОЧЕЧНИКОВ

С. ХОФМАН, МАЙНЦ

Опухоли надпочечников в детском возрасте сильно отличаются от взрослых форм, как с точки зрения частоты их встречаемости, так и с точки зрения их локализации и клинического проявления. В связи с этим часто возникают диагностические проблемы. Сравнение их со специфическими детскими заболеваниями только приводит на ложный путь. В противоположность этому, с точки зрения терапии практически нет разницы между опухолями надпочечников детского и взрослого возраста.

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27. XI. 1978. HU ISSN 0001—6527 Index: 26.021

ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

VOLUMEN XIX * 1978 * NO. 4

AKADÉMIAI KIADÓ, BUDAPEST

Acta paediat. Acad. Sci. hung.

ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

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Editorial office	Rédaction	Редакция	Redaktion

H-1083 Budapest, Bókay J. u. 53.

Annual subscription (one volume)	Abonnement par an (un volume)	Подписная цена за год (один том)	Jahresabonnement (ein Band)

$ 36.00

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 275—280 (1978)

Nationwide investigation of multiple malformations

By

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Received January 2nd, 1978

A nationwide programme for the evaluation of 1,339 newborns with multiple malformations (about 8% of all malformed babies) notified to the Hungarian Congenital Malformation Registry in the period 1973 to 1975, was launched on January 1st, 1973. As specific syndromes and anomalads, 696 cases (51.9%) were notified. On the basis of individual malformations, 87 cases were identified from 439 patients with notified associations, and 27 multiple malformations among 172 stillborns and infant deaths were recognized from autopsy records collected from pathologists. 341 surviving infants were officially referred to 'multiple malformation centres' for special examination. 57 infants of 129 cooperating families were identified. Benefits of this programme are (i) the proportion of specific syndromes and anomalads increased by 12.8%; (ii) the rate of unspecified multiple malformations decreased by 56.6%; (iii) examination of multiple malformations may be the most sensitive means to detect teratogens; (iv) 50.5% of the expected number of chromosome abnormalities in newborns was found; (v) the nationwide material of multiple malformed babies offers a possibility to clarify gene abnormalities and new syndromes.

Prevention is obviously better than cure and this axiom justifies the effort for mass, selective and multiphasic screening programmes [7]. But even after the manifestation of a disease, the accurate aetiological diagnosis may help to prevent recurrence and this particularly true for genetic and teratogenic anomalies.

The Hungarian Congenital Malformation Registry records the occurrence of malformations diagnosed and compulsorily notified from birth to the age of 1 year [1]. The recorded point prevalences at birth of all malformed babies and total congenital malformations were 33.6—34.6 and 29.6—31.4 per 1000 total births, resp., in the period 1972—1975. According to this Registry and the separate Monitor, the newborns with multiple (three or more different) malformations (MMs) represent a special category of congenital malformations.

(1) The occurrence of MMs is low, 7.5—8.5% of all notified congenital malformations, which means a point prevalence at birth of about 2.6—2.9 per 1000 total births;

(2) The majority of MMs is severe: 45.0% died in the infant period and further 6.9% were stillborn. (The completeness of recording fatal cases was nearly 100%.) There is, of course, a positive correlation between the severity of MMs and the completeness of their notification. According to

our estimation e.g. about 75% of Down syndromes are notified [4].

(3) MMs involve an extremely high number of various entities (perhaps over 1000), therefore the recognition of specific MMs is difficult and rare.

(4) Identification of MMs by the investigation of their localized malformations and history often allows to determine the aetiology.

Expectations

In the knowledge of the features of MMs, a programme was launched for nationwide processing and special evaluation of MMs data in Hungary on January 1st, 1973. This was facilitated by the following facts.

(i) In Hungary, 99% of deliveries take place in hospitals.

(ii) All infant deaths and the majority of stillborns are necropsied.

(iii) The registry of severe and visible MMs is practically complete.

The following purposes were defined for the programme.

(a) Nearly all known environmental factors, so-called teratogens (rubella, ionizing radiation, thalidomide, etc.) affecting humans produce MMs. Thus the monitoring and special evaluation of MMs seems to be the most sensitive means to detect a 'cluster' caused by old or new teratogens as soon as possible.

(b) Numerical and gross structural abnormalities of the autosomes and XO aberrations usually cause generalized malformations. Thus the majority of all chromosome abnormalities may probably be discovered by chromomosome analysis of the infants with MMs. (In the near future chromosome screening of all newborns cannot possibly be organized in most countries.)

(c) Most gene abnormalities show characteristic syndromes. (The localized manifestation is an exception to the rule [2].) Thus, evaluation of a national material of MMs may help to gain experience in syndromology [6] and to identify the specific syndromes accessible to prevention by genetic counselling.

This paper presents the most important data of the nationwide processing and special evaluation of 1,339 newborns with MMs (anomalads [5], specific malformation syndromes, associations and unspecified MMs) born in Hungary in the period 1973—1975 and notified up to March 31st, 1976 (Table I).

Results

1) 695 anomalads and specific syndromes were notified (51.9% of the total material). They were all included in the evaluation study. (Reliability of the notified diagnosis is difficult to estimate. Chromosome analysis in a representative sample of Down syndrome consisting of 110 cases, confirmed trisomy 21 in 92 children (83.6%) [4].

2) 439 MMs were notified, mentioning the individual malformations without the name of anomalads or syndromes. An attempt has been

TABLE I

Data and procedure of multiple malformation investigation in Hungary, 1973—1975

Notifications of specified anomalads and syndromes are accepted for evaluation

Anomalad	Syndrome				Associations + random combinations	Unspecified multiple malformations	PRE-Total
92; 6.9%	603; 45.0%				439; 32.8%	205; 15.3%	1339; 100.0%
	Monogen	Chromosome	Teratogen	Specified unknown origin	An attempt has been made to identify these cases on the basis of		
	118; 8.8%	473; 35.3%	9; 0.7%	3; 0.2%			
72	13	—	—	0	← Malformation reported	Detailed necropsy record	Specific clinical and laboratory examinations
17	3	3	1	—	← answered: 112		
1	11	37	13	1	← cooperated: 129		
							POST-total
182; 14.3%	145; 11.4%	513; 40.3%	23; 1.8%	4; 0.3%	317; 24.9%	89; 7.0%	1273; 100.0%
	685; 53.8%						66 Not multiple

made to recognize them on the basis of the combination of malformations described. E.g. abdominal muscle deficiency, dilatation of ureters and bladder with or without cryptorchidism were accepted as 'abdominal muscle deficiency anomalad', or posterior cleft palate, glossoptosis and micrognathia were assessed as 'Robin anomalad'. In this way 87 cases, 6.5% of the total material, could be classified.

Evaluation of the remaining 557 infants with associations and unspecified 'multiple' malformations (mentioned as "multiple", "syndrome", "monster" etc.) was continued in two directions.

3) Stillbirths and infant deaths were evaluated through correspondence: detailed necropsy records completed by personal opinion concerning the aetiology were collected from the pathologists. 172 such cases occurred among 557. The pathologists were requested to cooperate in 141 cases and suitable information was obtained in 112 cases. (31 cases had such a detailed description in the notification card that it did not seem worth-while to request further data.) Anomalads and syndromes could be classified in 27 cases. 49 unspecific MMs were promoted to associations. The detailed description revealed that 29 cases were not MMs.

4) Infants supposed to have survived beyond the neonatal period were officially invited to one of the six so-called "multiple malformation centres" organized for this programme. Each centre is provided with paediatricians interested in syndromology, genetics and teratology, and laboratory facilities (chromosome, serological, e.g. rubella, CID, toxoplasmosis, certain biochemical and immunological examinations) in order to establish the correct diagnosis in patients from 3—5 counties. 341 infants were referred to these specialists. In 44 cases, involving 3 or more malformations such as talipes, congenital dislocation of the hip, torticollis, scoliosis and congenital inguinal hernia, this examination did not seem reasonable, therefore the parents were not requested to cooperate. In 32 cases the address was incorrect. 129 families (41.7%) out of the remaining 309 cases presented their infants. The cause of the poor cooperation may have been the serious condition of the infant, the indifference of parents, etc. 57 MMs out of 129 were identified. Chromosome analysis was particularly effective in the Budapest centre. Attempts failed to identify any of known syndromes or anomalads in 41 cases; 20 infants had no MM.

(Detailed tables of anomalads and syndromes caused by gene abnormalities and environmental factors as well as of associations classified according to cardinal malformations will be sent at request.)

Pros and cons of the Programme

The main problems are as follows.

(i) The questionable reliability of specified diagnosis in newborns with MM notified to the Registry.

(ii) The incompleteness of notification, mainly in the mild or internal MMs.

(iii) The poor cooperation of parents in special examinations.

(iv) Infants notified with 2 malformations and therefore excluded from this study may nevertheless have MM.

(v) Syndromology is still a field unsettled in many respects (e.g. the classification of MMs is an unsolved problem in general, and particularly in the ICD VIIIth and IXth revision).

The benefits were as follows.

1. The proportion of specific syndromes and anomalads has increased by 12.8% (171 cases). Specification and especially the knowledge of the aetiology may be important in view of the estimation of prognosis and recurrence risk as well as for specific treatment and prevention.

2. The reliability of the MMs registry has improved significantly: the rate of unspecified MMs decreased by 56.6%, and 66 'no MM' were excluded.

3. Detection of a cluster of specific malformation syndromes helps to reveal teratogens. E.g. an obvious correlation was found between the 1974 rubella epidemic and the increased frequency of the combination of cataract, congenital heart defect and other malformations (Fig. 1).

4. 50.5% of the expected number of chromosome abnormalities could be detected (Table II). At first sight this proportion seems to be low, but several circumstances have to be taken into consideration. Thus, only peripheral blood cultures were performed; some severely affected infants died before the examination; several infants with MM have not been recognized and/or notified; the so-called minor malformations and functional anomalies, e.g. mental subnormality, are not or cannot be registered till the age of 1 year; few infants were taken to the centres for special examination.

5. The diagnosis of structural chromosomal abnormalities and recessive syndromes led to the detection of carriers. Alone in the Budapest centre 12 balanced chromosome abnormalities were found.

6. The nation-wide processing of MMs may offer a possibility to find new syndromes, to clarify the aetiol-

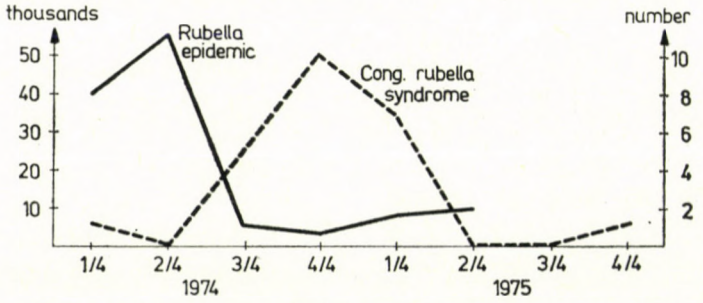

FIG. 1. Increased number of congenital rubella syndrome after rubella epidemic in Hungary 1974

TABLE II

Result of chromosome analyses*

Recognizable chromosome syndromes in infants	Occurrence among 55,679 newborns (per cent)	Expected figure (n = 540,045) No	Observed figure No	Per cent
Down	0.11	594	467**	78.6
Patau	0.005	27	11	40.7
Edwards	0.01	54	8	14.8
Deletions	0.01	54	5	9.3
Other structurals***	0.05	270	10	3.7
XO	0.003	16	12	75.0
Total	0.198	1015	513	50.5

* data of 7 well-known newborn studies in Arhus, Boston, Calgary, Edinburgh, Moscow, New Haven, Ontario-Winnipeg
** not all cases proved by chromosome analysis
*** including inversions and supernumerary markers

ogy of some others and to improve our knowledge of syndromology.

As far as we know this attempt was the first to organize a nationwide and partly follow up evaluation of MMs. (MMs were studied with a national register of malformations in Sweden [3].) A first attempt is always prone to imperfections but may allow to gain experience that makes this improved programme worth continuing and will perhaps encourage to establish similar ones.

ACKNOWLEDGEMENTS

We are indebted to the leaders of the "multiple malformation centres", Drs. L. Klujber, G. Kosztolányi, K. Méhes, Éva Oláh, Z. Papp, L. Szabó, G. Szemere, and to the cooperating pathologists, for valuable help in the study.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 281–284 (1978)

Relationship of renal threshold for bicarbonate reabsorption to urinary sodium excretion in premature infants

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Received February 5th, 1978

Renal threshold for bicarbonate reabsorption and urinary sodium excretion of nine healthy male premature infants with a mean birth weight of 1734 g (range 1650—1900) was determined on the 7th day of life, and subsequently weekly for 6 consecutive weeks, by applying a repeated NH_4Cl load. A close negative correlation was found between bicarbonate threshold and urinary sodium excretion ($p < 0.01$). It is suggested that the limited renal capacity to reabsorb sodium may account for the low bicarbonate threshold in premature infants.

During the first weeks of life the increasing acid input and the limited renal capacity to excrete hydrogen ions lead to metabolic acidosis in low-birth-weight neonates [7, 8]. The postnatal development of renal acidifying processes is considered to be the main factor in re-establishment of normal acid–base status [6, 7, 8, 12, 14, 15].

In a previous study we could demonstrate the rapid postnatal increase of the urinary hydrogen ion excretion in premature infants [6, 12]. The renal threshold for bicarbonate reabsorption was also found to increase from the very low value of 12 mmol/l in the first week to 17—18 mmol/l by the 4—6th week of life. No attempt was, however, made to explain the reasons for the low bicarbonate threshold in this early period of life.

In the light of the recent suggestion [2, 3] that besides functional nephron heterogeneity and alterations in the kinetics of the enzyme reactions underlying transport mechanisms, the phenomenon may be related to a low fractional reabsorption of sodium in the proximal tubule [4], we decided to reanalyse and complete our earlier data with a simultaneous measurement of urinary sodium excretion.

The present study was designed to investigate the relationship between renal bicarbonate threshold and urinary sodium loss in 1—6-week-old premature infants.

MATERIAL AND METHODS

Renal threshold for bicarbonate reabsorption of nine healthy male premature infants with a mean birth weight of 1734 g (range 1650—1900 g) was determined on the 7th day of life, and then weekly for 6 consecutive weeks, by applying a repeated NH_4Cl load.

The protocol of NH_4Cl administration, the timing of urine collection and blood

sampling, as well as the acid-base parameters of blood, and urinary hydrogen ion excretion have been described in detail [12].

Urinary sodium excretion was determined along with the bicarbonate threshold once weekly in urine samples which were collected during the control period of 12 hours preceding the administration of NH_4Cl. Sodium measurements were made by flame photometry.

The total CO_2 content of the blood at which hydrogen ion excretion was maximal was regarded as the renal threshold for bicarbonate reabsorption [2].

Statistical evaluation was performed by calculating the coefficient of correlation (r) and the equation of exponential regression (y).

Results

As it is shown in Figure 1, there was a close negative correlation between the renal bicarbonate threshold and urinary sodium excretion ($p < 0.01$). With a urinary sodium excretion of 10 μEq/min/1.73 m^2 the bicarbonate threshold was about 17—18 mmol/l, and with increasing sodium loss it decreased exponentially to reach a value of about 12 mmol/l at a urinary sodium excretion higher than 30 μEq/min/1.73 m^2.

Discussion

It has long been recognized that mineralocorticoid activity and renal sodium handling play an important role in the renal acidifying processes [9, 16].

In a series of papers we have shown that a close relationship existed between sodium homoestasis and acid-base regulation in premature infants during the first six weeks of life [6, 10, 11, 13, 14]. In support of

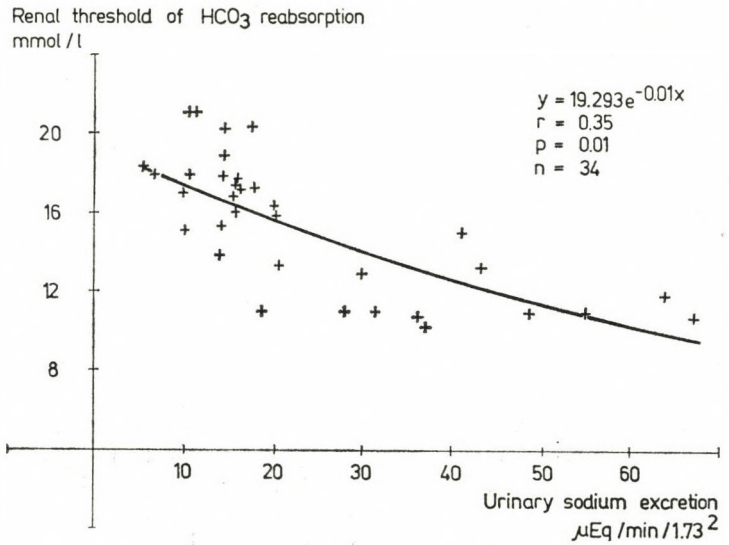

Fig. 1. Relationship between renal bicarbonate threshold and urinary sodium loss in 1—6 week-old premature infants

such a relationship the following findings are to be taken into account.

1. The initially low renal hydrogen ion excretion is associated with a high urinary sodium excretion but the development of renal capacity to excrete hydrogen ion results in a progressive increase in renal $Na^+ - H^+$ exchange [6].

2. Due to the increased urinary sodium excretion in the first two weeks of life, a negative sodium balance develops with subsequent hyponatraemia. The trend and time course of late metabolic acidosis and "physiological" hyponatraemia is similar.

In most cases it starts after the first week, becomes progressively more severe in the second and third weeks, and then corrects itself by the 5—6th weeks of life [10, 11].

3. In one-week-old newborn infants urinary sodium excretion decreases, hydrogen ion excretion increases parallel with birth weight, indicating the increasing rate of renal exchange of $Na^+ - H^+$ with maturity [13].

4. The present finding that the high urinary sodium excretion may, at least in part, account for the low renal threshold of bicarbonate reabsorption in premature infants may be interpreted as an evidence of the role of renal sodium handling in the maintenance of acid–base homeostasis.

The high urinary sodium excretion and the subsequent hyponatraemia with an increased activity of the renin-angiotensin-aldosterone system [1, 5] is characteristic of pseudohypoaldosteronism, which may be related to the functional and morphological characteristics of the immature kidney.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 285—290 (1978)

Relationship of metabolic acidosis to urinary sodium excretion in the newborn infant

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Received March 1st, 1978

The relationship between birth weight, postnatal age and acidosis-induced urinary sodium excretion was studied in 43 one-week-old newborn infants with birth weights of 1000—4300 g and gestational age of 28—41 weeks; and in 13 premature infants with birth weights of 1000—1970 g (mean 1620 g) and gestational age of 29—35 weeks (mean, 31.4 weeks) during the first six weeks of life.

Developmental changes were found in acidosis-induced urinary sodium excretion. Newborns with higher birth weight and postnatal age excreted significantly more sodium in response to acidosis than their lighter and younger matches.

It is suggested that the degree of acidosis must be taken into account when estimating the sodium requirement of newborn infants different in birth weight and postnatal age.

Previous studies have revealed a close relationship between sodium homeostasis and acid–base regulation in the neonatal period [11, 20, 22, 24]. In premature infants the limited renal capacity to reabsorb sodium in exchange for hydrogen ion (11, 22] and the low renal threshold for bicarbonate reabsorption [21] due in part to the increased urinary sodium loss [24] are the major factors to be considered in the development of late metabolic acidosis. Evidence is, however, accumulating that not only the urinary sodium excretion influences the acid–base homeostasis, but the degree of metabolic acidosis is also of great importance in controlling fractional sodium reabsorption in the kidney [9, 13, 14, 18, 19, 25].

In an attempt to clarify the role of acidosis in renal sodium handling during the neonatal period, a study was undertaken to investigate the effect of spontaneous or NH_4Cl-induced metabolic acidosis on urinary sodium excretion in newborn infants of various birth weights and of various postnatal ages.

Material and Methods

Two groups of healthy male newborn infants were selected for the study. Group I consisted of 47 one-week-old newborn infants with 1000—4300 g birth weight and of 28—41 weeks gestational age. Group II included 13 premature infants with 1000—1970 g (mean, 1620 g) birth weight and 29—35 weeks (mean, 31.4 weeks) gestational age.

The infants of Group I were studied on the 7th day of life in order to obtain informations as to the influence of birth weight on the relationship between metabolic acidosis and urinary sodium excretion.

The premature infants of Group II were studied on the 7th day of life and then once weekly for 6 consecutive weeks to find out whether postnatal development had any effect on the acidosis-induced changes in renal sodium handling.

The most important clinical characteristics of the newborn infants, the protocol of NH_4Cl administration, the timing of urine collection and blood sampling as well as the acid–base parameters of the blood, and urinary hydrogen ion and calcium excretion have been described in detail [23].

Urinary sodium excretion was determined from urine samples collected during a period of 12 hours, with determination of the acid–base status of the blood before and after NH_4Cl administration.

Sodium measurements were made by flame photometry, acid–base parameters of arterial blood were measured by the method of Astrup et al. [2]. Statistical evaluation was performed by calculating the coefficient of correlation (r) and the equation of exponential regression (y).

Results

Results are shown in Figure 1. It can be seen that metabolic acidosis did not correlate with urinary sodium excretion in infants weighing 1000—1500 g at birth. The increasing acidosis, however, tended to enhance the

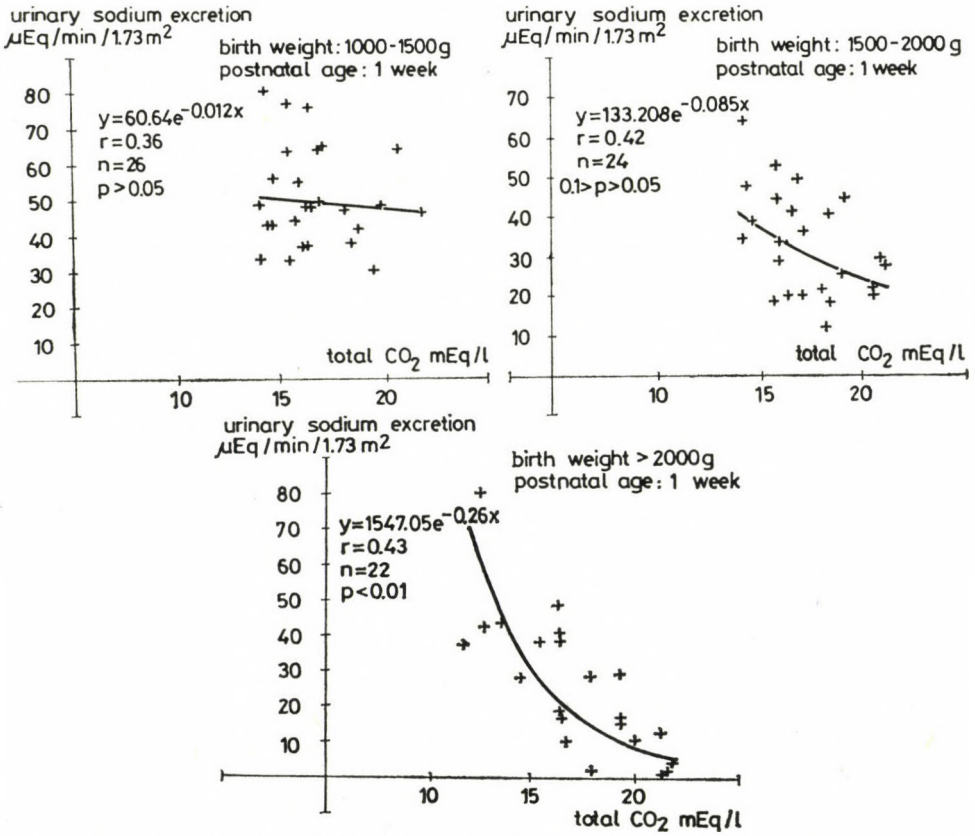

Fig. 1. Birth weight and acidosis-induced urinary sodium excretion in one-week-old newborn infants

urinary sodium loss without statistical significance in premature infants of 1500—2000 g birth weight. When the birth weight was higher than 2000 g, there was a significant inverse correlation between the total blood CO_2 content and renal sodium excretion; i.e. the increasing acidosis resulted in an exponentially increased renal sodium loss.

Figure 2. demonstrates the sequential changes in the acidosis-induced urinary sodium excretion of premature infants during the first six weeks of life. As it is shown, the acidosis did not influence renal sodium handling in the first week (Fig. 2/a). Its effect to raise the urinary sodium loss became more and more pronounced in the second (Fig. 2/b) and in the 3rd to 4th weeks (Fig. 2/c) and, finally, a close negative correlation was found between the total CO_2 of the blood and urinary sodium excretion in the 5th to 6th weeks of life (Fig. 2/d).

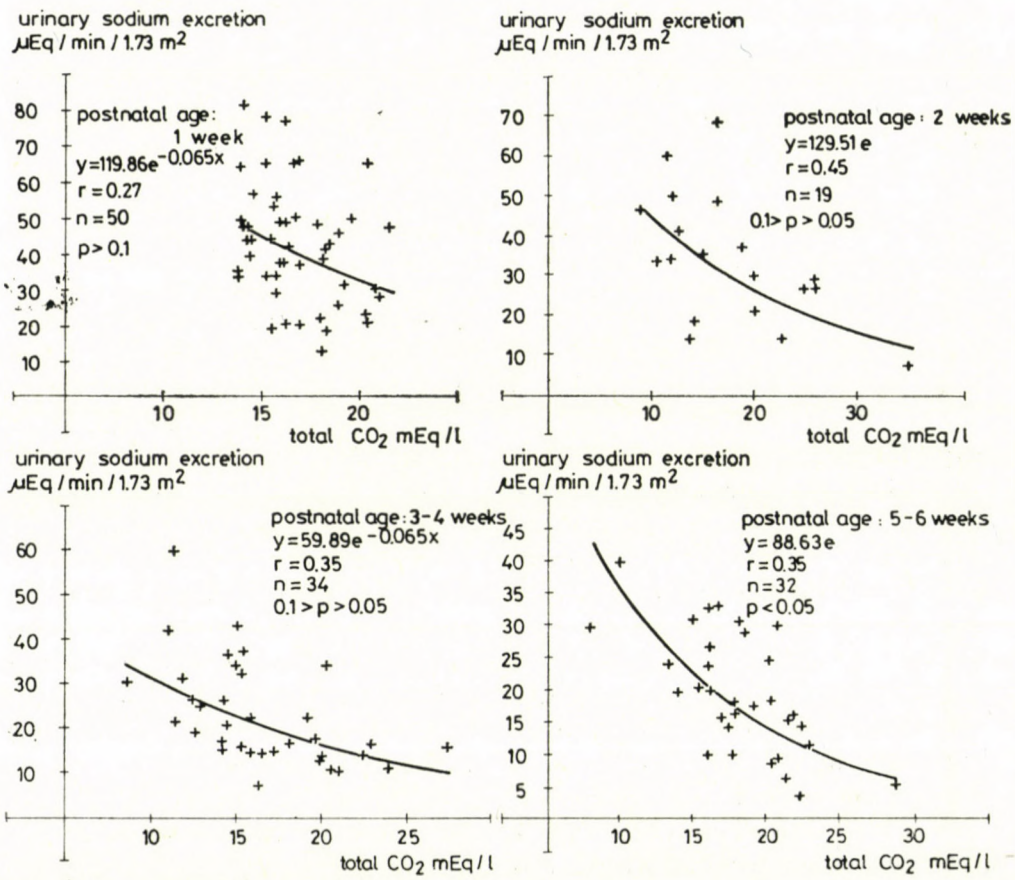

FIG. 2. Postnatal age and acidosis-induced urinary sodium excretion in premature infants

Discussion

The present findings are interpreted to indicate developmental changes in acidosis-induced renal sodium handling taking place either in utero (Fig. 1) or postnatally (Fig. 2).

Several studies have indicated that systemic metabolic acidosis results in a decrease of renal sodium reabsorption in rats [14, 19], dogs [9, 18], and also in humans [13, 25]. In spite of these findings the relationship between metabolic acidosis and renal sodium handling during the neonatal period is not quite clear. There is evidence indicating the existence of such a relationship even in the early period of life.

Late metabolic acidosis of low birth weight premature infants has been shown to cause a failure to gain weight [4, 12, 16, 26] and the increased urinary sodium loss due to acidosis has been considered an important factor in reducing the growth rate [5] Roy et al. recommended sodium supplementation in the form of NaCl or $NaHCO_3$ depending on the base deficit in very low-birth-weight infants for maintaining the normal plasma sodium concentration and for ensuring an adequate growth rate [17].

Our earlier observations that NH_4Cl administration to newborn infants resulted in an increased urinary sodium loss seemed to indicate more directly the modifying effect of acidosis on sodium handling by the neonatal kidney [11, 22]. In the present study we have obtained further information as to the role of metabolic acidosis in renal sodium excretion. It was pointed out that the lower the birth weight and the younger the neonate, the less pronounced the acidosis-induced urinary sodium loss.

We do not suppose that this is a consequence of the decreased responsiveness to acidosis of the immature kidney; it is rather due to factors overriding the effect of acidosis [1]. The main factors to be taken into account are the extracellular volume expansion [3], the high relative total sodium content of the body [15], the tubular unresponsiveness to mineralocorticoids [10], a functional and morphological glomerulotubular imbalance [8] with functional nephron heterogeneity [6, 7], and alterations in the kinetics of enzyme reactions underlying transport mechanism [6, 7].

As gestation advances or the premature infant grows older, the influence of the above-mentioned factors on renal sodium reabsorption is steadily decreasing and the effect of acidosis to enhance urinary sodium excretion becomes more evident.

On the basis of these findings it seems justified to suggest that the severity of acidosis must be taken into account when calculating the sodium requirement of newborn infants of various birth weights and various postnatal ages.

Acknowledgement

The authors are indebted to Professor E. Kerpel-Fronius for support in the study.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 291—297 (1978)

Bedeutung der EEG-Veränderungen bei verhaltensgestörten Kindern

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Eingegangen am 21. Februar 1978

Bei 732 verhaltensgestörten Kindern wurde die Häufigkeit der allgemeinen Veränderungen sowie der hypersynchronen Aktivität untersucht. Mittelschwere und schwere allgemeine Veränderungen kamen bei 11,5% der Fälle vor. Unter den einzelnen Verhaltenstypen wurde keine signifikante Abweichung gefunden. Die Verlangsamung trat — ähnlich wie bei gesunden Kindern — hauptsächlich im 7.—8. Lebensjahr auf. Allgemeine Veränderungen sind demnach bei verhaltensgestörten nicht häufiger als bei gesunden Kindern.

Eine hypersynchrone Aktivität (»Krampfpotential«) ließ sich bei 5,2% der verhaltensgestörten und bei 4—6% der gesunden Kindern nachweisen; unter den einzelnen Gruppen war keine signifikante Abweichung zu verzeichnen.

Es wird betont, daß ausschließlich aufgrund der EEG-Befunde die Diagnose der Epilepsie keinesfalls gestellt werden darf; in dieser Frage ist immer das Klinikum entscheidend. Die Diagnosen »latente oder larvierte« Epilepsie sind zu meiden. In solchen Fällen, also bei negativem klinischen Befund mit einer etwaigen EEG-Abweichung, darf keine antikonvulsive Therapie engeleitet werden.

Verhaltensstörungen sind Symptome einer komplexen Störung, die sich in einer Vielfalt von Erscheinungsformen manifestiert. Zur Zeit werden die klinischen Verhaltensstörungen aufgrund der Vorgeschichte und der klinisch-neuropsychiatrischen sowie psychodiagnostischen Symptomen in drei Gruppen eingeteilt: somatogene Verhaltensstörungen auf dem Boden einer nachweisbaren frühkindlichen Hirnschädigung [8, 14, 20]. psychogene Verhaltensstörungen als milieureaktive bzw. als eine Fehlentwicklung und die Kombination beider, das frühkindliche exogene Psychosyndrom [14].

Da die Funktion des Zentralnervensystems bei allen Formen betroffen ist, liegt es nahe, dem EEG eine wesentliche Bedeutung in der Diagnostik zuzuschreiben. Seit ihrer ersten Beschreibung [11] befaßten sich zahlreiche Verfasser mit den Zeichen dieser Störungen. Es wurde eine Fülle von Merkmalen beschrieben, und die EEG-Veränderungen untersuchte man auch unter Provokation (Hyperventilation, Photostimulation). Die Erfahrungen haben gezeigt, daß den Erwartungen entsprechend bei verhaltensgestörten Kindern das EEG häufig von der Norm abweicht. Da wir über zahlreiche EEG-Querschnittuntersuchungen gesunder Kinder verfügen, haben wir diese mit den EEG-Zeichen verhaltensgestörter Patienten verglichen.

Krankengut und Methoden

Das Probandenmaterial bestand aus 732 während der Jahre 1973—1976 an der Erziehungsberatung unserer Klinik behandelten 3—15jährigen Kindern. Bei allen lag eine psychogene Verhaltensstörung vor. Die Schwere der psychischen Symptomatik war unterschiedlich, mindestens aber so schwerwiegend, daß eine Untersuchung und Behandlung den Eltern notwendig erschien.

Aus der Anamnese ergaben sich keine Hinweise auf eine Hirnschädigung oder ein Schädeltrauma, die frühkindliche Entwicklung verlief bei allen normal. Die Kinder boten keine interne und neurologische Abweichungen, jeder Proband besaß mindestens normale Intelligenz. Fälle, in welchen zerebrales Anfallsleiden, Fieberkrämpfe oder auch nur respiratorische Affektkrämpfe nachweisbar waren, wurden nicht in Betracht gezogen.

Das EEG wurde mittels eines 8-Kanal Gerätes (Modell Zwönitz) in Ruhe und Wachzustand unter Hyperventilations-Provokation aufgenommen. Die Auswertung erfolgte nach anerkannten Prinzipien [3, 7].

Ergebnisse

Die klinische Symptomatik wurde nach den Leitsymptomen in 6 Gruppen gegliedert. Bei der Gruppierung war die führende Symptomatik ausschlaggebend (Abb. 1). Es zeigte sich eine auffallend hohe männliche Präponderanz mit einem Gipfel zwischen 7—10 Jahren (Abb. 2).

Veränderungen der Grundaktivität fanden wir bei 84 von 732 Kindern (11,5%). Die meisten Fälle kamen in den Gruppen 1 und 5 vor, signifikante Unterschiede konnten nicht beobachtet werden (Abb. 3). (30,4% wurden infolge der niedrigen Zahl der Fälle außer Acht gelassen.) Knaben und Mädchen — je 42 — kamen gleichmäßig vor. Die meisten Allgemeinveränderungen im Sinne einer Verlangsamung kamen bei beiden Geschlechtern im 7. und 8. Lebensjahr vor (Abb. 4). Hypersynchrone EEG-

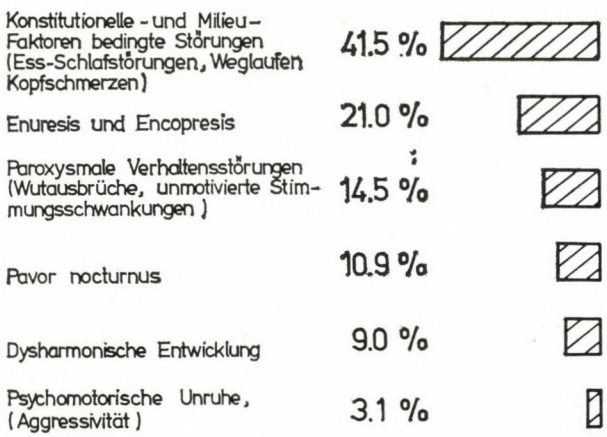

Abb. 1. Verhaltensstörungen und ihre prozentuale Häufigkeit nach dem leitenden Symptom

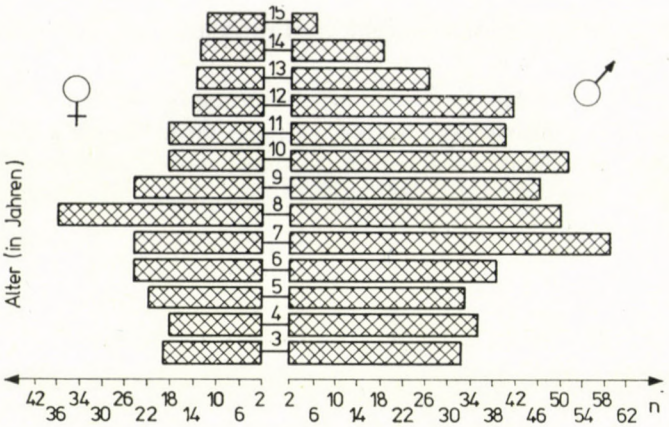

Abb. 2. Vorkommen der Verhaltensstörungen nach Geschlecht und Lebensalter

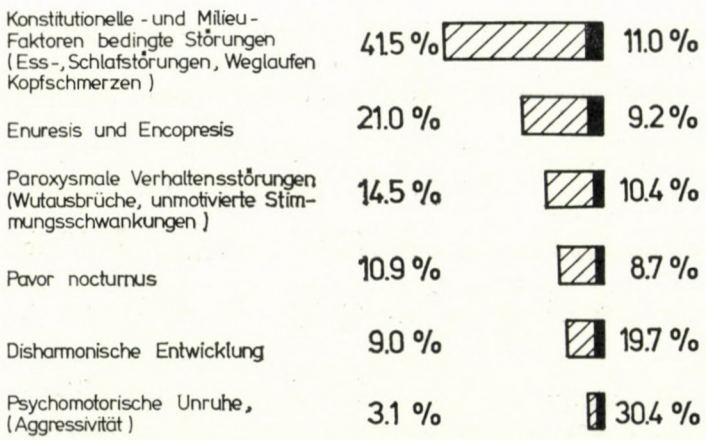

Abb. 3. Prozentuale Häufigkeit der Allgemeinveränderungen bei den einzelnen Verhaltensstörungen

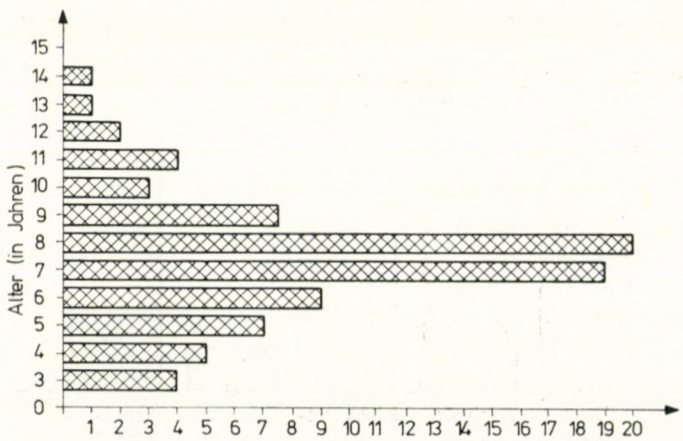

Abb. 4. Allgemeinveränderungen in den einzelnen Lebensjahren bei beiden Geschlechtern

Formen (spikes, spikes-wave-Komplexe, sharp-wave) fanden wir bei 38 von 732 Kindern (5.2%). Es wurden keine signifikante Unterschiede unter den einzelnen Gruppen verzeichnet (Abb. 5). Von den 38 Kindern waren 24 Knaben und 14 Mädchen.

Besprechung

Bei Verhaltensgestörten wurden praktisch alle Arten abnormer EEG-Befunde beschrieben [19]. Es wurde jedoch festgestellt [9], daß weder die Art der Störung, noch ihr mutmaßlicher Entstehungsmodus mit der Häufigkeit des Auftretens oder der Verteilung eines bestimmten EEG-Befundes signifikant korrelieren. Die Frage wird durch die Tatsache weiter kompliziert, daß die verschiedenen Untersucher die kindlichen Verhaltensstörungen unterschiedlich definiert und insbesondere die Unterteilung in somatogene und psychogene Gruppen unterschiedlich aufgefaßt haben.

Die Auswertung des EEG hat auch seine Probleme. Die Ableitung stellt nur einen begrenzten Ausschnitt der Realität dar, der für die untersuchte Verhaltensstörung möglicherweise ungünstig gewählt ist [10]. (Abb. 6).

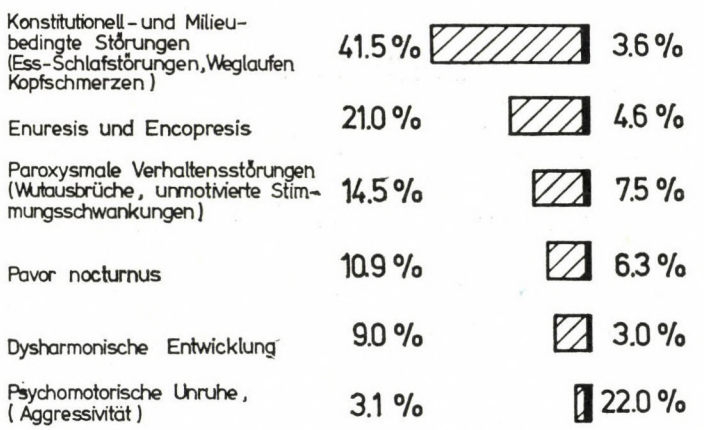

Abb. 5. Prozentuale Häufigkeit der hypersynchronen Aktivitäten bei den einzelnen Verhaltensstörungen

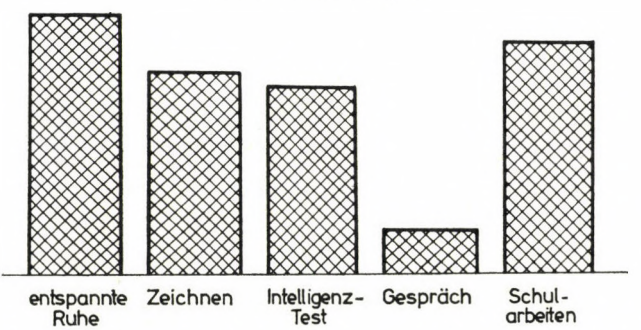

Abb. 6. Häufigkeit der hypersynchronen Entladungen unter psychischer Belastung verschiedener Intensität (nach Guey 1970)

Die Aufnahmebedingungen schreiben ein ruhiges, entspanntes Dasitzen vor. Statt dessen wäre es sinnvoll, gestörtes Verhalten direkt, d. h. während es sich ereignet elektroenzephalographisch zu registrieren. Die Variabilität der Befunde ist somit der konventionellen visuellen EEG-Analyse und der Uneinheitlichkeit der Nomenklatur zuzuschreiben.

Wir haben deswegen zwei solche EEG-Merkmale ausgesucht, deren Nomenklatur einheitlich ist bzw. die von den üblichen Hirnstrombildern stark abweichen: 1) die Veränderung der Grundaktivität und 2) die hypersynchronen Potentiale.

Mäßige bis starke Allgemeinveränderungen fanden wir bei 84 Kindern. (Leichte Allgemeinveränderungen wurden nicht bewertet, sie sind bei der Varianz des normalen kindlichen EEG auch schwierig abzuwägen.) Nach der Altersverteilung lag der Gipfel im Alter von 5—9 Jahren (Abb. 4). Fast die Hälfte [35] von den 84 Kindern waren 5—7 Jahre alt. Wenn wir das mit solchen zuverlässigen Untersuchungen [4, 13, 16] vergleichen, die bei normalen Kindern die gleichen Werte aufzeigten, so ist es anzunehmen, daß die Verlangsamung in diesem Alter völlig physiologisch und als Zeichen des Hirnreifens aufzufassen ist.

Hypersynchrone EEG-Formen fanden wir bei 38 Kindern (5,2%). Da Spitzenherde im EEG bei 4—6% von gesunden Kindern vorkommen [5, 6, 12], sieht man, daß diese bei Verhaltensstörungen keine Häufung aufweisen (Abb. 7. und 8). Die hypersynchronen Aktivitäten — oder mit der irreführenden Benennung Krampfpotentiale — beweisen bei den verhaltensgestörten Kindern überhaupt nichts, nicht einmal eine somatogene, also organisch bedingte Ur-

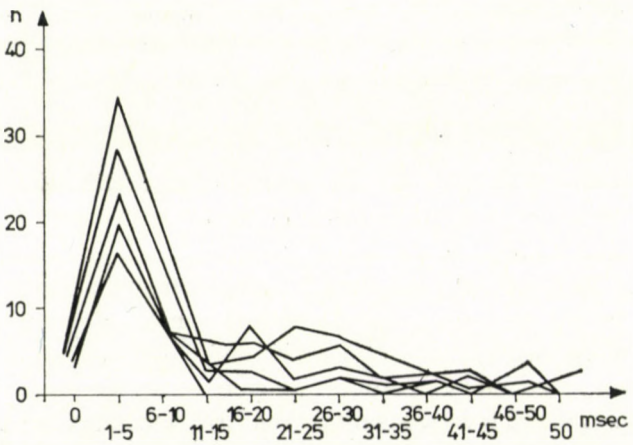

Abb. 7. Verteilung der Phasendifferenzen — ausgedrückt in m/sec — von Alpha-Wellen rechts und links okzipital bei einer Gruppe von gesunden Kindern. Sie wurden mittels Computer-Analyse bestimmt und stellen ein exaktes Maß für die Synchronie der Grundaktivität dar. Der Gipfel von Werten zwischen 1 und 5 m/sec zeigt eine große Synchronie

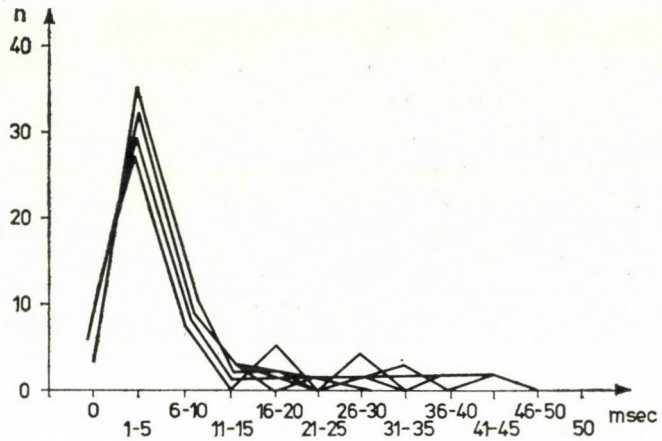

Abb. 8. Bei einer Gruppe verhaltensgestörter Kinder konnten grundsätzlich die gleichen Verhältnisse festgestellt werden; die Variabilität war jedoch eindeutig größer (nach Martinius Hoovey 1971)

sache der Beschwerden. Früher sprach man gern auch von »maskierter Epilepsie«, wenn inkriminierte Verhaltensstörungen mit hypersynchroner Aktivität einhergingen. Man muß aber zu einer klaren Entscheidung gelangen, ob eine Epilepsie vorlag oder nicht. Hypersynchrone Aktivität (Krampfpotentiale) bedeutet bei weitem nicht eine Epilepsie: hier sind die Anamnese und das klinische Erscheinungsbild entscheidend. Auf keinen Fall sollte man also zu einer »Probe-Therapie« greifen, um eine exakte Diagnose zu erhalten [17]. Man muß immer bedenken, daß die Diagnose der Epilepsie auch heute noch erhebliche emotionelle und soziale Konsequenzen mit sich zieht und daß selbst eine entsprechende medikamentöse Therapie schwerwiegende Folgen haben kann.

Schlussfolgerungen

Mit den obigen Ausführungen sollte verdeutlicht werden, daß die Relevanz der EEG-Befunde bei Verhaltensstörungen umstritten ist, umstrittener, als man im allgemeinen annimmt. Damit soll jedoch nicht gesagt werden, daß es sinnlos sei, das EEG als diagnostische Hilfsmittel bei Verhaltensstörungen einzusetzen.

Neuerdings wurde der Versuch unternommen, EEG-Zeichen der Reife (»hirnbioelektrische Reife«) für die Beurteilung von kindlichen Verhaltensstörungen heranzuziehen [18]. Zur Beurteilung der hirnbioelektrischen Unreife dienen verschiedene Parameter [1, 2], die mit den Eigenschaften der Grundaktivität im Zusammenhang stehen, wie Rhythmik, Frequenz, Kontinuität, Synchronität und interhemisphärische Synergie. Es ist denkbar, daß diese Parameter einmal

interessante und relevante Befunde ergeben werden. Ihre exakte Beschreibung erfordert jedoch automatische und computer-gesteuerte Analysemethoden [15] (Abb. 7, 8). Kommt es bei einem verhaltensgestörten Kind im Laufe seiner Entwicklung zur Organisation einer vorher unregelmäßigen Grundaktivität oder zum Verschwinden hypersynchroner Potentiale, so wird man diese Änderung des Hirnstrombildes als ein günstiges Zeichen, als eine Reifung werten.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 299—301 (1978)

Effect of taste and temperature on neonatal sucking behaviour

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Received March 5th, 1978

The sucking behavour of 10 healthy newborns was studied while feeding them with milk of different types (V formula and EBM) and temperature (23.5°C and 37.5°C) on the 4th, 5th, and 6th days of life. Total feeding time, duration and number of intervals, frequency and pressure were analysed from 120 sucking patterns. The babies did not alter their sucking behaviour on feeding with different milks, but they reacted to the different temperature in one of three trials.

INTRODUCTION

Normally, a healthy newborn experiences only the taste of amniotic fluid or breast milk, or sugar water of room or body temperature. Any change in the feeding habit may raise the question whether the newborn was able to distinguish differences in taste and temperature.

One of the first to study the infant's sensitivity to taste stimuli was Canestrini [2] who judged it on the basis of the fontanelle and breathing curve. Then Nelson [7] studied their taste preference to, and distinction of, various temperatures and fluids, and Maller and Desor [6] by measuring the ingested amount of food. Johnson and Salisbury [4] fed newborns with different milks, and found differences in their breathing, heart rate and sucking pattern.

In view of some differences in the above results we have made a study of the sucking pattern on feeding with different kinds of nutrients of different temperature.

MATERIAL AND METHODS

The sucking pattern was studied in 10 healthy newborns; their mean gestational age was 40 (38 to 42) weeks, their mean birth weight 3370 g. Nine babies were delivered vaginally, one by Caesarean section. Their Apgar score was 9 to 10 and the perinatal period uneventful.

All babies were bottle fed. The sucking pattern was recorded by a multichannel monitor connected to a transducer.

The test meals were offered at the usual feeding time at the age of 4, 5 and 6 days. The procedure was repeated each time in the order, cold V formula, warm V formula, warm EBM, cold EBM. The amount given was 20 ml/kg. The temperature of cold milk was 23.5°C, of the warm milk, 37.5 °C.

Thirty sucking patterns were recorded with each type of feed, thus a total of 120 were obtained. The total feeding time, the duration and number of intervals, mean sucking frequency during 2 min and mean total pressure during 2 min were compared with V formula and EBM, at two different temperatures.

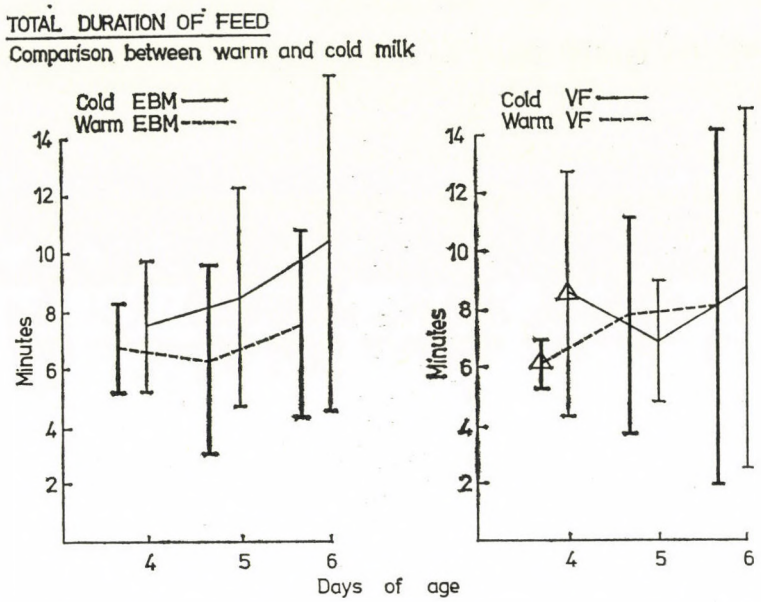

FIG. 1. Total duration of feed (comparison between warm and cold milk)

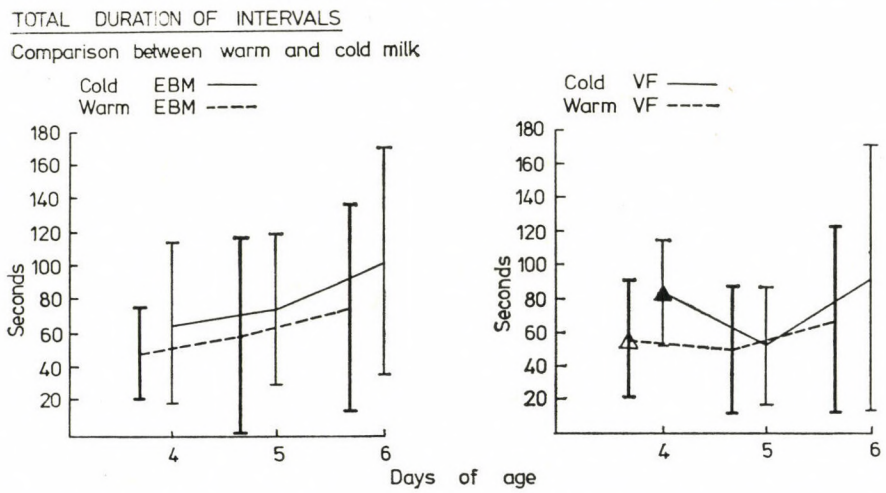

FIG. 2. Total duration of intervals (comparison between warm and cold milk)

RESULTS

The duration of feeding, the length and number of the intervals and the frequency of sucks/min differed significantly in one of the three trial feedings with cold and warm V formula. This meant that the feeding time, the duration of intervals was longer, the number of intervals was higher and the frequency of sucks lower with cold milk. Sucking pressure

was not affected in any case, nor did the temparature of EBM cause changes in the sucking pattern. Milks different in taste (such as EBM and formula V) failed to cause differences in any of the parameters.

Discussion

Neonatal sucking behaviour is known to affect somatic development and may reflect the neurological condition of the baby.

In the newborn, the taste buds, which appear in the 12th week of gestation, are fully mature. The two kinds of milk applied were both sweet and the differences in their taste were not relevant. In any case, the newborns did not react to it as they did not alter their sucking behaviour.

Sucking behaviour, however, is a complex process and is not considered to reflect taste discrimination [8]. Nor is there, as it has been shown in fetal sheep, a direct correlation between the neural response and behavioural responsiveness [1].

On the other hand, the sucking behaviour displayed a significant change in one among three trials on feeding with cold and warm V Formula. A change in the sucking pattern occurs when the temperature of milk is below 20°C or above 40°C [5], and it was shown [9] that in all homeothermic animals the response of the gustatory nerve is greatest at the temperature of the tongue.

Acknowledgement

Z. M. is indebted to the Wellcome Trust for a research fellowship.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 303–314 (1978)

Lymphocyte subpopulations and development of immune functions in the newborn baby

by

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Received March 1st, 1978

The distribution and dynamics of T, B and O cell populations were investigated in healthy term and preterm babies of 22–38 weeks gestational age, in relation to gestational age and birth weight, using the single slide method. Children 1-14 years old served as controls.

Development of immunological competence in the fetus destined to ensure a smooth adaptation of the newborn is an important problem. The process of immune response in both intrauterine and extrauterine life is brought about by the interaction of a number of factors. This is well illustrated in the figure of Astaldi et al. [2] (Fig. 1). There are

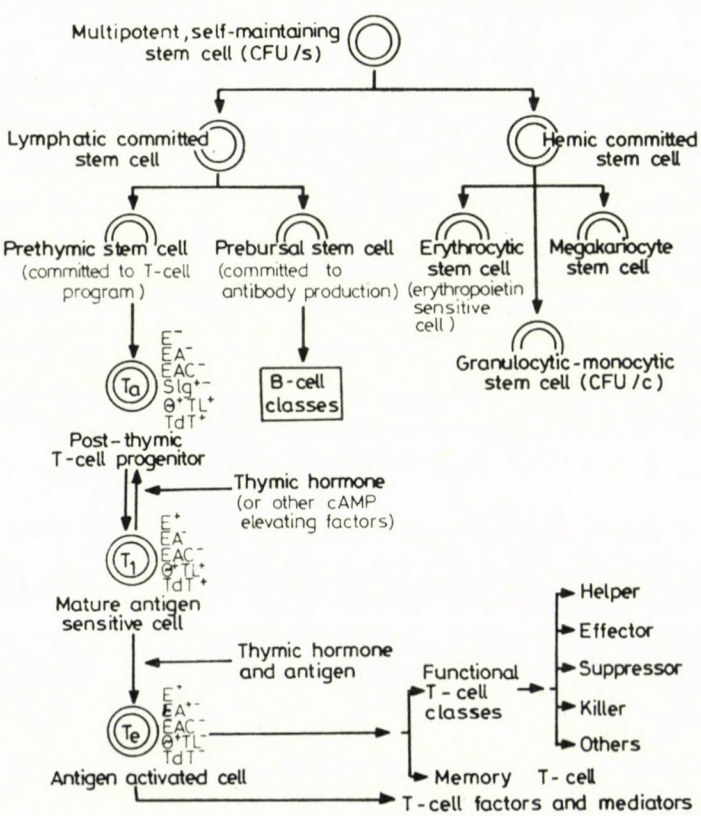


FIG. 1. The mechanism of immune response (After Astaldi et al. 2)

various ways to test the functional capacity of the immune response. The following approaches lend themselves for the purpose.

1) Studies on the maturation and development of phagocyting functions [3, 17, 22, 26, 36];

2) the appearance of circulating immunoglobulins [25, 30, 37, 39, 42];

3) the appearence and dynamics of surface membrane markers [9, 13, 14, 18, 19, 24, 32, 33, 44].

4) changes in enzyme functions affecting the immune functions [1, 15, 16, 23, 28, 38];

5) the effect of various realizing factors [31, 39, 40, 43, 45]; and

6) the isolation of the two lymphocyte subpopulations (T and B cells) on the basis of their electrophoretic mobility [8, 27, 34].

Most of the references cited above were concerned only with part of the development of immune competence, for example the time of the first or measurable reactions, the events following an antigenic stimulus, or the changes in inducibility and response to infections. Since the papers of Sterzl [39, 40] no comprehensive review has been published offering detailed information based on experimental work.

During the past few years we have attempted to study the development of immune competence and its changes during post-natal adaptation by means of complex methods. The present paper reports on some results of this work.

Lymphocyte subpopulations

Part of the methodology developed for the discrimination of T and B lymphocytes in human peripheral blood concerns the characteristics and maturation of surface membrane markers [13, 18, 19, 29].

B-cells carry on their surface receptor structures that derive from immunoglobulin molecules, and can therefore be demonstrated on the surface of these cells with the help of fluorescein isothiocyanate (FITC) conjugated anti-immunoglobulins. In addition, the presence of C_3 receptors can also be shown on these cells 37). B-cells also carry Fc receptors, binding the Fc part of immunoglobulins, that can be detected either with antigen-antibody complexes or with aggregated immunoglobulins [10]. The above methods identify about 25% of the normal adult peripheral blood lymphocytes as B-cells.

T-cells are characterized by the presence on their surface of sheep erythrocyte receptors; therefore, the demonstration of sheep red blood cell (SRBC) rosettes is suitable for the identification of this cell population.

The *total-rosette* technique, where lymphocytes are incubated with the SRBCs for 2 to 24 hr, identifies approximately 70% of normal, adult peripheral blood lymphocytes as T cells.

During a short incubation only the sensitive receptors will bind the erythrocytes. This technique, called the *active-rosette* method will dem-

onstrate approximately 25% T-cells in the peripheral blood. The most widely used rosetting techniques were described by Jondal [18, 19].

Another very sensitive but technically more difficult approach for the identification of T-cells involves the use of specific anti-T-cell sera [10].

On the basis of electrophoretic mobility it was established that T-cells belong to the "fast moving" category, having an electrophoretic mobility of over 1 micron $\cdot$ sec^{-1} $\cdot$ v^{-1} $\cdot$ cm, while B-cells move slower, their mobility being less than 1 micron $\cdot$ $sec^{-1} \cdot v^{-1}$ $\cdot$ cm [8].

Apart from studying the distribution and dynamics of T and B cells in preterm and term newborns, LDH isoenzyme investigations were carried out for differentiation of the two cell types [20].

T and B cells differ not only in their membrane structure but also in other functional properties. T lymphocytes for example have a higher neuraminidase activity but a lower sulphydryl and ribonuclease sensitive phosphatase activity, and they differ in acid alpha-naphthyl-acetate esterase and cholinesterase activity [23, 28]. Freeze-fracturing of their membrane also demonstrates considerable differences [29].

Some of the lymphocytes in human adult peripheral blood do not carry surface markers, and were therefore termed *nil-cells*. Greaves et al. [13]. described a method for their isolation, where sedimented lymphocytes were further separated on a nylon-wool column containing bound anti-immunoglobulin.

Opinions differ about the functional role of nil-cells. Using separated nil-cells obtained from malnourished children, Chandra [5, 6] demonstrated their lytic capacity on xenogeneic not target cells. The mechanism of this spontaneous lymphocytotoxity is not known. The phenomenon which might have important practical consequences was referred to as "in vitro veritas" by Podleski [35]. Chandra [6] described a suppressor effect of nil-cells on the PHA-induced DNA synthesis of T-cells. According to his view, the reduced cellular immune response of malnourished children could be explained on this basis. If this proves true, nil-cells might play an important role in combating infections.

In our studies, the method of Christiansen et al. [9] with minor modifications was used for the identification of the three lymphocyte subclasses. The method involves the use of membrane markers and is assessed on the same slide.

The relationship of lymphocyte populations to gestational age and birth-weight.

Patients and Methods

Patients. All tests were performed on newborns of less than a week of age, hosipitalized at our department. The male : female ratio was 1 : 1. Healthy children between 1 and 14 years of age served as controls.

When determining the relationship of lymphocyte subclasses to gestational age, the following groups were examined.

Less than 28 gestational week,	6 babies
29—36	11 babies
over 37	13 babies
controls	11 children.

There was a similar grouping according to birth-weight,

1001—1500 grams,	10 babies
1501—2500 grams,	10 babies
over 2500 grams,	11 babies
controls	9 children.

Lymphocyte suspension. 2—3 ml peripheral blood was drawn into 500 IU heparin, and sedimented at 1100 *g* for 20 min on a Ficoll-Uromiro gradient of 1072 p/ml specific gravity. Lymphocytes obtained from the interface were washed twice with PBS for 10 min at 200 *g*. Cell concentration was adjusted to 2×10^6/ml. The whole procedure was done at 4 °C.

Sheep red blood cell (SRBC) suspension. Defibrinated sheep blood was washed three times at 800 *g* for 10 min and the suspension adjusted to 2%. Human AB serum inactivated at 60 °C for 10 min was added. Optimal cell concentration was 2×10^8/ml.

FITC-conjugated anti-human IgG and IgM sera. FITC-labelled anti-IgG (Hyland, Antiserum gegen human IgG-Gamma-Ketten spezifisch) and anti-IgM (Hyland, Anti-serum gegen human IgM-μ-Ketten spezifisch) sera were adjusted with PBS to 10 mg/ml concentration.

Lymphocyte labelling. Two parallel studies were started for each newborn. In the first, 100 μl · lymphocyte suspension was incubated with 100 μl anti-IgG serum, in the other with 100 μl anti-IgM serum at 4°C for 50 min. This was followed by washing the lymphocyte suspension twice at 200 *g* for 5 min to remove excess serum and the cells were resuspended in 100 μl volume. 100 μl of SRBC suspension was added to both samples and the mixture was incubated at 37°C for 15 min. The cell suspensions were then centrifuged at 150 *g* for 10 min and further incubated at 4°C for 2 hours. After careful resuspension, results were assessed on a slide.

Evaluation under the fluorescence microscope. A Fluoval fluorescence microscope was used, equipped with a HB 200 light source, B 223 g and G 241 filters, 40/0.95 apochromatic lenses and 6.3 × eyepieces. 200 cells were examined in each sample. Lymphocytes were considered to be T-cells when they bound 3 or more SRBS-s. B-cells were detected as exhibiting surface bound IgG. IgM positive cells were also counted, their number is given separately since their ratio in accordance with other findings, was considerably lower than that of the IgG bearing lymphocytes. Cells that failed to form rosettes and did not carry immunoglobulins on their surface were designed "O"-cells. The ratios of cell subpopulations are

given in percentage. An attempt was made to determine the absolute values per μl blood for the lymphocyte subclasses but this was made unreliable by the finding that the WBC count in newborns shows considerable variation even within a short interval.

Evaluation was done with the two-tailed *t*-test. The Tables show the mean values ($\bar{x}$), number of patients (n), standard deviation (s_x), the *t* values and the level of significance.

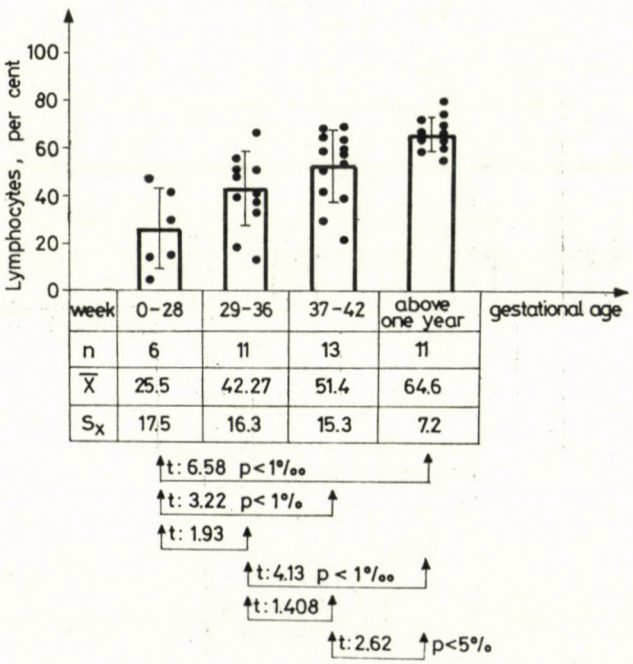
Results

T-cell subpopulation and gestational age. With the increase of gestational age the percentage of T-lymphocytes rises (Table I). Newborns of lower gestational age had lower T-cell values and the difference was significant. There was also a significant difference between any of the alternate groups.

B-lymphocyte subpopulation (IgG positive cells) and gestational age. In contrast to T-cells, the percentage of B-lymphocytes showed a decreasing tendency with gestational age (Table II). The lowest values were found in newborns of over 37 gestational weeks and the controls. However, a significant difference was only found between the control group and those with the lowest gestational age.

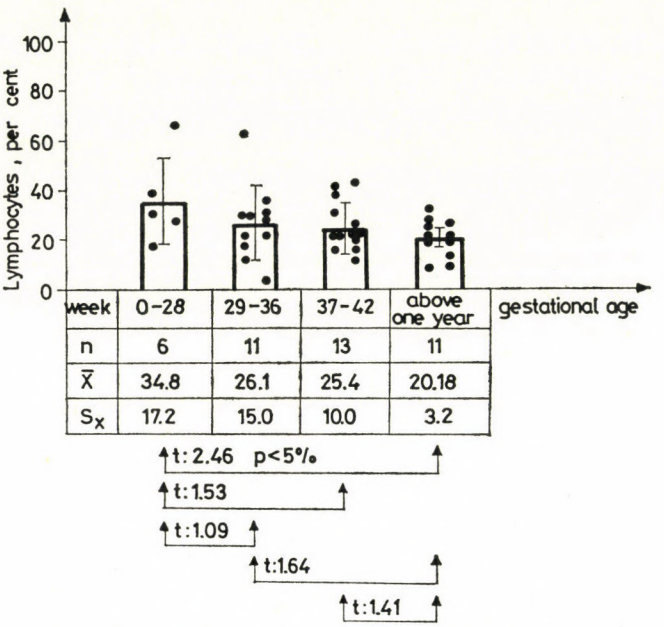
O-cell subpopulation and gestational age. With increasing maturity the number of O cells decreases (Table III). The values in the control group

Table I.



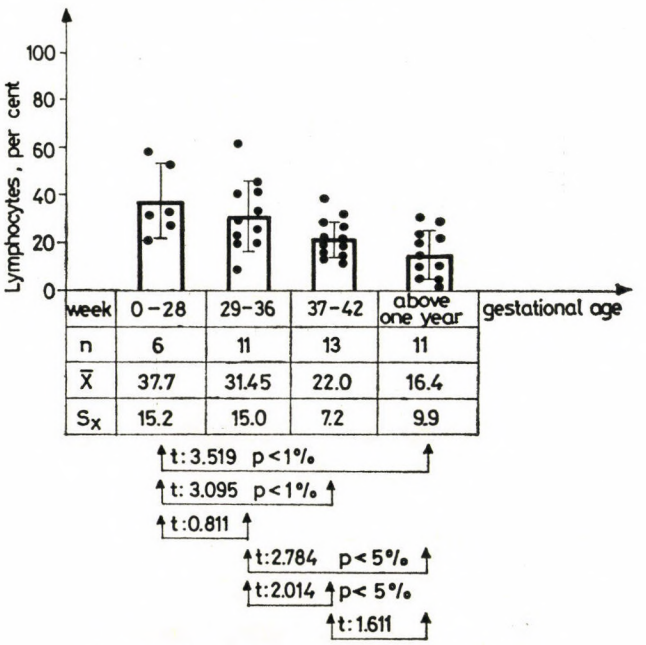
T cell subpopulation and gestational age

TABLE II



B cell subpopulation and gestational age

TABLE III



O cell subpopulation and gestational age

were higher than those reported for adults in the literature. Thus, the decrease continues until adulthood. In spite of the high values, the differences between the four groups were significant in all but two relationships.

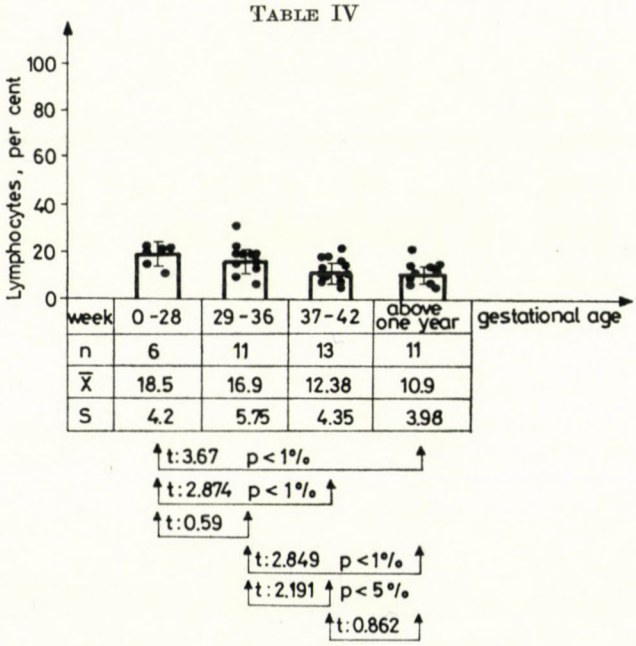
Lymphocyte surface IgM and gestational age. Similarily to IgG, the percentage of IgM bearing lymphocytes decreased with gestational age (Table IV). Since the number of IgM bearing lymphocytes in all the investigated groups was lower than that of the IgG bearing ones, the percentages are given separately for the two types of B-cell.

T-lymphocytes and birth weight. The number of E-rosette forming cells rose parallel with birth weight (Table V), similarily as with gestational age. The differences were significant in relation to the controls as well as between alternate birth weight groups.

B-lymphocytes (surface IgG positive cells) and birth weight. There was no direct relationship in the decrease of B-cells to increasing birth weight, as confirmed by statistical analysis (Table VI). The highest values were found in the 1001—1500 g group, followed not by the 1501—2500 g group but the one with birth weights above 2501 g.

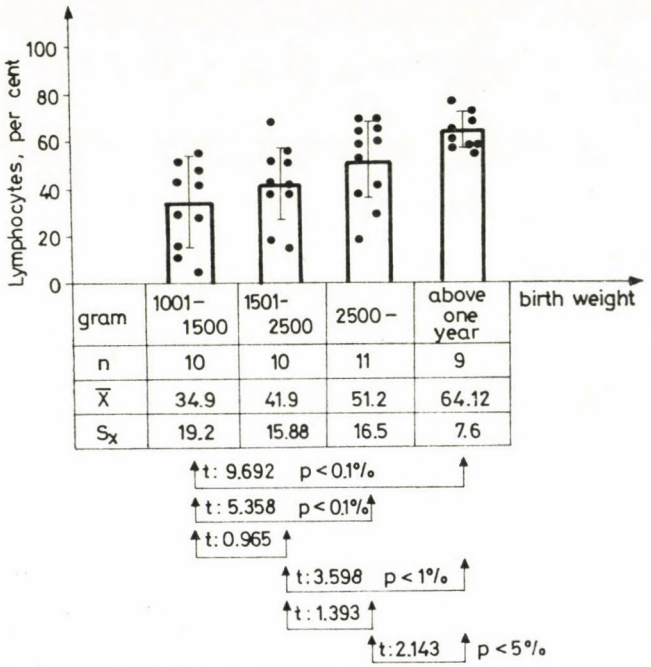
O-cell population and birth weight. The higher the birth weight, the less was the number of O-cells (Table VII). The highest values were found in the 1001—1500 g group, significant differences were, however, only found in two instances.

TABLE IV



Lymphocyte surface IgM and gestational age

TABLE V

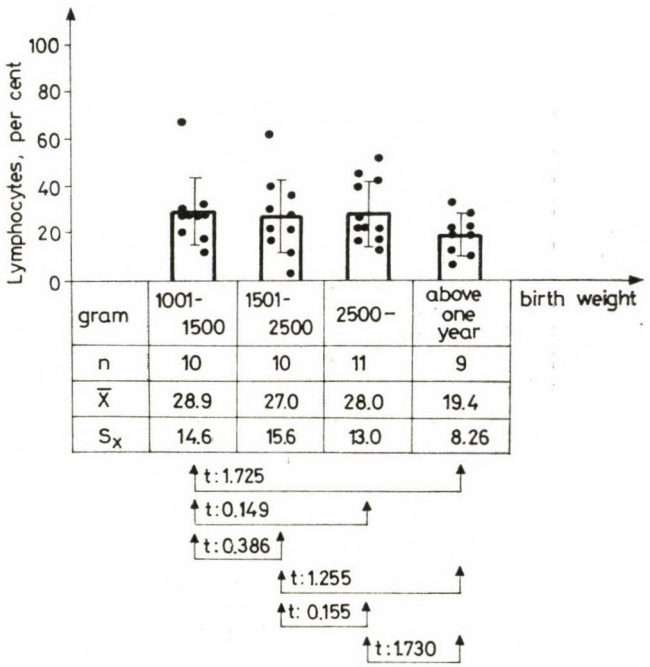


gram	1001–1500	1501–2500	2500–	above one year
n	10	10	11	9
$\bar{X}$	34.9	41.9	51.2	64.12
S_x	19.2	15.88	16.5	7.6

t: 9.692 $p < 0.1\%$
t: 5.358 $p < 0.1\%$
t: 0.965
t: 3.598 $p < 1\%$
t: 1.393
t: 2.143 $p < 5\%$

T cell subpopulation and birth weight

TABLE VI

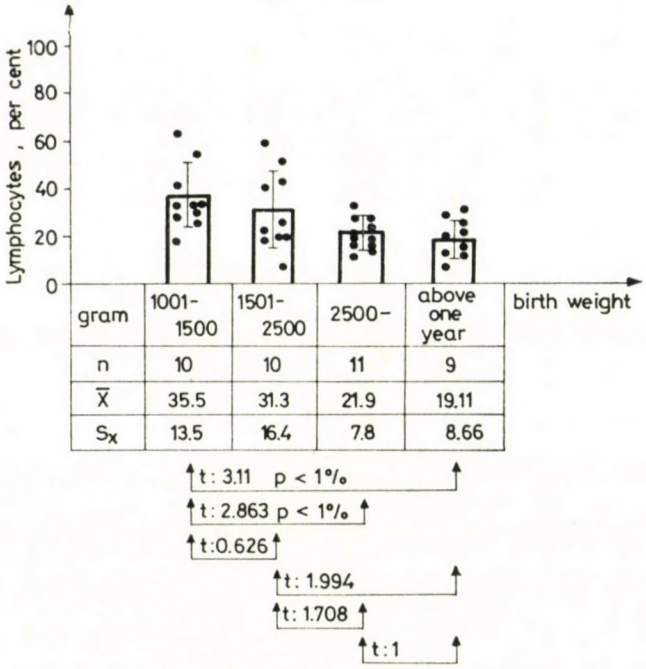


gram	1001–1500	1501–2500	2500–	above one year
n	10	10	11	9
$\bar{X}$	28.9	27.0	28.0	19.4
S_x	14.6	15.6	13.0	8.26

t: 1.725
t: 0.149
t: 0.386
t: 1.255
t: 0.155
t: 1.730

B cell subpopulation and birth weight

TABLE VII

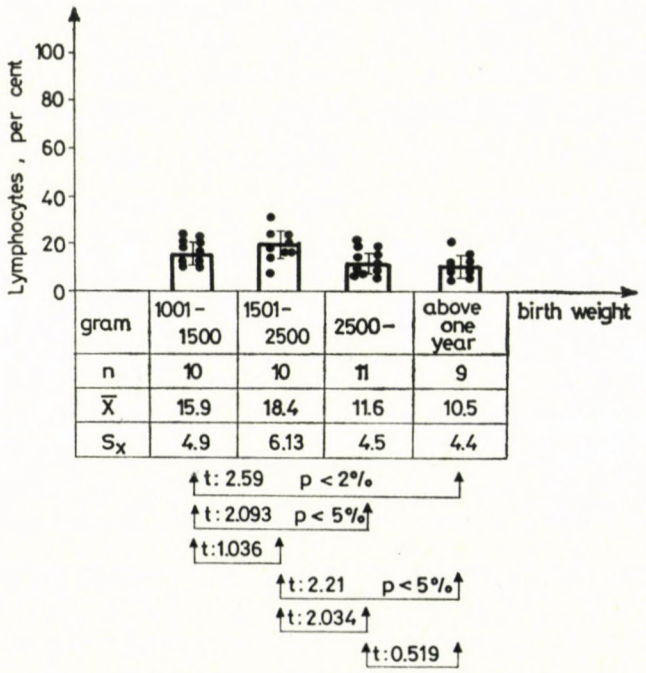


gram	1001–1500	1501–2500	2500–	above one year
n	10	10	11	9
$\bar{X}$	35.5	31.3	21.9	19.11
S_x	13.5	16.4	7.8	8.66

t: 3.11 p < 1%
t: 2.863 p < 1%
t:0.626
t: 1.994
t: 1.708
t:1

O cell subpopulation and birth weight

TABLE VIII



gram	1001–1500	1501–2500	2500–	above one year
n	10	10	11	9
$\bar{X}$	15.9	18.4	11.6	10.5
S_x	4.9	6.13	4.5	4.4

t: 2.59 p < 2%
t: 2.093 p < 5%
t:1.036
t: 2.21 p < 5%
t: 2.034
t:0.519

Lymphocyte surface IgM and birth weight

Lymphocyte surface IgM and birth weight. The distribution of IgM positive cells in the sub-groups was different from that of the IgG bearing cells. The highest values were found in the 1501—2500 g group, followed by the 1001—1500 g group (Table VIII). Significant differences were found in 3 instances.

Discussion

The aim of the present study was not the earliest detection of circulating T, B and O lymphocytes, but the determination of the ratio of immune-competent cells and their dynamics in newborns, with special regard to preterm babies. In other words, we wished to establish the normal values for these age groups. On the basis of 162 tests, carried out from 81 blood samples the following conclusions were drawn. (i) The ratio of T lymphocytes in peripheral blood increases parallel to gestational age and birth weight.

(ii) When analysing B cells, the ratio of IgM bearing lymphocytes was lower than that of the IgG bearing ones. As to their dynamics, both cell types showed a decreasing ratio with advancing gestational age. A similar but less marked change was found in relation to birth weight. We have no explanation for the phenomenon.

(iii) The decrease in the ratio of O-cells was closely related to the increase in gestational age and birth weight. The fact that even the control values were considerably higher than the normal adult values argues for a continuous decrease in this cell type throughout childhood.

The studies were designed to provide normal values for further analysis of the immune-reactivity during the period of post-natal adaptation. They should provide useful information for research workers engaged in this field.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 315–318 (1978)

Ösophagogastrobulboskopie im Kindesalter

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(Eingegangen am 1. März 1978)

Bei 5 Kindern wurde in Narkose Ösophagogastrobulboskopie mit dem Fiberskop Typ Olympus GIF-D_2 durchgeführt. Der Eingriff wurde in 4 Fällen durch Hämatemesis und/oder Meläna und bei einem 3jährigen Mädchen zwecks Entfernung eines verschluckten Eheringes indiziert. In 2 Fällen, in denen die Ursache der wiederholt aufgetretenen Blutungen nicht einmal mittels explorativer Laparotomie festzustellen war, lieferte die fiberskopische Untersuchung eine ätiologische Diagnose. Der Befund sprach in einem Fall für Ösophagus-Varizen und im anderen für ein blutendes Duodenalgeschwür. In einem Fall konnten mittels Fiberskopie nicht nur die eine potentielle Blutungsgefahr bedeutenden Varizen, sondern auch die Blutungsursache, multiple Magenerosionen nachgewiesen werden. Bei einem 11jährigen Mädchen ließ sich anhand des fiberskopischen Befundes die Anwesenheit eines peptischen Geschwürs ausschließen.

Aufgrund der ermittelten Erfahrungen wird betont, daß — insofern andere Untersuchungsverfahren keine Diagnose liefern — die Ösophagogastrobulboskopie auch im Kindesalter durchgeführt werden muß, insbesondere im Falle von Magenblutungen, vor der Indizierung der Operation.

Dank der Entwicklung der flexiblen Fiberskope kann die endoskopische Untersuchung des oberen Verdauungstrakts heute bereits auch im Kindesalter vorgenommen werden. Mit Hilfe der sog. »Kinderendoskope« vom Typ GIF-P und auch anderen Typen können sogar Säuglinge untersucht werden [2, 3, 4]. Laut MUNTE und GUTZEIT [6] eignet sich zur Untersuchung von Kindern unter 5 Jahren der Typ GIF-P und über 5 Jahren der Fiberskoptyp GIF-D.

Trotz der geeigneten technischen Möglichkeiten berichteten nur wenige Autoren über eine größere Zahl von bei Kindern durchgeführten Untersuchungen, die Entfernung eines Fremdkörpers inbegriffen. Wir haben die Gastrobulboskopie in 5 Fällen durchgeführt, in einem Fall zwecks Entfernung eines Fremdkörpers aus dem Magen, in 3 Fällen wegen wiederholter Magenblutung und in 1 Fall wegen okkulter Blutung.

Die im Operationssaal vorgenommenen Untersuchungen fanden in 1 Fall in intratrachealer Narkose und in den übrigen Fällen in intramuskulärer Ketamin-Narkose statt.

FALLDARSTELLUNGEN

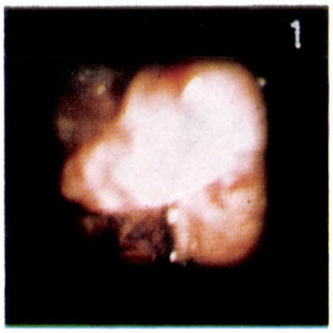
Fall Nr. 1. Das 9jährige Mädchen wurde wegen Meläna und wiederholter Hämatemesis untersucht. Anläßlich der vor drei Monaten wegen schwerer Blutung vorgenommenen explorativen Laparotomie konnte die Blutungsquelle nicht aufgefunden werden. Im Laufe der vor der Endoskopie durchgeführten Röntgenuntersuchung

gelang der sichere Nachweis der Varizen nicht. Endoskopischer Befund: Der ganze Ösophagus ist mit Varizen bedeckt, auf dem 5—6 cm langen präkardialen Abschnitt große gewundene Phlebektasien, in der Kardia und im subkardialen Magenbereich ebenfalls Varizen. Es lagen auch Splenomegalie und Hypersplenie vor. Anläßlich der im Interesse der Klärung der Ursache der portalen Hypertension vorgenommenen perkutanen Splenoportographie konnte eine V. portae-Thrombose nachgewiesen werden. Operation (Prof. Dr. T. KARLINGER): Splenektomie, Magendissektion nach TANNER und Unterbinden der linksseitigen gastrischen Venen. Der sich in der postoperativen Phase entwickelte subphrenische Abszeß und der dadurch bedingte septische Zustand konnten durch Freilegung des Abszesses und antibiotische Therapie behoben werden, wonach Patientin in symptom- und beschwerdefreiem Zustand entlassen wurde (Abb. 1—2).

Fall Nr. 2. Zur ersten Klinikaufnahme des sich in schwerem, ausgeblutetem Zustand befindlichen 10-jährigen Knaben kam es im Herbst 1975. Im Frühling 1976 mußte er wegen Hämatemesis und Meläna abermals aufgenommen werden. Bei der explorativen Laparotomie konnte die Blutungsursache nicht eindeutig geklärt werden, es erhob sich die Verdachtsdiagnose einer hämorrhagischen Gastritis. Appendektomie. Im Herbst 1976 trat wieder Meläna auf; normale Magen-Darm-Passage. Ösophagogastrobulboskopie: Geschwür auf der Vorderwand des Bulbus duodeni. Im Besitz der endoskopischen Diagnose wurde keine Reoperation durchgeführt. Die Blutung hörte auf, der Knabe konnte nach einer Ulkuskur in gutem allgemeinen, beschwerdefreiem Zustand entlassen werden (Abb. 3).

Fall Nr. 3. Der 9jährige Knabe wurde wegen wiederholt aufgetretener Meläna untersucht. Aufgrund der bestehenden Splenomegalie erhob sich die Verdachtsdiagnose einer Varixblutung — nachdem eine hämatologische Erkrankung ausgeschlossen wurde. Im Laufe der wiederholten Ösophagusuntersuchung meldeten sich keine auf Varix weisende Röntgenzeichen; normale Magendarm-Passage. Ösophagogastrobulboskopie: nicht blutende Varizen im distalen Ösophagusdrittel, im Magen sickernd blutende multiple Erosionen. Nach einigen Tagen hörte die Blutung auf (Abb. 4—5—6).

ABB. 1. Fall Nr 1 Kleinfingerbreite diagonal gelegene Varix in der Speiseröhre
ABB. 2. Fall Nr 1 Präkardiale Varizen
ABB. 3. Fall Nr 2 Duodenalgeschwür mit Blutung am oberen Rand
ABB. 4. Fall Nr 3 Varizen in der Speiseröhre
ABB. 5. Fall Nr 3 Varizen im unteren Drittel der Speiseröhre
ABB. 6. Fall Nr 3 Blutende Magenerosionen
ABB. 7. Fall Nr 4 I. Atrophisch erscheinende Magenmucosa im Antrum vor dem Pylorus
ABB. 8. Fall Nr 4 I. Atrophisch erscheinende Magenmucosa im Corpus. Blutspur nach der Biopsie
ABB. 9. Fall Nr 5 Ehering im Magen bei der großen Kurvatur
ABB. 10. Fall Nr 5 Ergreifen des Ringes mit der Biopsiezange
ABB. 11. Fall Nr 5 Der entfernte Ring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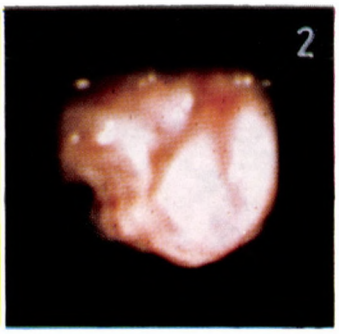
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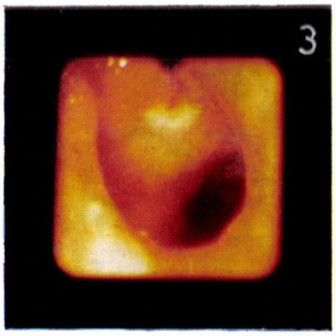
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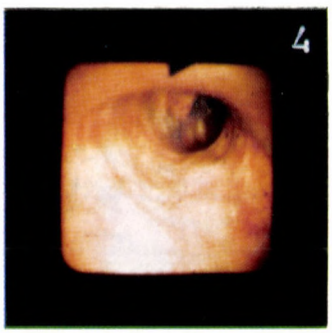
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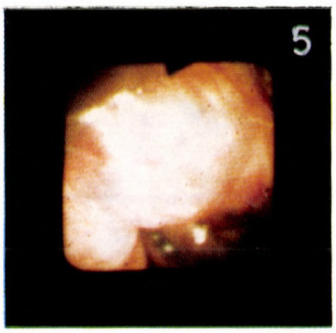
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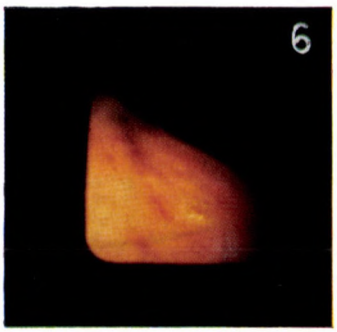
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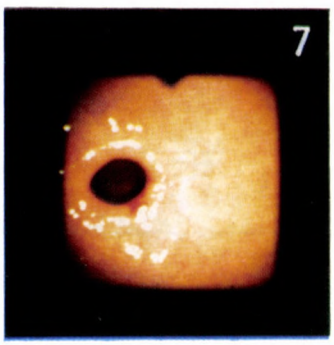
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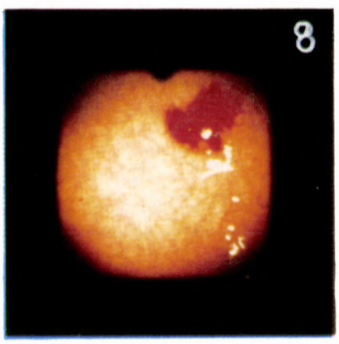
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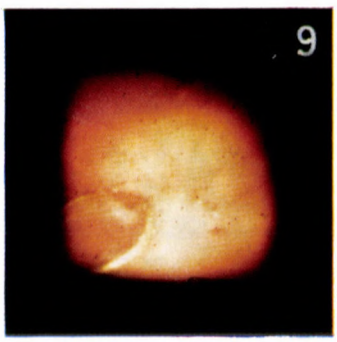
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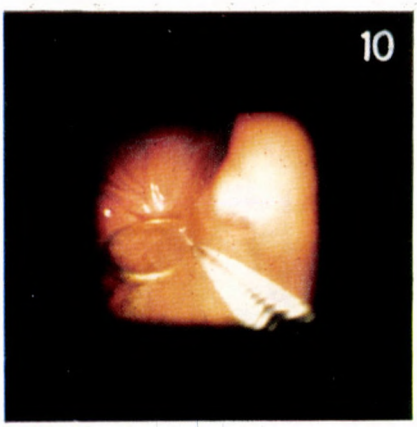
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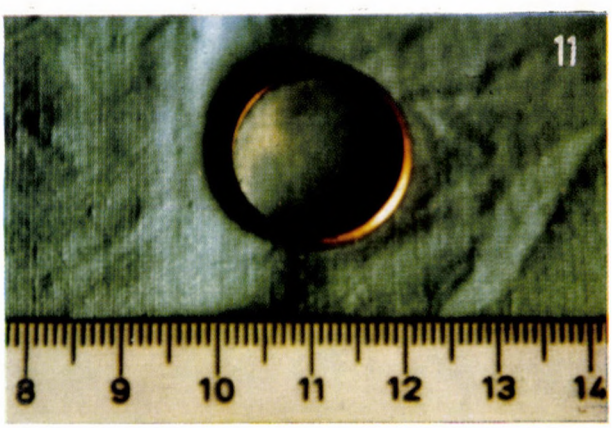
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Fall Nr. 4. Bei dem 11jährigen Mädchen erhob sich wegen schwerer Eisenmangelanämie und zeitweise auftretender okkulter Blutung ein Ulkusverdacht. Endoskopie: keine Blutungsquelle im Ösophagus, Magen bzw. Duodenum, so daß ein peptisches Geschwür ausgeschlossen werden konnte. Der Befund der multiplen Magenbiopsien sprach für atrophische Gastritis (Abb. 7—8).

Fall Nr. 5. Das 3jährige Mädchen verschluckte den Ehering seines Vaters und wurde in eine Kinderchirurgische Abteilung eingeliefert. Die während der 1wöchigen Beobachtungszeit mehrmals durchgeführten Kontroll-Röntgenuntersuchungen zeigten, daß sich der Fremdkörper noch im Magen befindet; wir unternahmen deshalb einen Versuch zur endoskopischen Entfernung des Fremdkörpers. Das zur Routineuntersuchung von Erwachsenen dienende Instrument konnte in Intratrachealnarkose überraschend leicht eingeführt werden. Im Magen waren mehrere Mukosaverletzungen zu beobachten, die wahrscheinlich durch den sich frei bewegenden Ring verursacht worden sind. Den Ring erblickten wir am tiefsten Punkt der großen Kurvatur unter dem Saft. Mit dem Biopsielöffel gelangten wir in das mittlere Drittel des Korpus und versuchten den Ring anzupacken. Beim Schließen des Löffels glitt aber der Ring immer wieder aus der Zange. Schließlich gelang es den Ring auf den offenen Löffel zu hängen und mitsamt des Instruments in den Ösophagus hochzuziehen. Die Kardia konnte leicht passiert werden, in der Höhe des Ösophaguseingangs stieß aber der Ring auf ein Hindernis und rutschte vom Löffel ab. Mit der Fremdkörperzange eines unverzüglich eingeführten starren Ösophagoskops gelang uns schließlich die Entfernung des Eherings. Da keine Komplikationen auftraten, wurde das Mädchen nach zwei Tagen in beschwerdefreiem Zustand entlassen (Abb. 9—10—11).

Besprechung

Wie ersichtlich, kommen auch im Kindesalter gewisse, die Durchführung einer Endoskopie erfordernde Krankheiten vor. In der Mehrzahl der Kinderabteilungen fehlen aber die entsprechenden Instrumente und auch ein entsprechend gechultes Team. Eine Besserung dieser Lage ist von der Zusammenarbeit der endoskopischen Zentren und der Kinderabteilungen zu erwarten.

Über die Technik wird noch viel diskutiert. Tedesco und Mitarb. [8] durchführten die Untersuchungen bei größeren Kindern meist ohne Narkose und bedienten sich eines speziellen Kinderendoskops. Graham und Schwartz [5] untersuchten auch Säuglinge ohne Narkose. Im Mangel vorangehender Erfahrungen mit dem Kinderendoskop hielten wir es als sicherer, die Untersuchungen in Narkose durchzuführen. Zur Anwendung des Fiberskops Typ GIF-D_2 ermutigte uns die Tatsache, daß wir bei Erwachsenen, meistens ambulantär, mehr als 5000 Ösophagogastrobulboskopien ohne Komplikationen

durchgeführt haben. AMENT [2] empfahl die Anwendung des Fiberskops Olympus Typ GIF-P_2 sogar in blutenden Fällen; seinen Vorschlag begründete er damit, daß während das zur Untersuchung der Kinder früher gebräuchliche Instrument GIF-P_1 nur in zwei Richtungen, das Fiberskop Typ GIF-P_2 — ähnlich wie die für Erwachsene hergestellten Instrumente GIF-D — in vier Richtungen bewegbar ist.

Die Vorteile der Endoskopie lassen sich in folgendem zusammenfassen:

In den Fällen Nr. 1. und 2. konnte die Blutungsursache mittels Röntgenuntersuchung nicht festgestellt werden, während die Endoskopie eine ätiologische Diagnose lieferte. In Fall Nr. 1. bildete der endoskopische Befund, aus dem die Anwesenheit der Varizen zu entnehmen war, die Grundlage der Operationsindikation; in Fall Nr. 2. erwies sich anhand der fiberskopischen Untersuchung die konservative Terapie als geeignet. In Fall Nr. 3. konnten die Ösophagusvarizen und die blutenden Magenerosionen ebenfalls nur mit dem Endoskop nachgewiesen werden. Der sich in Fall Nr. 4. erhobene Ulkusverdacht konnte anhand des Befundes der Ösophagogastrobulboskopie ausgeschlossen werden.

Unseres Erachtens, und dieselbe Anschauung vertreten auch MUNTE und GUTZEIT [6] muß die Ösophagogastrobulboskopie, falls andere Untersuchungsverfahren keine Diagnose liefern, auch im Kindesalter, besonders bei Magenblutungen vor der Indizierung der Operation durchgeführt werden.

Die fieberskopische Untersuchung könnte in der Kindergastroenterologie nebst dergenauen Diagnostizierung der blutenden Läsionen des oberen Verdauungstrakts bzw. der endoskopischen Fremdkörperentfernung auch in anderen Fällen eine wertvolle Hilfe leisten- wie z. B. bei der gezielten Biopsie.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 319–327 (1978)

Ten years domestic salt fluoridation in Hungary

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Received March 2nd, 1978

Results are presented regarding the caries reduction achieved over a 10 yr period using 250 mg F per kg of domestic salt, and compared with data from a fluoridated water area and from a control group. The frequency of caries-free children in the 4 to 6, 7 to 11 and 12 to 14 age range in the experimental group rose from 8.06%, 4.74% and 1.43% to 46.75%, 43.98% and 7.92% respectively, and dmft and DMFT indices dropped from 5.35, 3.62 and 6.60 to 2.80, 1.45 and 3.65. There was no significant change in the percentage of caries-free children or in the indices of the control group. The ratio of dmft and DMFT to teeth and the differences in the extent of caries among specified teeth are also presented. The data support the assumption that fluroidated salt prevents dental caries both in deciduous and permanent dentitions. The results were similar as those obtained in a water fluoride area. The optimum and tolerated F intake, water and salt ingestion, F intake from foods and the urinary F levels are also discussed.

Salt was first suggested as a vehicle for fluoride by Wespi [28] and in Switzerland fluoridated salt was put on sale with a F concentration of 90 mg/kg from 1955 [29]. Production of salt containing 250 mg F/kg commenced in one canton during 1970 and in another in 1975 [8]. Initial results were worthy of attention, as they clearly showed a caries-inhibiting effect of fluoridated salt [4, 6]. Further studies with salt have been carried out in Colombia [7, 10] and Spain [7, 26].

In Hungary, a preliminary experiment was started in 1965 to solve the technical problems. Since 1966, a clinical trial has been conducted under realistic field conditions using different F-concentrations. In 1966, salt containing 250 mg F (552 mg NaF); in 1968, 200 mg F (442 mg NaF); and in 1972, 350 mg F (773 mg NaF) per kg was put on sale, and some of the results obtained have already been published [13, 14, 15, 17, 18]. By 1976, after 10 years experience with the 250 mg F/kg salt dosage, the data justify a detailed report on the practicability of the method.

Method

The salt which was fluoridated was that used by housewives for cooking [12, 20]; it is therefore termed "domestic salt" rather than "table salt". Restaurants, common kitchens, student canteens, nursery and school kitchens employ the same

preparation (visible salt). The salt used by bakeries and the food industry (hidden salt) was not fluoridated. Fluoride is added to the salt by spraying concentrated NaF solution over a layer of NaCl running on a conveyor belt.

F concentration of salt, water, urine, vegetables, fruits, cereals, egg, meats, meat tissues, soups, cooked vegetables and dishes of meat served with cereals or vegetables was determined by the Orion ion-specific electrode method. Meat tissues were separated from bone, fat, tendons and membranes. All foods, raw or cooked, were cut into small pieces, then spread in a thin layer and dried under infrared light to constant weight. The dry material content was calculated, and the material then burnt to ash. From these, basic solutions were made and aliquots were adjusted to pH 5.5 with acetate buffer and the F content determined using the direct potentiometric method. Evaluation of data was done by the help of a calibration curve. It was essential to know the F content of the above foods and fluids to evaluate the effectiveness of salt fluoridation.

The fluoridated salt is marketed in villages where no other salt is available. By this "compulsory" measure a similar situation is created as with the fluoridation of drinking water. The F content of drinking water in both the experimental and control villages was 0.2 ppm.

Dental examinations were performed each year during the last 2 weeks of May, when the subjects were examined by two teams, each consisting of a dentist and chairside assistant; neither team was informed of the other's findings. Results were computerized, the caries data being expressed as dmft and DMFT indices (average number of decayed, missing and filled deciduous and permanent teeth per child; dmft symbolizing deciduous and DMFT permanent teeth).

Children

Table 1 shows the number and age of participating children. Initially there was only one control village but later two more were included. The examined children in the experimental group are representative of the village as around 500 normally reside there with only small yearly fluctuations. To obtain a more accurate comparison of the cariostatic effect of salt, a further group was examined in 1977 from an area where the water contained at least 1 ppm F for 27 years [1, 22].

Results

Caries-free children. As shown in Table II, the number of caries-free children in all three fuoridated age groups rose significantly, although there was no change in the control group.

The dmft and DMFT indices. The average number of decayed, missing and filled deciduous and permanent teeth per child is shown in Table III. When the experiment started in 1966, the dmft index for the experimental group aged 4 to 6 was 5.35, and ten years later this had dropped to 2.80, corresponding to a decrease of 48%. The differences between experimental and control village indices in 1976 was 3.18, a difference of 53%. In the 7 to 11 year age-range, the experimental DMFT index was 3.62 in 1966, and ten years later it had been reduced to 1.45, a decrease of

TABLE I

Number and age of children examined

Age* range		Fluoridated salt 250 mg/kg			Water fluoride 1 ppm	Control		
		**1966		**1976	**1977	**1967		**1976
4— 6	M	4.06		4.6	4.09	4.06		4.06
	N		62	77	55		78	311
7—11	M	8.05		8.07	8.09	8.09		8.06
	N		190	158	340		236	1041
12—14	M	12.06		12.08	12.06	12.03		12.06
	N		140	82	250		212	606
Total	N		392	317	645		526	1958
Exact data for	M	3.10		3.05		4.01		4.00
2— 6	N		82	137	—		92	424

* = Next birthday
** = Year of examination
M = Mean age: years and month
N = Number

TABLE II

Caries-free children, per cent

Age range	Fluoridated salt		Water fluoride	Control	
	1966	1976	1977	1967	1976
4— 6*	8.06	46.75	60.08	11.54	13.82
7—11**	4.74	43.98	52.65	12.71	17.91
12—14**	1.43	7.92	23.60	0	0.82

* = Deciduous dentition
** = Permanent dentition

TABLE III

Average number of decayed, missing and filled deciduous and permanent teeth per child

Age range	Fluoridated salt		Water fluoride	Control	
	1966	1976	1977	1967	1976
4— 6 dmf	5.35	2.80	1.37	5.94	5.98
7—11 DMF	3.62	1.45	1.06	3.35	2.80
12—14	6.60	3.65	2.58	7.33	7.20
Exact date for 2 — 6 dmf	4.18	1.43	—	5.19	4.56

dmf = Decayed, missing or extractions indicated and filled

60%. Comparing the 1976 indices from experimental and control villages, a difference of 1.35 (48%) was evident. In the 12 to 14 year age-range the experimental DMFT index was 6.60, and ten years later this had dropped by 45% to 3.65. Comparison of the 1976 data shows a difference of 3.55 (49%).

The ratio of dmft and DMFT to the number of teeth examined is shown in Table IV. In the experimental group the ratio dropped significantly when compared to that of 1966. In the control group no change could be seen.

The cariostatic effect of fluoridated salt could also be demonstrated by differences in caries among the various

TABLE IV

Ratio of decayed, missing and filled deciduous and permanent teeth to the teeth examined, per cent

Age range	Fluoridated salt		Water fluoride	Control	
	1966	1976	1977	1967	1976
4— 6*	26.77	11.30	7.41	29.68	30.37
7—11**	27.53	12.59	8.59	26.86	22.90
12—14**	25.61	14.77	10.34	29.68	28.42

* = Deciduous dentition
** = Permanent dentition

TABLE V

Differences in the extent of caries among the different types of permanent teeth per 100 children, aged 12 to 14 years

Tooth		Water fluoride	Fluoridated salt	Control
M_2		12.2	12.1	33.9
M_1		71.6	126.2	166.5
PM_2	Upper jaw	5.8	7.9	36.4
PM_1		6.6	7.9	41.9
C		0.2	0	5.7
LI		7.0	10.3	67.6
CI		4.2	12.1	78.0
CI		0.2	0	6.2
LI		0.2	0	4.5
C	Lower jaw	0.2	0	0.7
PM_1		1.2	6.1	5.9
PM_2		6.2	8.5	18.9
M_1		112.6	151.8	183.6
M_2		30.4	32.3	76.7

CI = Central incisor; LI = Lateral incisor; C = Canine; PM = Premolar; M = Molar

permanent tooth types in 12 to 14 year old children. In Table V, the data relate to scores per 100 children. After ten years, no caries was found on the upper canines or the lower incisors and canines. All other specified teeth had a lower caries attack in the experimental group as compared to the controls.

Discussion

The caries inhibiting effect of fluoridated domestic salt was obvious not only in the permanent but also in the deciduous dentition. The original age-range of the experimental and control groups was 2 to 6 years but for comparison with those exposed to F in drinking water for a lifetime the age was reduced to 4 years. The original data are shown in Tables I and III.

As seen in Table I, there was a difference in the mean age of children aged 2 to 6 years between the experimental and control groups in 1976, the children in the experimental group being 7 months younger. No significant age difference could be observed in the 7 to 14 age group. The number of children examined in all groups varied, as in 1976 more control subjects were examined. Statistical analysis of the experimental and control data for 1976 yielded for the age group 2—6 years: $t = 7.39$ ($P < 0.05\%$); for the age group of 7—11: $t = 2.51$ ($P < 1\%$); and for the age group of 12—14 years: $t = 8.24$ ($P < 0.05\%$). Thus the differences between indices was significant in all the three age groups.

After ten years, in the fluoridated salt group the percentage of caries-free children increased while the dmft and DMFT indices decreased significantly. The level of caries reduction observed in naturally fluorided areas could not be reached although the variations were small (Tables II, III, IV and V). This may have been due to two factors, i.e. either that salt fluoridation commenced only ten years previously, or because the F concentration was not adjusted to a level high enough to ensure ingestion of the optimum amount.

Optimum and tolerated intake of fluorine has been studied on the basis of body weight, and the calorie and fluid requirements of subjects belonging to different age groups [9, 16]. As the main F-source is normally the drinking water, that amount of F which is ingested daily with drinking water containing 1 ppm F should be considered optimal. This amounts to 0.045 mg per kg body weight in infants, and decreases with age to 0.026—0.020 mg in adults i.e. half that for infants on a mg/litre basis. When calculating an upper limit, excessive intake should also be borne in mind. During the first eight years of life, the excess intake per day cannot exceed 1.72 mg (in adults 5.8 mg), even if the water contained 1.5 ppm F. Salt fluroidation, as an alternative to water fluoridation, should be based on the knowledge of the maximum permissible individual dose

of F per day and the maximum individual ingestion of salt [11].

Drinking water ingestion by children was critically reviewed by Marthaler [5]. He found that individual levels of ingestion were obliquely distributed with the bulk of the population ingesting less water, although a small percentage consumed a great amount. We found [25] the same in smelters during work (their ingestion of protective drinks being monitored summer and winter; Table VI). Here, 2.06% of the subjects ingested over 5 litres per day, i.e. with water containing 1 ppm F, about 2% consumed 5 mg F or more daily.

Similar results were obtained for the intake of domestic salt [20] per kg body weight/day, with 0.83% taking excessive quantities (Table VI).

The diet is mostly low in F [2, 24]. According to our data [24] the daily dietary intake in Hungary contains at most about 0.39 mg per kg of F (Table VII). The amount of F ingested with food is unpredictable [27]. Nevertheless, human urinary concentrations depend on, and in fact are nearly equivalent numerically to, the drinking water concentrations [3, 19, 21, 22]. Thus, the important role of water as a main source of F is supported by the urinary F level.

Studies of salt ingestion are difficult to undertake. The first question to be decided is the kind of salt that has to be fluoridated? We are fluoridating the domestic salt, but it was a surprise to find that considerable amounts of salt purchased for household use were not ingested, more than 60% of each purchase being discarded [20]. Furthermore the more industrial foods are consumed, the less the domestic salt ingestion. The decision as to which kind of salt should be fluoridated is really a question of philosophy and policy. If the salt used in bakeries and the food industry were fluoridated, this would amount to a compulsory measure. Consequently that problem must also be taken into consideration before the introduction of large scale production of a homogeneous and stable fluoridated salt [7].

The urinary concentration of F is a convenient and established method of estimating F intake by a population, group or individual [3, 7, 23]. Urinary F concentration can vary throughout the day because a single dose of fluoride is excreted in a few hours [3, 21]. Thus a spot sample of an individual will not reflect his F ingestion. It is more meaningful if two fractions (a.m. and p.m.) are obtained from the individual, and the F concentration of the pooled urine is determined. This technique is suitable for large-scale monitoring of F ingestion with salt. When salt containing 200 or 350 mg F per kg is ingested for months or years, the urinary F level also increases. Table VIII shows the results of our experiment. Here the 250 mg F (since 1966) and the 200 mg F (since 1968) groups had reached a steady state but in spite of the prolonged ingestion of the salt we do not see sufficient F concentrations in the urine. The

TABLE VI

Water and domestic salt ingestion per kg body weight

N	NN	Mean body weight kg	Mode	Median	Mean	SD	Mean + 3 SD
		water, ml					
97	291	69.0	22.9	30.2	35.2	16.0	83.2 = 2.06%
		domestic salt, gram					
242	581	55.6	0.020	0.060	0.066	0.037	0.177 = 0.83%

N = Number of persons observed
NN = Number of observations (days)

TABLE VII

F content of foods

	Mode	Median	Mean	SD
	mg/kg			
Foods without fish	0.12	0.16	0.28	0.14
with fish	0.12	0.17	0.39	1.02
Dishes of cooked food	0.14	0.20	0.21	0.09

350 mg F group, however, had been consuming that concentration since September 1972, and in the urine of adults the expected level of F has been obtained.

TABLE VIII

Urinary F levels after long term consumption of fluoridated salt (200, 250 and 350 mg F per kg salt), mg per litre

F in salt	Age range	F concentration mean ± SD
200 mg/kg	2–14	0.75 ± 0.32
	Adults	0.69 ± 0.31
250 mg/kg	2–14	0.86 ± 0.35
	Adults	0.85 ± 0.45
350 mg/kg	2–14	0.73 ± 0.20
	Adults	1.10 ± 0.49

CONCLUSION

Long term use of fluoridated domestic salt prevents dental caries not only in the permanent but also in the deciduous dentition. The effectiveness of fluoridated salt is similar to that which could be observed after drinking water with optimum F content. Unfortunately, to adjust salt to an adequate F concentration is difficult and may only be achieved by studying the dietary and nutritional habits of the group involved. In the case of fluoridated domestic salt, an approximate estimate of salt ingestion can be done from the quantity of salt sold, 60% of which

is known to be discarded. Thus urinary tests for fluoride ingestion may be monitored accurately. However, the greater the consumption of industrial foods the more difficult it is to decide which salt was to be fluoridated and to estimate the daily ingestion. If salt other than that used in households is to be fluoridated, the decision is more or less a question of philosophy and policy.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 329—333 (1978)

Sprungseilübung: eine neue physikalische Belastungsmethode bei asthmatischen Patienten

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(Eingegangen am 3. März 1978)

Bei im Durchschnitt 8 ½jährigen asthmatischen Kindern beiderlei Geschlechts, die auf Belastung mit Bronchospasmus reagierten, wurden bei Sprungseilübung vergleichende Belastungsuntersuchungen durchgeführt. Der sich nach den Sprungseilübungen entwickelte Bronchospasmus war ausgeprägter und dauerhafter, als nach der traditionellen Fahrrad-Ergometer Belastung.

Die an Asthma bronchiale leidenden Kinder — und auch ihre Umgebung — beunruhigt die Tatsache, daß sich bei ihnen nach körperlicher Anstrengung unter Umständen Dyspnoe entwickelt.

Herxheimer [3] und Pearson [10] waren die ersten, die zur Untersuchung des bei Asthmakranken unter Wirkung einer physikalischen Belastung zustandekommenden Bronchospasmus objektive Methoden anwendeten. Die Erscheinung wird von einigen Autoren belastungsbedingter Bronchospasmus [2, 7, 16, 18], von anderen belastungsbedingtes Asthma (Exercise-induced Asthma) genannt [4, 8, 9, 14]. Zur Untersuchung der Reaktion dient die Bestimmung von verschiedenen Atemfunktionswerten nach 6—8minütiger physikalischer Belastung: FEV_1 (in der ersten Sekunde der forcierten, raschen Exspiration gemessenes Volumen), PEFR (Exspirations-Maximalfluß), dynamische Compliance (Dehnbarkeit der Lunge) und Resistance (Atemwegswiderstand).

In der Praxis werden folgende Belastungstests angewandt: Treppensteigen, Laufen, Spaziergang, Fließbandtest (Treadmill) und die am häufigsten gebräuchliche Methode, das Fahrrad-Ergometer; das letzterwähnte Verfahren eignet sich zur Bestimmung der Leistung in den verschiedenen Belastungsstufen in mKp/sec bzw. Watt/sec [8, 9, 11, 12, 18].

In den ersten 1—2 Minuten der Belastung meldet sich eine vorübergehende Bronchusdilatation [6]. Im Falle einer 6—8 Minuten lang dauernden Belastung entwickelt sich der Bronchospasmus meistens nach 3—5 Minuten, mitunter aber nur nach 10 oder sogar 20 Minuten.

Der belastungsbedingte Bronchospasmus meldet sich nicht bei allen Asthmatikern [12]. Seine Auslösbarkeit und Intensität hängt in erster Linie vom Belastungstyp und weniger von der Belastungsdauer bzw. der

Schwere der Krankheit sowie der Dauer und der Intensität der Belastung ab [14]. Im Material von SLY [16] betrug die Prozentzahl der Fälle, in denen sich nach Spaziergang ein Bronchospasmus entwickelte 39%, während SILVERMAN und ANDERSON [14] die Erscheinung nach freiem Laufen in 75% ihrer Fälle beobachteten. ANDERSON und Mitarb. [1] wandten bei einem Patienten 6minütige verschiedene Belastungen — Schwimmen, Ergometer, Treadmill und freies Laufen — mit identischer Intensität an. Das Maß der Reaktion erhöhte sich folgender Reihenfolge nach: Schwimmen, Ergometer, Treadmill, und freies Laufen; die Effektivität des letzterwähnten Belastungstyps haben auch andere Autoren beobachtet [6, 11, 17].

Die Ursache der unterschiedlichen Ergebnisse der verschiedenen Belastungstests und auch der Pathomechanismus sind ungeklärt. Angesichts dieser Tatsache und davon ausgehend, daß in diesem Mechanismus eventuell auch die Qualität der Bewegung (z. B. Rütteln) eine Rolle spielen könnte, wandten wir bei unseren Asthmakranken versuchshalber einen neuen Belastungstest an.

METHODIK

Das Sprungseil gehört unter die Lieblingsspielzeuge der Kinder; Sprungseilübungen beanspruchen wenig Platz und die »Ausrüstung« ist einfach. Diese bekannten Umstände sowie die Tatsache, daß sich an dieser Bewegung der ganze Körper beteiligt, veranlaßten uns zur Erprobung der Sprungseilübung als Belastungstest. Kinder, die das Spiel nicht kannten, hatten vor der Untersuchung eine Möglichkeit sich zu üben. Die Belastungen fanden in den Vormittagsstunden statt, die Belastungsdauer betrug 8 Minuten, die Frequenz des Hüpfens machte rund 80/min aus. Diese spielerische Belastung machte allen Kindern Freude und sie tolerierten die Übungen gut. In unserem Untersuchungsmaterial befanden sich 8 an Bronchialasthma leidende, auf Belastungen mit Bronchospasmus reagierende Kinder. Die Patienten waren vor der Untersuchung symptomfrei und erhielten vor der Belastung 3 Tage lang keine Antiasthmatika. Vor der Belastung wurden die Ruhe-FEV_1-Werte — die höchsten Werte von 3 nacheinander folgenden Messungen — sowie die Ruhe-Pulszahl bestimmt; danach folgten Sprungseilübungen 8 Minuten lang und schließlich nach 1—3—5—10—20 und 30 Minuten abermals Pulszahl und FEV_1-Bestimmungen. Am nächsten Tag kam es zu einer neuen, ebenfalls 8 Minuten lang dauernden Belastung mit dem Fahrrad-Ergometer; die FEV_1-Werte wurden ebenso wie oben beschrieben vor und nach der Belastung bestimmt. Das Maß der Belastung bestimmten wir aufgrund der früher ermittelten, Bronchospasmus auslösenden Stufe, im allgemeinen mit einer Intensität von 1—1½ Watt/kg. Für eine positive Reaktion wurde eine im Vergleich zum Ausgangswert 30% übertreffende Verringerung des FEV_1 betrachtet. Kontrollhalber wurden bei einer aus 10, durchschnittlich 9jährigen (6—14jährigen), gesunden Kindern bestehenden Gruppe beide Belastungstests angewendet.

ERGEBNISSE

Die Sprungseilübungen wurden von beiden Gruppen gut toleriert, die Pulszahl übertraf nach der Untersuchung den Wert von 170/min nicht.

Der bei einem asthmatischen Mädchen am Ende der Belastung aufgetretene asthmatische Anfall konnte mit Terbutalin gelöst werden. Die Verringerung des FEV_1 betrug in diesem Fall mehr als 50% des Ausgangswertes. Durch die Sprungseilübung wurde in sämtlichen Fällen ein Bronchospasmus ausgelöst. Das Maß der Verringerung der FEV_1-Werte betrug wesentlich mehr als 30% des Ausgangswertes; die durchschnittliche FEV_1-Verminderung machte 41% aus im Gegensatz zu den nach der Fahrrad-Ergometerbelastung ermittelten Durchschnitts-

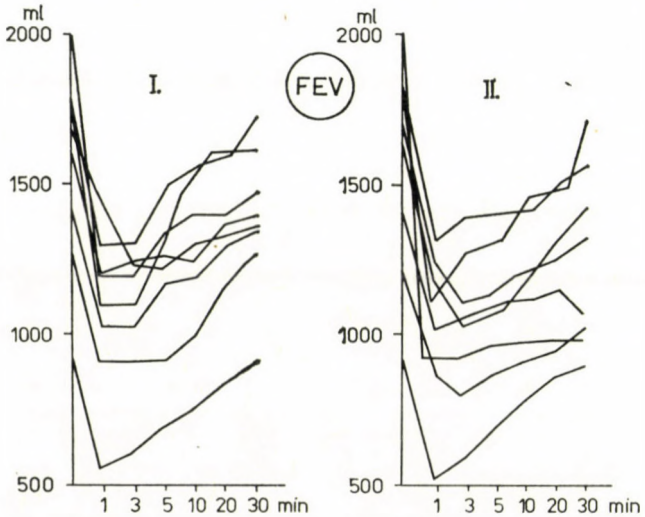

FIG. 1. Belastungsbedingter Bronchospasmus bei asthmatischen Kindern. I. Ergometer; II. Sprungseilübung

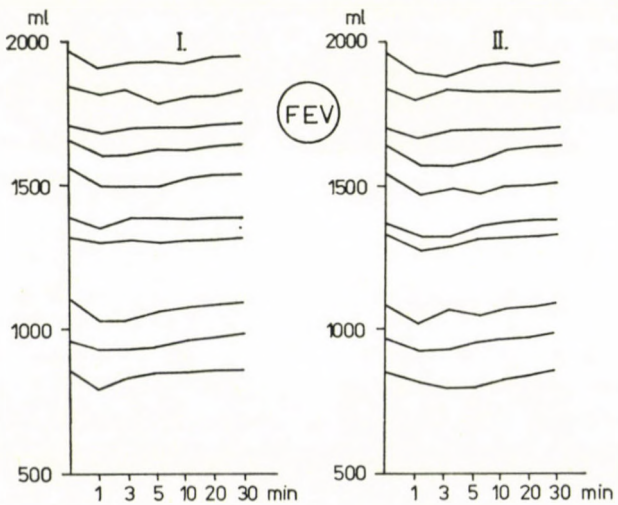

FIG. 2. Belastungstest bei gesunden Kindern. I. Ergometer II. Sprungseilübung

wert von 32% (Abb 1). Eine nicht ausgeprägte FEV_1-Verminderung konnte nach den Sprungseilübungen nur in 2 unserer Fälle verzeichnet werden. 30 Minuten nach den Sprungseilübungen ließen sich dagegen nur in zwei Fällen Ruhewerte registrieren, während nach der Fahrradbelastung die Zahl dieser Fälle 5 ausmachte. Das bedeutet, daß der sich nach Sprungseilübung entwickelte Bronchospasmus nicht nur ausgeprägter, sondern auch dauerhafter ist, als nach der Fahrradbelastung. Was die Ergebnisse der 10 Kontrollkinder anbelangt, waren weder auf Bronchospasmus weisende Werte, noch mehr als 10% des Ruhewertes ausmachende Verringerungen der FEV_1 vorzufinden (Abb. 2).

Besprechung

Der Pathomechanismus des belastungsbedingten Bronchospasmus der Asthmatiker ist ungeklärt. Die verschiedenen Hypothesen — Hyperventilation, Hypokapnie, Azidose — konnten nicht bestätigt werden [1, 6]. Anderson und Mitarb. [1] konnten mit 6minütiger Ganzkörpervibration keinen Bronchospasmus auslösen. Die Ursache des Freiwerdens der den Bronchospasmus auslösenden Mediatorsubstanzen ist somit unbekannt. Die Erfahrungen haben gezeigt, daß durch verschiedene Belastungen — vor allem durch Laufen, aber auch durch Fließband (Treadmill) und Fahrrad-Ergometer — unter Umständen ein Bronchospasmus ausgelöst werden kann. Der Bronchospasmus wird aber nur durch eine entsprechende Zeit lang dauernde und entsprechend intensive Belastung ausgelöst, und auch die Atemfunktionsparameter müssen nach der Belastung in entsprechenden Zeitpunkten registriert werden.

In der Praxis werden alle drei der oben angeführten Belastungstests angewandt, Anderson und Mitarb. [1] sowie Jones [6]. halten aber das Laufen für das effektivste Verfahren, da nach ihren Ergebnissen die Änderungen beim durch das Laufen ausgelösten Bronchospasmus am ausgeprägtesten waren. Im Besitz dieser Daten entschlossen wir uns, die Sprungseilübungen, die ebenso wie das Laufen den ganzen Körper in Bewegung bringen und obendrein auch noch eine gewisse schüttelnde Wirkung erzeugen, zur Belastung auszuproben.

Unsere Asthmakranken, die bei Ergometer-Belastung eine positive Reaktion aufwiesen, reagierten auch auf die Sprungseilübung mit Bronchospasmus. Gleichzeitig betrug die Änderung des FEV_1 der 10 gesunden Kinder weniger als 10% der Ruhewerte — dies entspricht den Beobachtungen von Silverman und Anderson [14], laut der die nach Belastung auftretende Verminderung des PEFR-Wertes bis 10% als normal gilt.

Beim Vergleich der Fahrrad-Ergometer und der Sprungseil-Belastung stellte es sich heraus, daß der nach dem letzterwähnten Test aufgetretene Bronchospasmus wesentlich ausge-

prägter ist. Die Beruhigungszeit, während der, der den Bronchospasmus ausdrückende Parameter — in unseren Untersuchungen der FEV_1-Wert — wieder die Ruhewerte erreicht, lag im allgemeinen zwischen 10 und 20 Minuten [6, 7]. Nach der Sprungseilübung verlängert sich dagegen dieses Intervall, weil innerhalb von 30 Minuten eingetroffene Ruhewerte nur in 2 Fällen registriert werden konnten.

Somit darf behauptet werden, daß sich die Sprungseilübung zur Herbeiführung des belastungsbedingten Bronchospasmus der Asthmatiker unbedingt eignet und sich unter den gegebenen Verhältnissen auch als vorteilhafter erweist als das Laufen.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 335—350 (1978)

Behandlungsmöglichkeiten grosser Nabelschnurbrüche und paraumbilikaler Bauchwanddefekte

Von

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(Eingegangen am 1. April, 1978)

Nabelschnurbruch und paraumbilikaler Bauchwanddefekt sind frühe embryonale Hemmungsmißbildungen unterschiedlicher Genese. Hinsichtlich ihrer therapeutischen Problematik jedoch sind sie als Einheit zu beurteilen. Die zur Zeit erfolgversprechendsten Behandlungsmethoden werden unter Zugrundelegung eigener Beobachtungen bei insgesamt 72 Neugeborenen mit einem vorderen Bauchwanddefekt aufgezeigt. Bei 49 Kindern lag ein Nabelschnurbruch, bei 23 Neugeborenen eine paraumbilikale Bauchwandlücke vor. Zur Beseitigung übergroßer Bauchwanddefekte wird die Anwendung eines freitransplantierten Coriumlappens empfohlen, den wir erstmals 1974 beim Kind angewandt haben, und dessen Wertigkeit durch Behandlungsverlauf sowie durch Nachkontrollen bei 12 Kindern dokumentiert wird.

Nabelschnurbruch und paraumbilikaler Bauchwanddefekt sind die Folge einer embryonalen Entwicklungsstörung bei der Ausbildung des vorderen Bauchwandgefüges. Unterscheiden sie sich auch grundsätzlich hinsichtlich ihrer Ätiologie, der klinischen Symptomalogie, wie auch durch die Art ihrer Behandlung, so ist ihnen eines gemeinsam: der persistierende Bauchwandbruch. Er ist gekennzeichnet durch einen, das Bauchdeckenniveau überragenden Tumor unterschiedlicher Größe, bei dem die Cutis den Bruchsack darstellt, der das vorgelagerte Intestinum zwar bedeckt, es aber gegen Traumen nicht zu schützen vermag (Abb. 1). Wachstum der Bauchorgane und intermittierende intraabdominelle Drucksteigerung führen zu einer Vergrößerung der Herniation, die eine zunehmende Instabilität der Bauchhülle wie auch die Möglichkeit einer Passagestörung nach sich zieht. Nicht zuletzt erfordert der große Bauchwandbruch auch aus kosmetischer Sicht eine operative Intervention mit dem Ziel der sicheren Bauchdeckenstabilisierung und der Normalisierung des Abdominalreliefs.

Es ist Anliegen dieser Arbeit die allgemeinen Behandlungsrichtlinien für den Nabelschnurbruch und den paraumbilikalen Bauchwanddefekt aufzuzeigen, insbesondere aber ein Verfahren anzugeben, daß sich zur Beseitigung übergroßer Bauchwandhernien unterschiedlicher Genese ausgezeichnet bewährt: Die freie Transplantation eines aus dem Narbenbereich gewonnenen denaturierten Coriumlappens [6, 8].

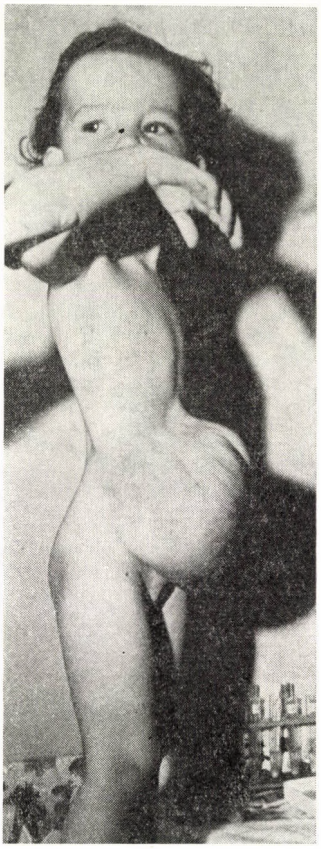


Abb. 1. Riesiger Narbenbruch nach paraumbilikalem Bauchwanddefekt bei einem 3jährigen Mädchen

Nabelschnurbruch

(Bisher gebräuchliche Bezeichnungen: Omphalozele, Exomphalos, Amniozele).

Der Nabelschnurbruch ist eine Hemmungsmißbildung, an der Bauchwand, Bauchorgane und die Nabelschnur gleichermaßen beteiligt sind. Die Zeitspanne der Entwicklungsstörung umfaßt die 6.—12. Fetalwoche, in der die Darmschlingen in Form der »Nabelschleife« das Coelom auch unter psychiologischen Bedingungen überragen. Aus bislang unbekannter Ursache kann die Retraktion der Darmschlingen und eine Verkleinerung des Nabelringes ausbleiben, was die Persistenz eines Nabelschnurbruches zur Folge hat. Er ist eine echte Hernie, bei der das Peritoneum die innere, das Amnion und die Warthonsche Sulze die äußere Bruchsackhülle bilden. Kennzeichen der frühen Entwicklungsstörung ist das Mißverhältnis zwischen dem kleinen Abdo-

men und dem großen Volumen der vorgelagerten Intestinalorgane (echter Nabelschnurbruch). Hiervon grenzen DRACHTER [1] und RAISCH [1, 2] den sog. »einfachen Nabelschnurbruch« ab, der durch einen kleinen Nabeltumor bei normal ausgebildeter vorderer Bauchwand gekennzeichnet ist. Die Entstehung dieser Bruchform weist auf einen Zeitpunkt, zu dem die Entwicklung der vorderen Bauchwand bereits abgeschlossen ist und die Darmorgane lediglich infolge eines mäßig erweiterten Nabelringes zu prolabieren vermögen.

Der bei der Geburt noch transparente Bruchsack ermöglicht für wenige Stunden eine Differenzierung seines Inhalts (Magen, Leberanteile, Milz, Darm), um dann rasch durch Eintrocknung oder Keimbesiedlung an Durchsichtigkeit zu verlieren.

Die Häufigkeit des Nabelschnurbruchs wird nach SINGER [14] mit 1—5 : 10 000 angegeben, womit er eine relativ seltene Fehlbildung darstellt. Demgegenüber ist die Frequenz (60%) intestinaler, kardialer, pulmonaler wie auch urogenitaler Begleitmißbildungen, von denen nach REHBEIN und SCHÄFER [12] etwa 40% lebensbedrohlich sein können, von entscheidender klinischer wie auch prognostischer Bedeutung. Gefürchtete Komplikationen des Nabelschnurbruchs sind in absteigender Wertigkeit:

1. Ruptur des Bruchsacks (Abb. 2)
2. Mechanischer Ileus,
3. Durchwanderungsperitonitis bei erhaltenem Bruchsack.

Während bei postpartal intakter Bruchsackhülle eine Verletzung derselben durch sorgfältige pflegerische Maßnahmen vermeidbar ist, schafft die intrauterine Ruptur eine Situation, die sowohl hinsichtlich ihrer Prognose als auch der Therapie der der paraumbilikalen Bauchwandspalte gleicht.

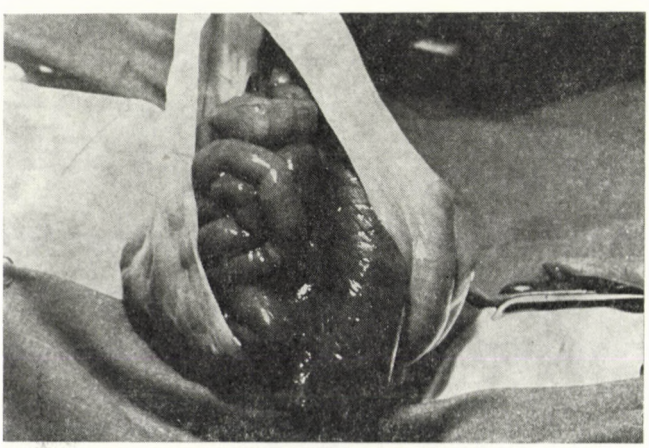


ABB. 2. Postnatal ruptierte Omphalozele

Behandlung

Es ist schwierig ein allgemein gültiges Behandlungsschema für den großen Nabelschnurbruch aufzuzeigen, da nicht nur die Relation zwischen Volumen der Hernie und Größe des Abdomens, sondern auch der Durchmesser der Bruchpforte von Bedeutung ist. Galt vor 15 Jahren die alleinige operative Behandlung als aussichtsreich, so gewinnt basierend auf den Beobachtungen von Grob [4] das konservative Vorgehen zunehmend an Bedeutung. Voraussetzung hierfür ist:

1. ein intakter Bruchsack,
2. eine Bruchpforte, die nicht kleiner sein darf, als ein Drittel des größten Umfangs der Amniozele,
3. ein unbehinderter Mekoniumabgang.

Somit stellt die dem Abdomen breitbasig aufsitzende Omphalozele stets die Indikation zur konservativen Behandlung, die bei der »Pilzform« des Nabelschnurbruchs nur unter Beachtung der angegebenen Parameter indiziert ist. Schwere pulmonale und kardiale Begleitmißbildungen erfordern wegen des hohen Operationsrisikos zwangsläufig eine konservative Haltung. Ziel der konservativen Behandlung ist neben der Stabilisierung des Bruchsacks die langsame Reposition der Bauchorgane bei gleichzeitiger Erweiterung der Bauchdecken. Wir gehen hierbei folgendermaßen vor:

Die Nabelschnur wird mit einem sterilen Seidenfaden umschlungen, der unter leichtem Zug an der Decke des Inkubators fixiert wird. Hierdurch wird das Abdomen entlastet und zugleich ein Umkippen des Bruchs verhindert. Weiterhin erleichtert diese Streckung das Zurückgleiten der Intestinalorgane. Wir glauben zudem, daß durch den leichten Dauerzug die Ausdehnung der Bauchdecken unterstützt und beschleunigt wird.

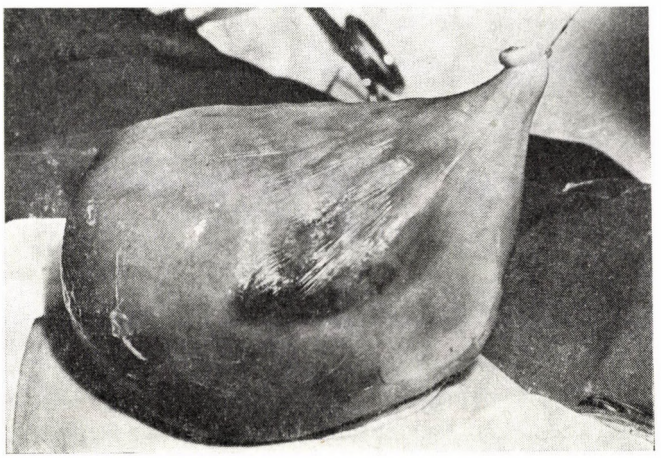


Abb. 3. Breitbasige Amniozele. Der Nabelschnurrest wird am Dach des Inkubators unter leichtem Zug aufgehängt

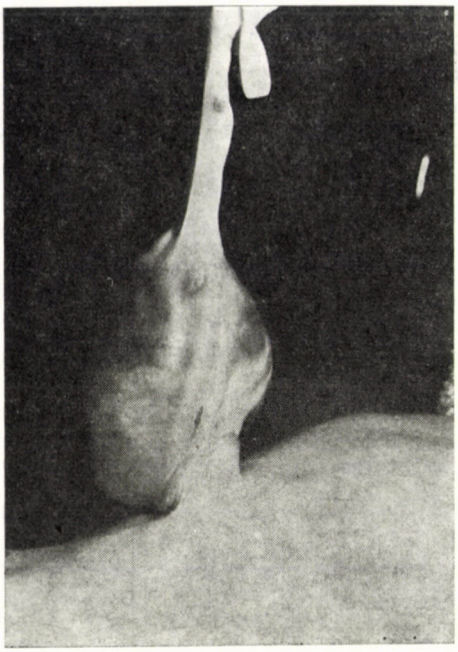


Abb. 4. »Pilzförmiger« Nabelschnurbruch mit enger Bruchpforte

Um den Bruchsack zu festigen, nehmen wir in den ersten Lebensstunden einen einmaligen Anstrich mit 2%iger Mercurochromlösung vor. Er ist ausreichend, um dem Bruchsack innerhalb weniger Stunden eine feste pergamentähnliche Konsistenz zu verleihen. Die Gefahr einer Quecksilberintoxikation wie sie Heule und Mitarb. [7], Ravitch [11] und andere nach wiederholten Mercurochrom-Pinselungen beobachteten, wird durch die einmalige sparsame Anwendung des Adstringens sicher ausgeschlossen. Zur Infektionsprophylaxe wird täglich 1—2mal ein antibiotikahaltiger Puderspray aufgetragen. Die Wahl des Chemotherapeutikums sollte heute, wie Singer [14] zu recht betont, wegen der Verschiedenheit der Hauskeime individuell vorgenommen werden.

Nach Abfallen der Nabelschnur besteht die Möglichkeit, am Nabelschnurrest einen neuen Faden, wiederum unter leichtem Dauerzug anzubringen, oder die Basis des Bruchsacks durch eine zirkulär angewickelte sterile Mullgaze zu stabilisieren. Bei breitbasigem Nabelschnurbruch kann die Umwicklung des Abdomens mit einer elastischen Binde erwogen werden. Tachypnoe, Zyanose und zunehmende Unruhe des Säuglings nach der Bandage sind stets als Zeichen eines zu forcierten Repositionsversuches zu werten.

Nach 2—4 Wochen löst sich in der Regel der Bruchsackschorf ab um eine Granulationsfläche frei zu geben,

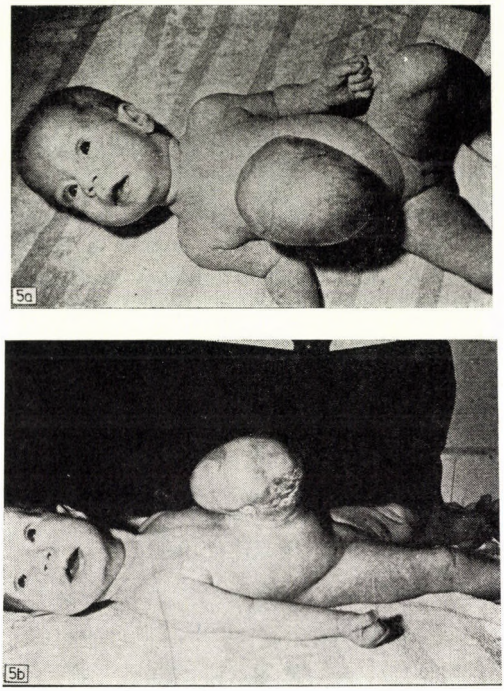


ABB. 5A + B. Konservativ behandelter weiblicher Säugling mit großer Amniozele, im Alter von 3 Wochen (A) und 6 Wochen (B). Beginnende Überhäutung des Bruchsacks

die von der Bauchdecke her langsam überhäutet wird. Der Endzustand des konservativ behandelten Nabelschnurbruchs ist die Narbenhernie, die oft als voluminöser Tumor das Bauchdeckenniveau überragt.

PARAUMBILIKALER BAUCHWANDDEFEKT

(Bisher gebräuchliche Bezeichnungen: Eventration, Paromphalozele, laterale Bauchwandspalte, Laparoschisis, Gastroschisis.)

Rupturierte Omphalozele und Gastroschisis ähneln sich vielfach auf den ersten Blick, da bei beiden Krankheitsbildern unbedeckte Darmorgane dem Abdomen vorgelagert sind. Unterschiede jedoch ergeben sich durch die Lokalisation der Bauchwandlücke, wie durch die Beschaffenheit der Nabelschnur, deren Integrität bei dem meist rechts neben dem Nabel belegenen Bauchwanddefekt stets gewahrt ist. Der Nachweis vorhandener Bruchsackreste sichert die Diagnose des perforierten Nabelschnurbruchs.

Ätiologisch liegt dem paraumbilikalen Bauchwanddefekt eine Entwicklungsstörung innerhalb der 4. Fetalwoche zugrunde. Hierbei fehlt dem Ektoblasten nach MÜNTENER [10] die die Bauchdecke stabilisierende Unterwanderung des Mesenchyms in einem umschriebenen Bereich. Die Spalte

selbst entsteht durch langsame Resorption der Epidermis.

Die Häufigkeit des paraumbilikalen Bauchwanddefekts wird mit 1 : 6—8000—30000 angegeben [12, 14], wobei Frühgeborene männlichen Geschlechts überwiegend betroffen sind. Das dem Abdomen vorgelagerte Darmkonvolut von braunroter bis grünlicher Färbung ist meist von einer weißlichen-gelben Fibrinschicht überzogen, die einen Hinweis auf die (primär sterile) fetale Peritonitis liefert. Eine Differenzierung einzelner Darmschlingen ist nicht möglich, da sie zu einem Konglomerattumor verschmolzen sind. Magen und Anteile der Leber können ebenfalls eventriert sein. Insgesamt erscheint der Darm verkürzt und verplumpt. Das Omentum majus fehlt. Weiterhin liegt stets ein erheblich verdicktes Mesenterium ileocolicocommune vor.

Das primär sterile Milieu des Eventrats erfährt frühestens bei der Passage des Geburtskanals eine bakterielle Kontamination, weiterhin durch Abdeckung mit nicht sterilem Verbandsmaterial, insbesondere aber durch die Applikation von Salbenverbänden, die der Keimvermehrung rasch Vorschub leisten. Die Unterkühlung des Neugeborenen mit einer paramedianen Bauchwandspalte stellt einen weiteren Risikofaktor dar.

Behandlung

Adäquate Sofortmaßnahmen sind:

1. Lagerung des Kindes in einem Transportinkubator,

2. Abdecken der Bauchorgane mit steriler feuchter (physiologische NaCl) Mullgaze,

3. Legen einer Magensonde zur Aspirationsprophylaxe.

4. Ausgleich der Körpertemperatur.

Nach Legen eines venösen Zugangs erfolgt die Sofortoperation, wobei folgende operative Möglichkeiten, abhängig von dem Volumen des Eventrats in Betracht kommen:

1. Primärer Bauchdeckenverschluss

Er stellt die Methode der Wahl bei der Eventration wie bei der rupturierten Omphalozele dar (Abb. 6AB). In der Mehrzahl der Fälle jedoch verbieten Größe der Bruchpforte wie auch das Volumen der vorgelagerten Darmorgane das einzeitige Vorgehen. Der Versuch der primären Reposition sollte stets nur bei gleichzeitiger Kontrolle des zentralen Venendrucks vorgenommen werden, um eine postoperative venöse Einflußstauung zu vermeiden. Ein Bruchpfortendurchmesser von 5 cm ist nach unseren Erfahrungen als oberste Grenze für einen primären Verschluß, unabhängig von dem Umfang der ausgetretenen Bauchorgane anzusehen. — Durch intraoperatives Absaugen des Darminhalts, wie durch Ausstreichen der Darmschlingen und digitale Bauchdeckendilitation läßt sich die Defektdeckung erleichtern. Eine Entfernung der fibrinösen Wandauflagerungen nehmen wir nie vor, und zwar aus folgenden Gründen:

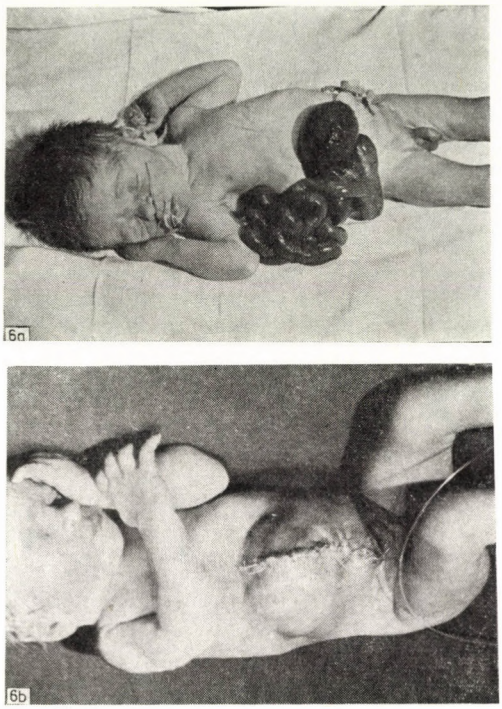


ABB. 6A+B. Primärer Bauchdeckenverschluß bei paraumbilikalem Bauchwanddefekt

1. Einmal verlängert die Präparation den Eingriff erheblich und führt häufig zu Serosadefekten mit der Gefahr weiterer und schwerer Adhäsionen. Zum anderen zeigen Relaparotomien schon wenige Tage nach dem Ersteingriff einen weitgehend normalen Aspekt der Darmwand, wie auch eine spontane Lösung der Darmschlingen voneinander. Es muß angenommen werden, daß das kindliche Peritoneum mit seiner großen Resorptionsfähigkeit den entscheidenden Faktor für die Defibrinisierung darstellt. Die partielle Resektion von Darmanteilen, die vielfach zur Verkleinerung des Konvoluts vorgenommen wurde [14 u. a.], muß wegen ihrer delitären Auswirkungen (Nahtdehiszenz, Stenose, sekundäre Atresie) abgelehnt werden. Aufgrund unserer Erfahrungen bei insgesamt 72 Neugeborenen mit einem Nabelschnurbruch und einem paraumbilikalen Bauchwanddefekt stellt somit nur eine »forme mineure« der letztgenannten Fehlbildung die Indikation zum einzeitigen Bauchdeckenverschluß.

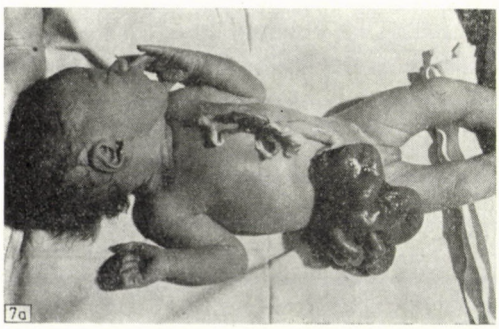
2. Mehrzeitige Verfahren

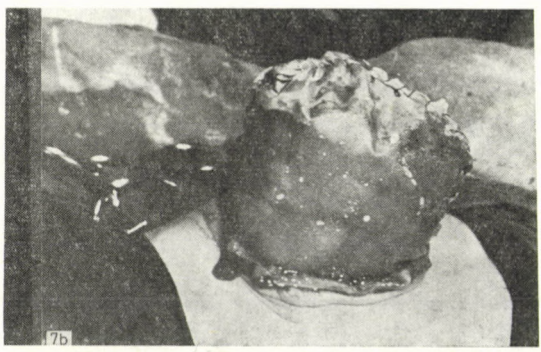
Sie dienen ausschließlich der Abschirmung der Intestinalorgane und somit der Verhinderung einer weiteren Keimbesiedlung. Die Bildung

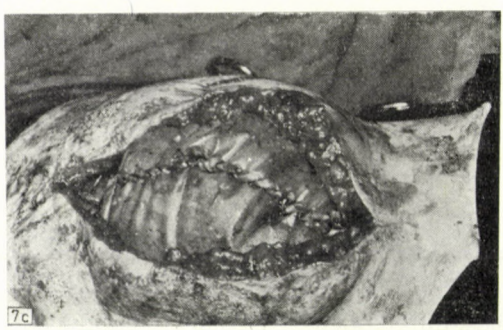
eines iatrogenen Bruchsacks kann durch die Anwendung verschiedener Materialien erfolgen.

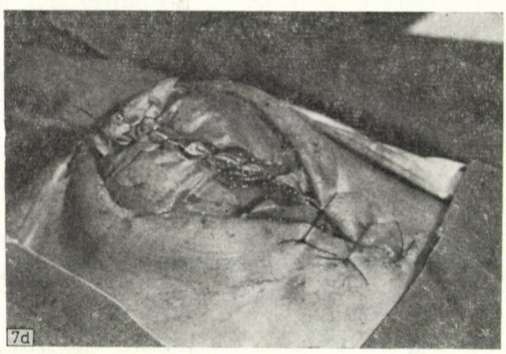
1. Eigenhaut,
2. Eihäute,
3. lyophilisierte Dura,
4. Kunststoffolien.

Um das Eventrat mit *eigener Bauchhaut* decken zu können, ist eine ausgedehnte Abpräparation der Cutis von ihrer Unterlage notwendig. In das so gebildete suprafasziale Cavum kann ein Teil der Bauchorgane, die im Abdomen selbst keinen Platz ha-









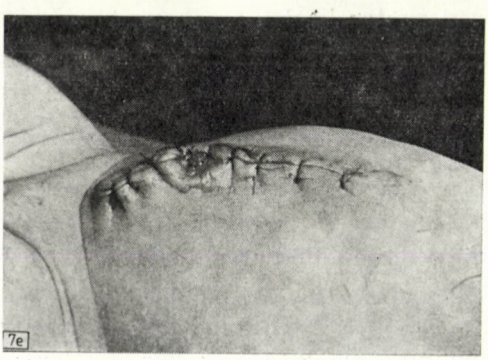


Abb. 7a—e. Schrittweiser Verschluß eines paraumbilikalen Bauchwanddefekts unter Anwendung eines vorgefertigten Silastic-Beutels. Eine Adaptierung der Bauchhaut ist nach 14 Tagen möglich

ben, gelagert, und über ihnen die Haut verschlossen werden. Vielfach wurden laterale Entlastungsschnitte wie auch Hautverschiebeplastiken [5] angewandt, um eine spannungsfreie Naht zu erzielen. Die Ergebnisse dieser eingreifenden Prozeduren waren insgesamt enttäuschend. Ausgedehnte Verwachsungen der Darmschlingen mit der Haut erschweren die Nachoperation, die wegen häufiger Stuhltransportstörungen vielfach rasch erfolgen muß, oder machen sie unmöglich.

Durch die Interposition *geburtseigener Eihäute* bietet sich eine nahezu physiologische Defektdeckung an [3]. Sie bietet den Vorteil des raschen Einheilens und der absoluten Keimsperre. Ihre Anwendbarkeit jedoch setzt die Konservierung der Plazenta auf der jeweiligen geburtshilflichen Abteilung voraus.

Das Anheften *lyophilisierter Dura* an der Muskulatur oder der Bauchdecke hat sich in unseren Händen nicht bewährt. Durch rasche Eintrocknung des Gewebes bildet sich eine lederartige Platte, die eine innige Verbindung mit den darunter liegenden Organen eingeht. Zudem konnten wir vielfach eine partielle Ablösung der Duraplatte in den Randpartien beobachten, was stets eine Sekundärinfektion zur Folge hatte. Obwohl Joppich [9] über gute Erfahrungen unter Anwendung dieser Technik referierte, haben wir die Duraimplantation verlassen und in den letzten Jahren nur noch ein *Silastic-Sheet* angewandt. Wir benutzen vorgefertigte Silikonbeutel verschiedener Größe, die über das Eventrat gestülpt und an der Bauchwandfaszie mit einer fortlaufenden Seidennaht fixiert werden. Es ist vorteilhaft, die Bauchhaut mit einer zweiten Nahtreihe an der Kunststoffolie zu fixieren. Als zusätzliche Infektionsprophylaxe hat sich uns das Auftragen von Zyanoakrylat auf den Hautrand bewährt. Der »Bruchsack« wird wie bei dem Nabelschnurbruch unter leichter Anspannung am Dach des Inkubators aufgehängt. Durch vorsichtiges Twisten des Beutels oder durch schrittweises Verschieben einer aufgesetzten Darmklemme wird eine langsame Reposition der Bauchorgane herbeigeführt. Nach 14 Tagen bis 3 Wochen kann der Kunststoff entfernt und die Bauchdeckennaht vorgenommen werden.

Behandlung der Bauchwandhernie

Die Beseitigung des Bauchwandbruchs nach großer Omphalozele und paraumbilikalem Bauchwanddefekt nehmen wir im Alter von 7 Monaten bis 1 Jahr vor. Um einen sicheren Bruchpfortenverschluß zu erzielen, bedienen wir uns seit 1974 eines *autologen*, freitransplantierten *Coriumlappens*, der allen bislang benutzten Tranplantaten wie auch anderen Operationsmethoden überlegen ist [6, 8]. Der Wert des Verfahrens konnte von uns bislang bei 12 Kindern mit übergroßer Bauchwandhernie durch Langzeitkontrollen bis zu 4 Jahren überprüft werden.

Eigene Operationstechnik

Die Größe des benötigten Vollhautlappens wird am relaxierten Patienten bestimmt. Nach Raffen der den Bruch bedeckenden Haut wird die Resektionsgrenze markiert (Abb. 8). Unter wetzsteinförmiger Schnitteführung wird die Cutis durchtrennt, wobei die Länge des Lappens etwa der Längsausdehnung der Bruchlücke entspricht. Nach Abpräparation der subkutanen Fettschicht wird das Präparat bis zur Implantation in einer Penicillin-Lösung aufgehoben. Von den Spitzen des entstandenen Hautdefekts wird der Hautschnitt nach kranial wie nach kaudal erweitert und die Haut flankenwärts über die lateralisierte Rektusmuskulatur hinaus mobilisiert. Meist kann eine Eröffnung der Bauchhöhle vermieden werden. Im kranialen und kaudalen Bereich werden die Mm. recti, soweit dies ohne Spannung möglich ist, mit Seidennähten vereinigt. Der zentrale Bauchwanddefekt wird dann zunächst durch eine aus der vorderen Rektusscheide gebildete Türflügelplastik stabilisiert.

Als Nahtmaterial benutzen wir Dexon $3-3\times O$ entsprechend dem Alter des Kindes. Der Hautlappen wird nun 1—2 min. in eine heiße (70—90°) NaCl-Lösung gebracht und anschließend kurz in eine konzentrierte Jod-Lösung eingetaucht. Infolge der »Verbrühung« läßt sich die denaturierte Epidermis innerhalb weniger Sekunden ohne Hinterlassung von Epithelinseln mit der Pinzette entfernen. Das Coriumtransplantat wird über dem Defekt ausgespannt und seine Ränder mit dem freien Schnittrand der vorderen Rektusscheide unter Spannung

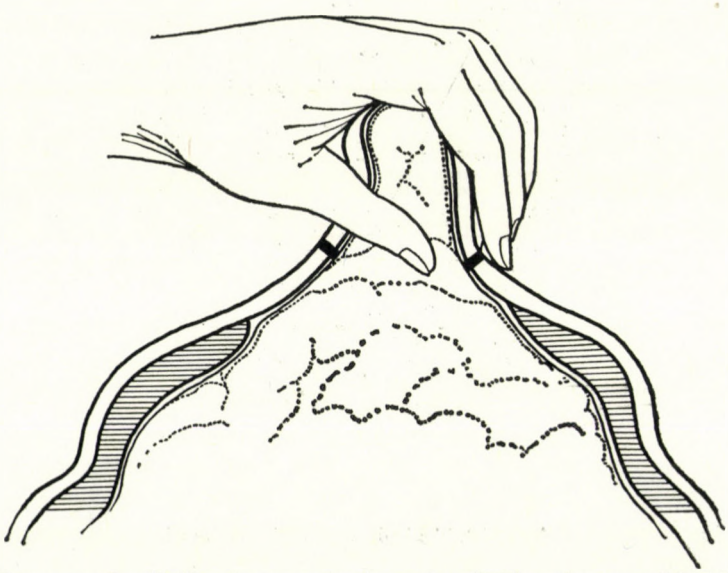


Abb. 8. Bestimmung der Größe des zu entnehmenden Vollhautlappens (Markierung der Resektionsgrenze)

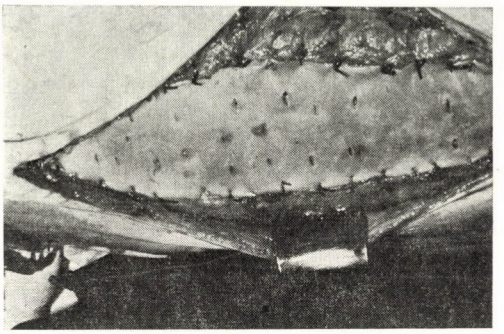


Abb. 9. Freies Coriumtransplantat in situ

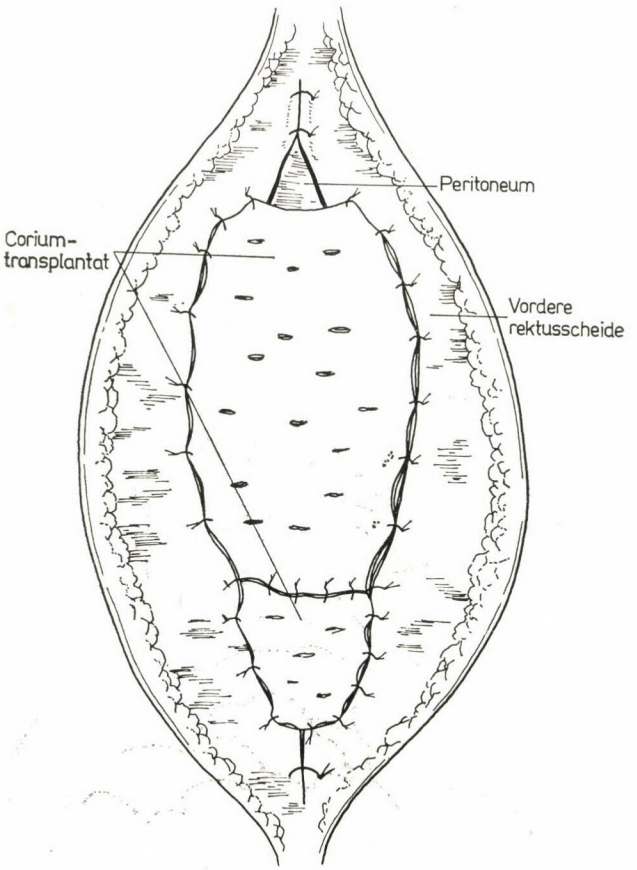


Abb. 10. Technik der »Flick«-Plastik

vereinigt (Seidenknopfnähte 3×O) (Abb. 9).

Mehrere punktförmige Perforationen des Transplantats mit dem Skalpell sind zur Verhinderung einer Serombildung unumgänglich. Nach Einlegen einer Redondrainage für 24 Stunden werden Subcutis und Haut in typischer Weise durch Knopfeinzelnähte vereinigt. Postoperativ umwickeln wir das Abdomen für 3 Wochen mit einer elastischen Binde. Während der ersten 14 Tage ist eine Antibiotikaprophylaxe angezeigt.

Erweist sich intraoperativ, daß der gewählte Coriumlappen zu klein ist, um die Bruchlücke in vollem Umfang zu überbrücken, so kann be-

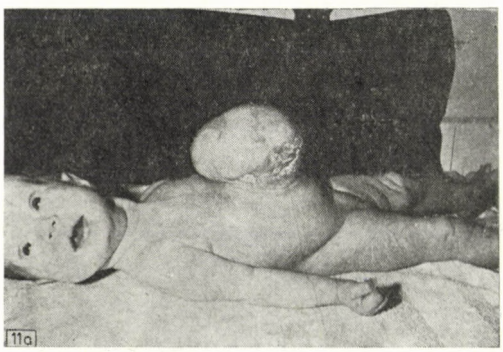


Abb. 11a. 6 Wochen alter weiblicher Säugling mit riesiger Amniozele

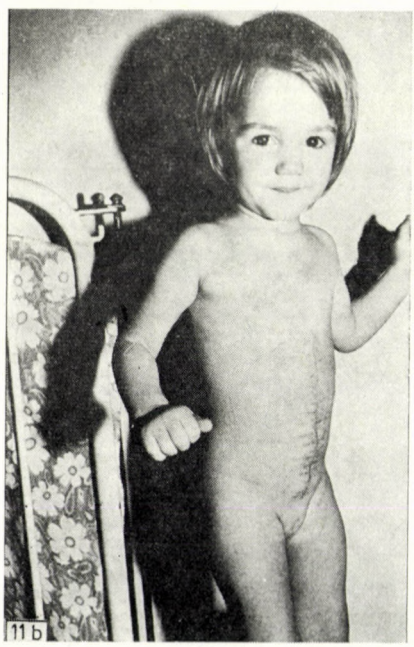


Abb. 11b. Dasselbe Mädchen im Alter von 2 Jahren (ein halbes Jahr nach der Cutislappenplastik). Stabile Bauchdecken, normales Bauchwandrelief

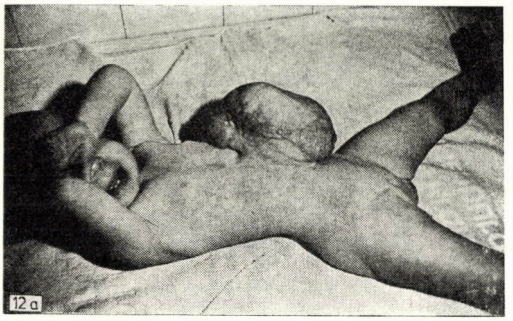
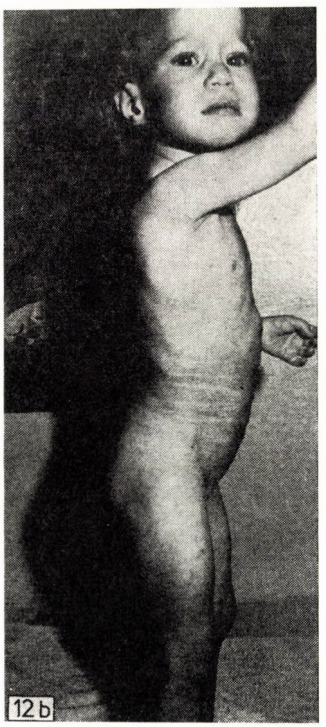


Abb. 12a. 2 Monate alter weiblicher Säugling mit großer Narbenhernie nach konservativ behandelter Amniozele



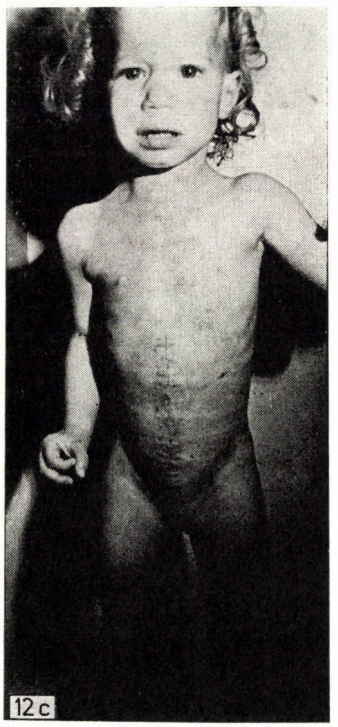
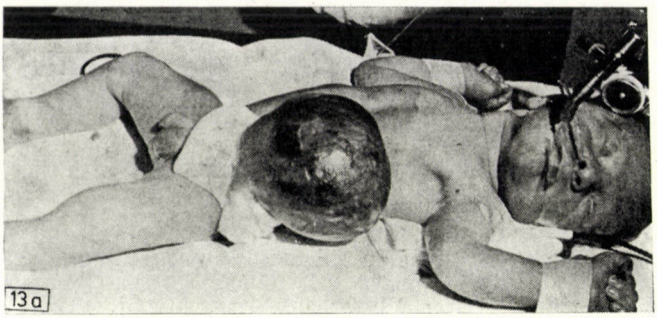
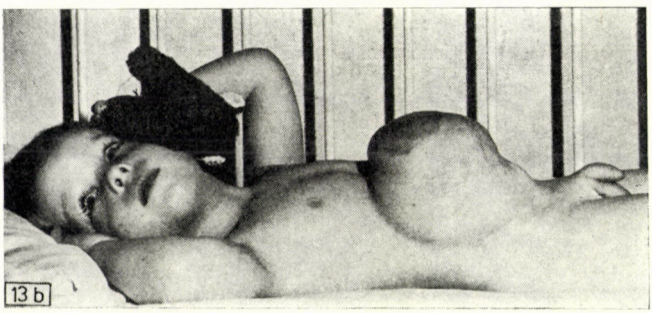


Abb. 12b+c. Dasselbe Mädchen im Alter von 2 Jahren (ein halbes Jahr nach der Cutislappenplastik)

denkenlos ein zweiter oder dritter Lappen »angeflickt« werden. Manchmal kann diese Zusatzplastik erforderlich sein, um im kranialen oder kaudalen Bruchpfortenbereich eine sichere Bauchdeckenstabilisierung zu erzielen (Abb. 10). Bei 2 unserer Patienten war dieses Vorgehen notwendig.

Unsere Behandlungsergebnisse seien anhand einiger Bilderbeispiele dokumentiert. (Abb. 11—13).





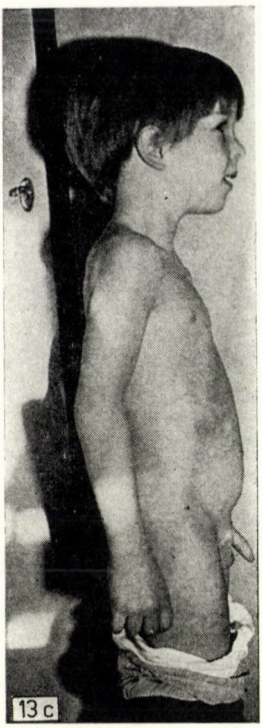


Abb. 13a—c. Männliches Neugeborenes mit übergroßer Amniozele (A); der Säugling mit 2,5 Monaten (B); derselbe Junge mit 4 Jahren (3 Jahre nach der Cutislappenplastik) (C)

Bei einem unserer Kinder stellte sich 10 Tage nach der Operation eine partielle Nahtdehiszenz infolge eines subkutanen Seroms ein. Obwohl der Coriumlappen frei lag, erfolgte keine Abstoßung des Transplantats, eine Beobachtung, die auch Herczeg [6] und andere beim Erwachsenen machen konnten. Voraussetzung zur komplikationslosen Einheilung des Coriumlappens und seiner Umformung in eine elastische Aponeurose ist:

1. Implantation des Lappens unter Spannung [13],

2. enger Kontakt des Transplantats mit der Rektusmuskulatur, die den Mutterboden zur Revaskularisierung darstellt.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 351—355 (1978)

Mit Enterobacterial Common Antigen (ECA) nachweisbaren Antikörper bei Pyelonephritis im Kindesalter

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(Eingegangen am 21. April 1978)

Im Serum von pyelonephritischen Kindern wurden mit der indirekten Hämagglutinationsmethode Antikörper gegen mit Enterobacterial Common Antigen (ECA) sensibilisierten Schaf-Erythrozyten nachgewiesen. Bei 10 gesunden Kindern fiel die Reaktion negativ aus, bei akuter Pyelonephritis war die Reaktion stets positiv. Bei chronischer Pyelonephritis zeigten die Titerwerte wesentliche Streuungen und wurden häufig als negativ qualifiziert. Unter den Bedingungen der angewendeten Methode entspricht der Wert der diagnostischen Titergrenze einer Verdünnung von 1 : 64.

Bei urogenitalen Infektionen ist die Entscheidung der Frage, ob sich die Infektion ausschließlich auf den unteren Abschnitt des Urogenitaltrakts lokalisiert oder ob es sich um eine Pyelonephritis handelt, von grundlegender Bedeutung [12]. Bei Pyelonephritis muß mit der Invasivität des Krankheitserregers und mit der Immunantwort des Organismus rechnen. Theoretisch scheint der Nachweis der spezifischen Antikörper gegen den aus dem Harn gezüchteten Krankheitserreger als die einfachste und effektivste Methode zu sein [2, 3, 5, 15], die jedoch wegen zahlreicher technischer Schwierigkeiten als Routineverfahren nicht empfohlen werden kann.

In vorliegender Arbeit wollen wir über unsere Erfahrungen mit den Antikörpern gegen das Enterobacterial Common Antigen (ECA) berichten.

Material und Methodik

Unser Krankengut bestand aus 30 Kindern im Alter zwischen 2 und 14 Jahren. 10 Mädchen litten an akuter Pyelonephritis, in die Gruppe der chronischen Pyelonephritis gehörten 10 Kinder; 6 waren Mädchen und 4 Knaben.

Bakteriologische Untersuchung: Der Harn der Patienten wurde wiederholt auf Endo-Agar und Blutagar geimpft. In sämtlichen Fällen fand auch eine Keimzahlbestimmung aus frischem Mittelstrahlharn statt. Bei der Beurteilung der Bakteriurie wurden auch die bei niedriger Keimzahl gewonnenen Befunde berücksichtigt, vorausgesetzt, daß konsequent übereinstimmende Werte zu verzeichnen waren.

Der Wert der Sedimentation wurde bei 20 mm/St als negativ betrachtet. Die Osmolarität des Harns wurde nach 12-stündigem Dursten unter einem Wert von 950 mOsm/l und einem spez. Gewicht unter 1020 als pathologisch qualifiziert.

Die Herstellung des ECA erfolgte mit der Methode von Marx und Petcovici [10]. Aus dem E. coli 014 »Kunin«-Stamm

wurde in Schüttelkultur (Casein hydrolysatum) Massenzüchtung durchgeführt. Nach Zentrifugieren wurden 200 g feuchte Bakterien mit 2 000 ml 96%iger Ethanollösung versetzt, die Suspension bei ständigem Umrühren auf 60 °C erwärmt und Weitere 20 Minuten lang bei dieser Temperatur aufbewahrt. Es folgte ein kräftiges Zentrifugieren (13 000 *g*) der Suspension und die Konzentrierung des Supernatants in Vakuum bei 40 °C zu einer viskösen Flüssigkeit. Zunächst wurde die Flüssigkeit in 40 ml 85%iger Ethanollösung gelöst, zentrifugiert, das Supernatant mit 3 Volumen Azeton ausgefällt, zentrifugiert (6 000 *g*) und das Sediment in 4 ml destilliertem Wasser aufgenommen. Das auf diese Weise gewonnene Antigen wurde bei −20 °C konserviert und zur Sensibilisierung in einer Verdünnung von 1 : 10 verwendet.

Indirekte Hämagglutination: Sensibilisierung der gewaschenen Schaf-Erythrozyten bei 37 °C 2 Stunden lang, Entfernen des Antigenüberschusses durch dreimaliges Waschen mit Salzwasser; vor der Untersuchung wurden die zu untersuchenden Sera bei 56 °C 30 Minuten lang inaktiviert.

Die technische Ausführung der Hämagglutination erfolgte mit der Methode nach Takátsy [14]. Kontrollhalber kam E. coli 014-Kaninchenserum zur Anwendung.

Ergebnisse

Bei akuter Pyelonephritis ergab die mit ECA durchgeführte passive Hämagglutination in allen 10 Fällen ein positives Ergebnis, außerdem ließ sich in allen Fällen auch eine signifikante oder konsequente Bakteriurie verzeichnen; in 8 Fällen meldete sich Pyurie. Die Sedimentation ergab in sämtlichen Fällen hohe Werte, in 9 Fällen war die Konzentrationsfähigkeit eingeengt. Das Ergebnis der Pyelographie viel in 5 Fällen positiv aus. Die mit ECA durchgeführte passive Hämagglutination war bei 4 chronischen Pyelonephritisfällen positiv; signifikante oder konsequente Bakteriurie meldete sich in 6 Fällen und Pyurie ebenfalls in 6 Fällen. Eine positive Sedimentation ließ sich in 4 Fällen registrierten. Die Konzentrationsfähigkeit war in sämtlichen Fällen eingeengt. Das Ergebnis der Pyelographie fiel in sämtlichen Fällen positiv aus. Für die akute Pyelonephritis war in 9 Fällen E. coli verantwortlich. E. coli-Keimzahl: 10^4/ml Harn: 4 Fälle; 10^3/ml Harn: 2 Fälle; 10^1/ml Harn, 1 Fall. In einem Fall handelte es sich um eine doppelte Infektion: Keimzahl: E. coli 10^3 bzw. Proteus 10^4. In 4 Fällen gesellte sich zur chronischen Pyelonephritis eine E. coli-Bakteriurie, Keimzahl: 10^2/ml Harn 2 Fälle, 10^3/ml Harn 2 Fälle, 10^5/ml Harn 1 Fall. In einem Fall lag eine Proteus-Bakteriurie vor [Keimzahl: 10^4/ml Harn]. Bei der in einem weiteren Fall beobachteten doppelten Infektion zeigten die Keimzahlwerte folgendes: 10^1/ml Harn E. coli und Proteus. In 4 Fällen war die Harnkultur steril. Bei akuter Pyeolonephritis waren in sämtlichen Fällen Titerwerte von 1 : 64 bis 1 : 1 : 1024 zu beobachten. Bei chronischer Pyelonephritis zeigten die Titerwerte bedeutende Streuungen, von 1 : 2 bis 1 : 512.

Besprechung

Die Erfahrungen sprechen dafür, daß das Erscheinen der Antikörper ein sicheres und brauchbares Zeichen

der Mikrobeninvasion ist. In unseren früheren Beobachtungen erwies sich der Nachweis der spezifischen Antikörper gegen den Krankheitserreger als ein brauchbares Mittel [15]. Über ähnliche Erfahrungen berichteten mehrere Verfasser [1, 4, 5, 9, 11, 17]. Bei gemischten Infektionen müssen sämtliche Mikrobenspezies bzw. Klons als Antigene verwendet werden.

Individuell kann jedes Serum nur mit einem homologen Antigen getestet werden. Bei chronischer Pyelonephritis ist die Untersuchung der Antigenstruktur unerläßlich, da bei einer Exazerbation die Bestimmung des Krankheitserregers unbedingt erforderlich ist [15].

Das sog. Common-Antigen der enteralen Bakterien bietet neue und

TABELLE I

Mit ECA-Antigen sensibilisierten Erythrozyten durchgeführter Hämagglutinationstest bei akuter und chronischer Pyelonephritis und bei gesunden Kontrollpersonen

Gruppe	Reziproke Titerwerte									
	nicht als positiv bewertbar					Positive Werte				
	2	4	8	12	32	64	128	256	512	1024
Akute Pyelonephritis	—	—	—	—	—	2	6	—	—	2
Chronische Pyelonephritis	1	—	3	—	2	1	2	—	1	—
Normale Kontrollpersonen	1	1	1	4	3	—	—	—	—	—

TABELLE II

Vergleich der Werte der ECA-Hämagglutination sowie der sich auf Bakteriurie und klinische Laboratoriumsdaten beziehenden Ergebnisse

Untersuchung	Akute Pyelonephritis	Chronische Pyelonephritis
Reziproke ECA-Hämagglutinationswerte	64—1024 ($\bar{x}$ = 294.4)	2—512 ($\bar{x}$ = 208.0)[1]
Bakteriurie[2]	10^1—10^4 [10/10]	10^1—10^5 [6/10]
Pyurie[3]	8/10	6/10
Sedimentation [4]	10/10	4/10
Konzentrierung[5]	9/10	10/10
Pyelographie[6]	5/10	10/10

1 = Durchschnittswert anhand der in das positive Bereich fallenden Titerwerte; 2 = die Bakteriurie wurde auch bei niedriger Keimzahl (10^1) als positiv betrachtet, vorausgesetzt, daß sich diese Befunde konsequent meldeten; 3 = Zahl der Fälle mit über 5 Leukozyten pro Sichtfeld im ganzen Material; 4 = Zahl der Fälle mit über 20 mm/St BKS im ganzen Material; 5 = Zahl der Fälle mit einem spez. Gewicht unter 1020 bzw. einem mOsm Wert unter 950 im ganzen Material; 6 = Zahl der pyelographisch positiven Fälle im ganzen Material.

wesentlich einfachere Möglichkeiten. Es ist seit langem bekannt, daß dieses Antigen in sämtlichen zu den Enterobacteriaceaen gehörenden Mikroben vorgefunden [8] und durch Ethanolfraktionierung getrennt werden kann [13]. Die ECA-Antikörper lassen sich auch im normalen Humanserum nachweisen — allerdings ergeben sie nur niedrige Titerwerte [8]. Der Nachweis der Anti-ECA-Antikörper gelang nicht nur bei urogenitalen Infektionen, sondern auch bei Darminfektionen. WHANG und NETER [16] fanden, daß die Anti-ECA-Titerwerte in Normalseren maximal 1 : 40 ausmachten; in 5 der 6 Fälle von chronischer urogenitaler Infektion registrierten sie Titerwerte zwischen 1 : 80 und 1 : 320. Nach ANDERSON [1] ließen sich bei akuten Harnwegsinfektionen bedeutende Streuungen, d. h. Titerwerte zwischen 1 : 8 und 1 : 512 verzeichnen.

Im Laufe der vorliegenden Untersuchungen fanden wir bei gesunden Probanden verhältnismäßig niedrige Titerwerte, indem der Maximalwert 1 : 32 ausmachte. Bei akuter Pyelonephritis konnten indessen stets positiv bewertbare hohe Titer demonstriert werden. Für das zuverlässigste und konsequenteste Zeichen der akuten Pyelonephritis erwies sich in unseren Fällen der Anti-ECA-Wert. Die bei chronischer Pyelonephritis häufig vorkommenden Remissionen und Exazerbationen sind mit Bakteriurie und erhöhtem Anti-ECA-Titer verbunden. Mit der indirekten Hämagglutinationstechnik konnten wir ausschließlich in die IgM-Gruppe gehörende, d. h. über eine kurze Halbierungszeit verfügende Antikörper nachweisen. Bei chronischer Pyelonephritis werden durch den Mangel an Antikörpern keine diagnostischen Probleme verursacht, zumal in Kenntnis der wesentlichen Schädigung der Nierenfunktion und der röntgenmorphologischen Daten die Diagnose eindeutig ist. Unseres Erachtens bietet der Nachweis der ECA-Antikörper mit der indirekten Hämagglutinationstechnik zur Diagnostizierung der akuten Pyelonephritis eine nicht zu unterschätzende Hilfe.

Herrn Prof. Dr. K. JOBST wollen wir für seine Hilfe bei der Bestimmung der Harnosmolarität unseren herzlichen Dank zukommen lassen.

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Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (4), pp. 357—365 (1978)

Transverse diameter of chest and heart after birth asphyxia in the newborn infant

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Received April 25th, 1978

The transverse diameter of the chest and heart was measured in 745 newborn infants after birth asphyxia. Both diameters showed a good correlation with birth weight. The great individual variations of the measurements were due to different degrees of birth asphyxia observed in the infants and to their different responses to compensate asphyxia. A wet lung and an increased transverse diameter of the chest (above the 90th percentile) indicate a good, and a decreased transverse diameter of the chest (bellow the 10th percentile) indicate a bad prognosis for survival. The cardiomegaly usually disappears after the first 12 hours of life, but in some cases it persists for more than 5 days, depending on the severity of birth asphyxia.

Adaptation to extrauterine life of the cardiorespiratory system of the newborn infant is prolonged after birth asphyxia; the absorption of amniotic fluid in the lungs is delayed, dystelectasis and emphysema develop, the physiological shunts in the heart remain open, the size of the heart increases [2, 9, 11, 13, 14, 15, 16]. These changes are clearly seen on the chest X-rays and the transverse diameter of the chest and the heart can be measured. When studying the X-ray picture of the wet lung it is important to assess the degree of emphysema (increased chest diameter) and dystelectasis (decreased chest diameter). In the present paper we have compared the transverse diameter of the chest (TDC) and the heart (TDH) in normal infants and in infants who had experienced different degrees of asphyxia at birth. A comparison was made between these measurements and the severity of birth asphyxia.

Materials and Methods

The records of 745 newborn infants admitted for birth asphyxia were evaluated, and a retrospective analysis was made. Infants of diabetic mothers, small-for-dates newborns, infants with congenital heart disease, hypoglycaemia or hypocalcaemia were excluded from the study. The criteria for the diagnosis of birth asphyxia or postasphyctic syndrome were

1) factor(s) predisposing to asphyxia in the history of pregnancy or delivery;

2) a 1 minute Agar score less than 7;

Supported by grant No. 3—23—0502—04—1/M of the Hungarian Ministry of Health.

3) pH less than 7.30, with a Base excess less than −5mE/l and a pCO_2 above 40 mm Hg;

4) clinical signs suggesting that the infant had experienced birth asphyxia (tachypnea, cyanosis, neurological signs, etc.).

The infants studied were divided into mild, moderate and severe groups, depending on the X-ray picture of the chest and heart. The classification was based on principles accepted in the literature [11, 14, 16]. TDC and TDH were measured in each case. The technique of roentgenograph and measurements has been described earlier.

Roentgenograms were made within the first 12 hours of life, then at 24, 48, 72 hours and on the 5th postnatal day.

Statistical evaluation was done by correlation and regression analysis, the latter by parabolic approach ($d = c\sqrt{m}$).

Cases in which the TDC was above the 90th or below the 10th percentile were analysed individually in the first 12 hours, after 24 hours and on the 5th day of life. The same was done if the TDH was above the 90th percentile within 12 hours and on the 5th day of life.

Results

Data for the pregnancies and deliveries are given in Table I. In the roentgenograms, wet lung disease (27.7%), cardiomegaly (23.1%) or the two typical changes together (49.1%) were the most striking findings. According to the classification of Nielsen [11] and Wesenberg [15, 16], 43.9% of the cases were considered mild, 43.9% moderately severe and 12.8% severe.

There was a close correlation ($p < 0.001$) between birth weight and the two diameters in all age groups (Figure 1a and 1b, Table II).

Table I

Maternal pathological conditions during pregnancy Factors predisposing to perinatal asphyxia

Number of cases	Pathological conditions
8	Congenital heart disease
3	Epilepsy
4	Hypertension
2	Asthmatic bronchitis
6	Shirodkar cerclage
1	Appendectomy
1	Gastric surgery
1	Gynaecological surgery
1	Tuberculosis
1	Purulent bronchitis
1	Oophoritis
1	Trichomonas infection
1	Criminal abortion

Number of cases	Predisposing factors
58	Umbilical cord twisted around neck
24	Protracted delivery
3	Precipitated delivery
16	Placenta praevia
119	Premature ruptura of membranes
29	Meconium stained amniotic fluid
34	Signs of intrauterine asphyxia
1	Placenta zonaria
51	Placental infarction
3	Uterine neck contraction
14	Breech presentation
11	Transverse presentation
1	Vertex presentation
3	Face presentation
2	Occipital presentation
1	Footling presentation
2	Dystocia
6	Fraction of arm
8	Prolapse of cord
3	Short umbilical cord
4	Persistent membranes
4	Traction of leg
2	Contracted pelvis
1	Myoma of uterus
1	Rupture of membranes during amnioscopy

The individual TDC data in postasphyctic babies were different from the normal values in all age groups. Within the first 12 hours of life we

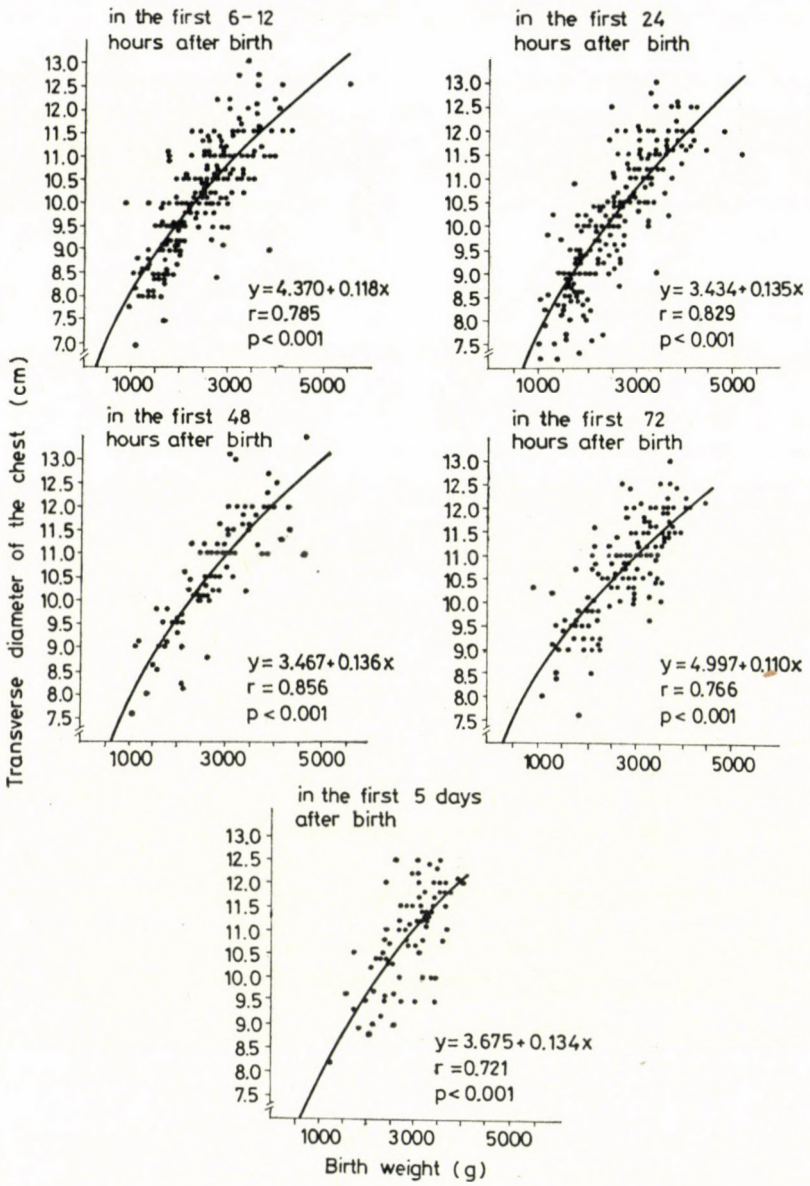

FIG. 1/A

had data only from babies with a birth weight between 1250—2250 g. Most of the TDC measurements were within the 10th and 90th percentile in this group of babies, and only a small fraction was above the 90th percentile. Later, at 24, 48 and 72 hours and at 5 days of life more data were below the 10th percentile (Figure 2b).

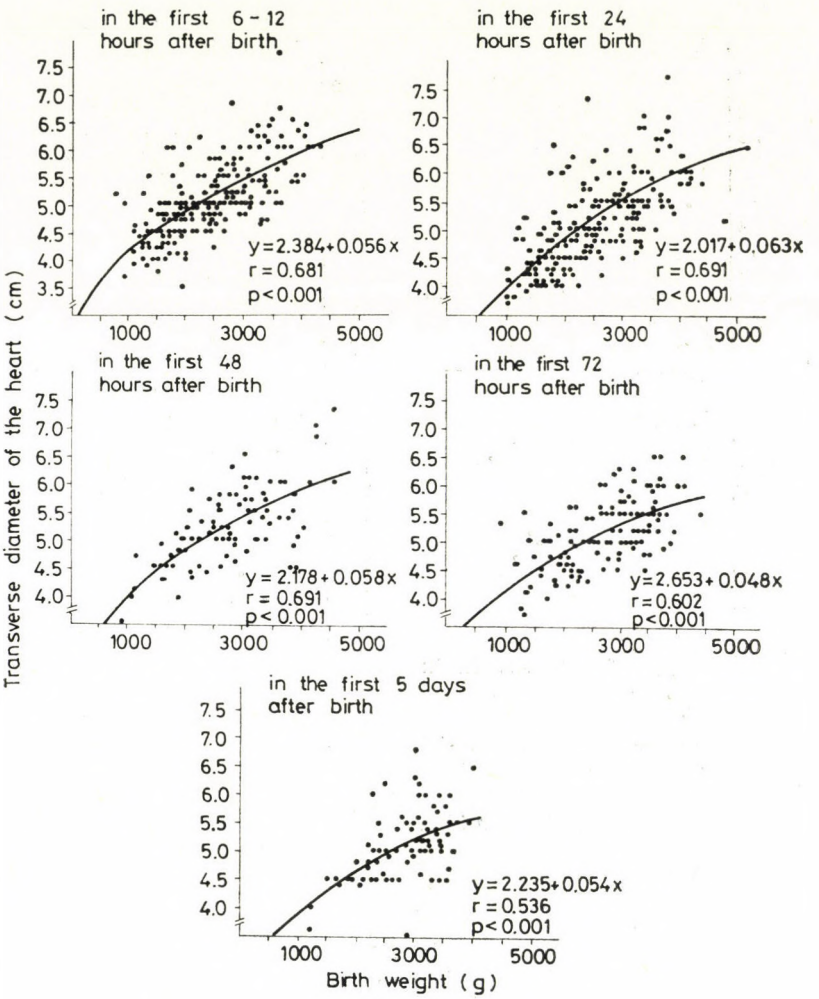

FIG. 1/B

All cases with a TDC above the 90th or below the 10th percentile were analysed individually. In both groups asphyxiating factors had occurred during pregnancy or delivery twice as often as in the other babies (Table III).

In cases with a TDC above the 90th percentile, the dominating radiological sign was emphyseme and with a TDC below the 10th percentile, dystelectasis of the lung.

In the first 12 hours of life, two babies died in the first and 11 in the second group. Asphyxiating factors were similarly frequent in babies with a TDH above the 90th percentile, if the measurements were made at 12 or 24 hours or 5 days. Mortality rate in these cases decreased with

TABLE II

			Time of investigation after birth				
			6—12 hours	24 hours	48 hours	72 hours	5 days
Postasphyctic cases	Birthweight	Mean	225	217	86	134	81
		N	2425	2505	2765	2747	2860
		SD	795	830	855	747	614
	TDC	Mean	10.107	10.111	10.542	10.707	10.802
		SD	1.211	1.364	1.358	1.073	1.130
	TDH	Mean	5.081	5.100	5.011	5.165	5.105
		SD	0.053	0.755	0.722	0.601	0.612
Control cases	Birthweight	N	130	217	164	177	136
		Mean	1651	2214	2274	2230	2531
		SD	456.0	707.0	789.0	773.0	579.0
	TDC	Mean	8.786	9.716	9.750	9.832	10.400
		SD	1.035	1.082	1.220	1.204	0.856
	TDH	Mean	4.11	4.51	4.12	4.37	4.59
		SD	0.454	0.524	0.548	0.506	0.367

TABLE III

In brackets, total number of postasphyctic cases

Transverse diameter of chest	Number of cases*	Number of factors of predisposing to birth asphyxia	Died
12 hours after birth			
TDC > the 90th percentile	18(745)	34(832)	2
TDC 10th—50-th percentile	36(745)	53(832)	11
24 hours after birth			
TDC < 90th percentile	28(745)	45(832)	2
TDC < 10th percentile	32(745)	58(832)	4
5 days after birth			
TDC > 90th percentile	13(745)	22(832)	—
Transverse diameter of heart			
12 hours after birth			
TDH > 90th percentile	61(745)	125(832)	13
24 hours after birth			
TDH > 90th percentile	60(745)	142(832)	6
5 days after birth			
TDH > 90th percentile	21(745)	38(832)	—

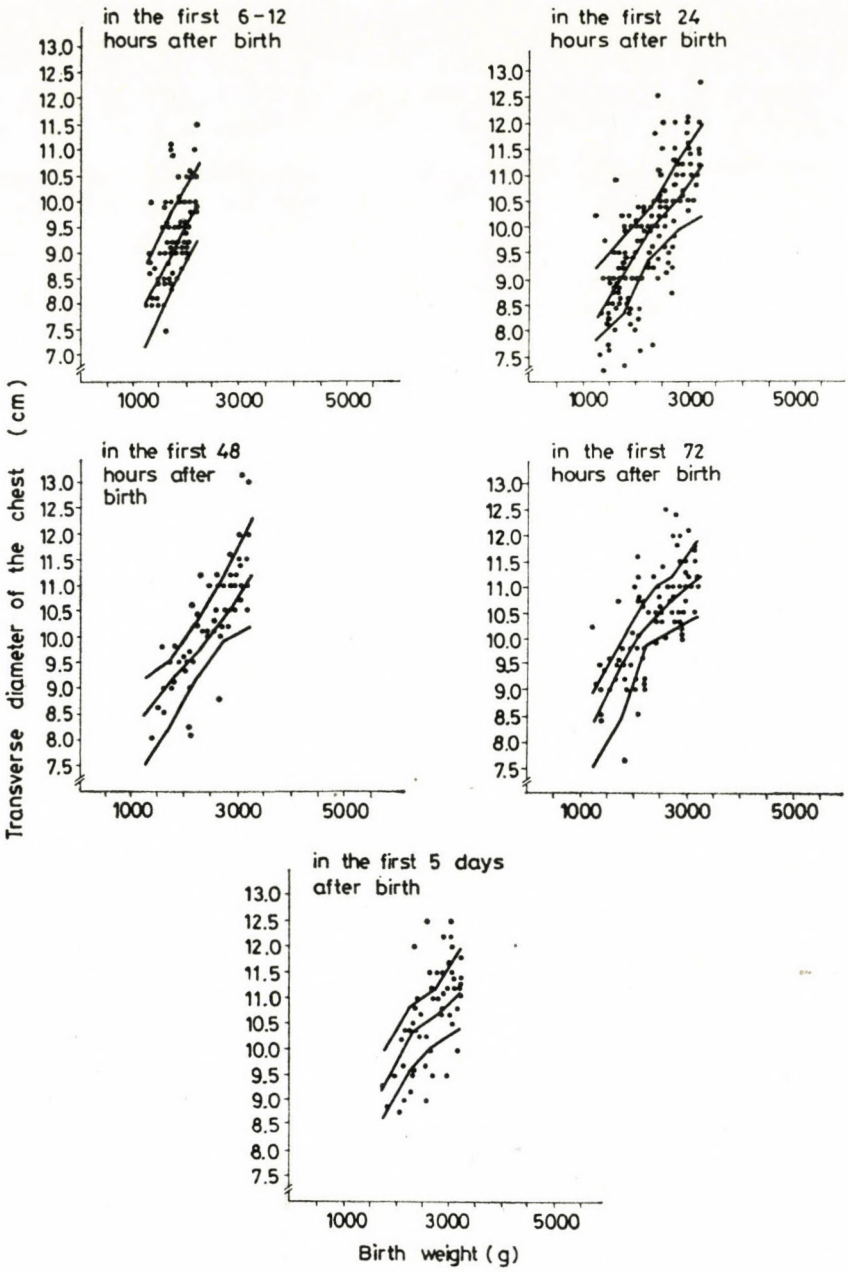
in the first 6–12 hours after birth
in the first 24 hours after birth
in the first 48 hours after birth
in the first 72 hours after birth
in the first 5 days after birth
Transverse diameter of the chest (cm)
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
1000
3000
5000
Birth weight (g)

FIG. 2/A

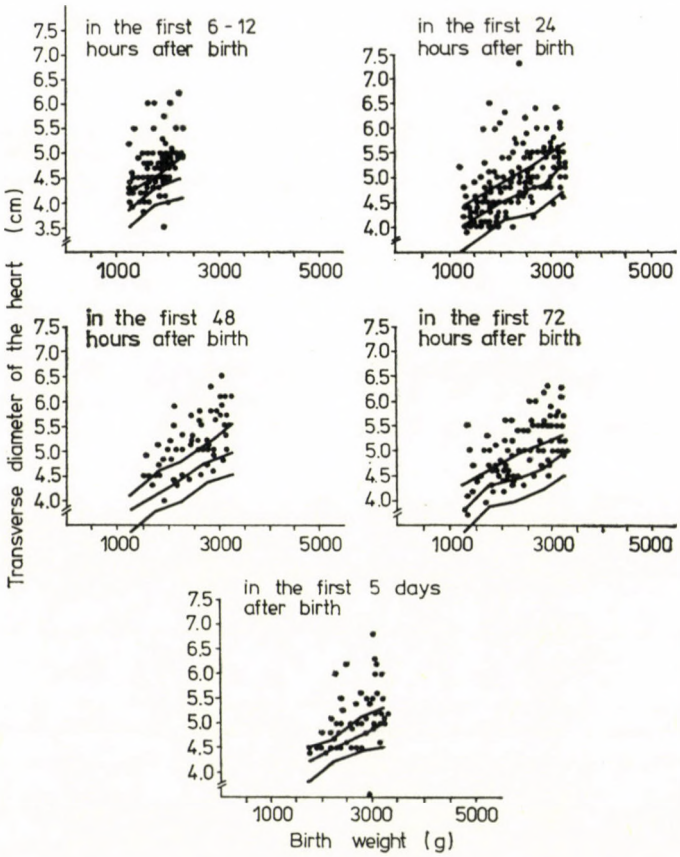

FIG. 2/B

increasing postnatal age (Table III).

Mean TDC, TDH and birth weight were higher in postasphyctic babies than in the normal control group. The increase in mean TDC and birth weight was proportional, but the increase in mean TDH was higher than the increase in birth weight.

DISCUSSION

There are several pathological processes which may change the size of the newborn chest and heart and lead to a disturbance in cardiorespiratory adaptation to extrauterine life [1, 5, 9, 16].

Measuring the volume of the lung or the heart by different methods [8, 10, 12] is not useful in everyday practice, while the TDC and TDH measured on the newborn's chest roentgenogram are useful indicators of the postasphyctic state.

The TDC was measured at different times postnatally. Opinions differ concerning the period that is necessary for cardiovascular adaptation after birth asphyxia. Karlberg's data

show that the process may take more than two days [7], according to Martin and Friedel [9] it takes between two days and a week, and according to Nielson [11] between two and six days. Wesenberg observed complete cardiorespiratory adaptation after 72 hours even in severely asphyxiated babies [16].

In our cases, 12 hours after birth asphyxia the chest roentgenogram showed a patchy pattern with atelectasis and emphysema in both lung fields. This patchy appearance decreased gradually by the 5th day of life, but after severe asphyxia the changes persisted for more than 5 days. Generally, in the first 12 hours of life emphysema, thereafter dystelectasis was the dominating finding on the newborn's chest roentgenogram.

Emphysema was more common among babies with a birth weight over 2000 g. There was a great variability in the measurements due partly to the heterogeneity of the newborn population observed and the different degrees of birth asphyxia. The extent of dystelectasis and emphysema was closely related to the severity of asphyxia and to the individual compensation capacity of the baby. Mean birth weight of the infants studied was higher than in the control group. The newborn infants tolerate birth asphyxia better than preterm infants, as the latter develop hyaline membrane disease after intrauterine or intrapartum asphyxia.

The survival rate was high among babies whose TDC was above the 90th percentile in the first 12 hours of life. On the basis of the above findings, an increased TDC means a good prognosis for survival, while a decreased TDC with a patchy radiographic appearance of the lungs means a poor prognosis in the asphyxiated newborn infant.

Burnard and James [2] reported on a gradual decrease of the TDH in the first 5 days. In our babies who had experienced birth asphyxia, cardiomegaly was a frequent finding in the first 12 hours of life, then its frequency decreased in the next 12 hours. Subsequently the number of infants with cardiomegaly remained unchanged until the 5th day.

The small number of our cases does not allow to draw definite conclusions, but it appears justified to infer that cardiomegaly in low birth weight babies is a worse prognostic sign than in severely asphyxiated term newborn infants.

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Recensiones

Diabetes Mellitus B. Herausgegeben von K. Oberdisse. Handbuch der Inneren Medizin. Fünfte Auflage. Band 7. Stoffwechselkrankheiten Teil 2. B. Springer Verlag, Berlin—Heidelberg—New York 1977. XXVII + 1254 Seiten mit 222 Abbildungen. Preis DM 392.

Diese ganz ausgezeichnete Monographie wurde von 32 international anerkannten Autoren geschrieben. Der erste Band befaßt sich mit theoretischen Fragen, der zweite mit der klinischen Praxis.

In den ersten zwei Kapiteln werden die epidemiologischen und pathophysiologischen Aspekte der Fettsucht sowie des Diabetes mellitus und der Hyperlipoproteinämien ausführlich besprochen. Die Zusammenhänge der Fettsucht mit dem Plasmacholesterin und Trygliceridniveau, die genetischen Beziehungen, der exogene Einfluß von Kohlenhydrat-, Alkohol- und Fettkonsumption auf die Hyperlipämien, Fettleber, Mikroangiopathie, ferner die Diät und die Medikation werden ausführlich behandelt.

Ein kurzes Kapitel befaßt sich mit der diabetischen Angiopathie und Neuropathie. Die Bedeutung der diabetischen Stoffwechselstörungen bei beiden Veränderungen wird betont. In bezug auf die diabetische Mikroangiopathie wird gezeigt, daß während der Diabetiker früher meist einer metabolischen Entgleisung erlag, bilden in den letzten Jahrzehnten immer mehr die Gefäßkomplikationen die Todesursache. Die Mikroangiopathie scheint in den verschiedenen Ländern gleich häufig und von Umweltfaktoren unabhängig aufzutreten, die arteriosklerotischen Gefäßveränderungen sind hingegen von Kontinent zu Kontinent unterschiedlich ausgeprägt, so daß sie in Zusammenhang mit Ernährung und Rauchgewohnheit sowie anderen Umweltfaktoren diskutiert werden müssen.

In einem der größten Kapitel, Diabetes und Nieren, werden alle denkbaren Beziehungen geschildert; vom Standpunkt der Vorbeugung sind auch hier eine gute Behandlung und Fürsorge am wichtigsten. Neurogene Blasenstörungen treten bei jugendlichen Diabetikern häufig auf. Die diagnostische Verwertung der Bakteriurie und Proteinurie, ferner die Fragen der Therapie, z.B. Dialyse und Nierentransplantation werden ausführlich besprochen.

Im Kapitel Diabetes und Auge werden nach einem historischen Überblick die Beziehungen zwischen Diabetes und den verschiedenen Teilen des Auges diskutiert. Es folgt eine umfangreiche Besprechung der Retinopathia diabetica. Die neuen Möglichkeiten der Behandlung, z.B. Licht und Diathermiekoagulation sind beschrieben.

Das Kapitel über die diabetische Neuropathie betont die große Bedeutung der Zuckerstoffwechselstörungen und der herabgesetzten Glukoseutilisation. Die Häufigkeit der Neuropathie bei diabetischen Kindern ist ungefähr 16%, meistens ist die Vibrationsempfindung herabgesetzt. Bei juvenilen Diabetikern findet man oft eine neurogene Blasenstörung.

Ein Kapitel befaßt sich mit den Sexualstörungen der diabetischen Männer: 50% aller zuckerkranken Männer leiden an einer Impotentia coeundi. Die endokrinologischen Beziehungen, der Einfluß der Stoffwechsellage und die ungünstige Prognose der chronischen Impotenz werden diskutiert. In kürzeren Abschnitten werden die Probleme der Leber beim Diabetes sowie die Relation des exogenen und endogenen Pankreas mit dem Diabetes beschrieben. In dem Kapitel Haut und Diabetes wird außer den wohlbekannten Beziehungen zwischen Pruritus, Necrobiosis lipoidica und Rubeosis diabetica

unter anderen auch das selten vorkommende Wernersche Syndrom besprochen. Es folgt das wichtige Kapitel über Coma diabeticum, in dem die Definitionen, die Formen und Kriterien des Comas in einer sehr modernen Auffassung dargelegt sind: Ketoazidotisches, nicht ketoazidotisches (hyperosmolares, hyperglykämisches) Coma und Laktatazidose. Epidemiologie, Biochemie, Pathophysiologie sind eingehend beschrieben, zusammen mit der Klinik und Therapie und den Möglichkeiten der Insulinbehandlung. Die Fragen der Prognose und des Todes sind auch besprochen. Das Kapitel über Spontanhyperglykämien befaßt sich mit der Pathophysiologie, den diagnostischen Techniken und den allgemein angewandten Belastungsuntersuchungen.

In einem kurzen Kapitel wird die ambulante Betreuung des Diabetikers beschrieben. Die Wichtigkeit der Schulung der Patienten, der Muskeltätigkeit und des Sportes sind betont. Die Diät der normgewichtigen und übergewichtigen Diabetiker ist separat angegeben. Die Diätbehandlung bei speziellen Diabetesformen wie z. B. bei labilem Diabetes, bei Schwangerschaft im Alter usw. ist auch eingehend behandelt.

Das Kapitel über die Insulintherapie befaßt sich nach einer historischen Einleitung, mit den verschiedenen Insulinpräparaten, mit der Bedeutung der Kontrolle des Blutzuckers und Harnzuckers, den Lokalreaktionen, der Technik der Insulindosierung und die Komplikationen der Insulintherapie. Die Fragen der Insulinallergie und Insulinresistenz sind in einem selbständigen Abschnitt beschrieben. Das nächste Kapitel befaßt sich mit der Pharmakologie der blutzuckersenkenden Sulfanylharnstoff- und Pyrimidinderivate. Die toxische und teratogene Wirkung, und die Pharmakokinetik der Sulfanylharnstoffderivate und deren Interferenz mit der Wirkung anderer Stoffe sind eingehend besprochen. Das Kapitel über die Sulfanylharnstofftherapie bietet eine ausführliche Besprechung und Charakterisierung der einzelnen Präparate. Neben den Vorteilen dieser Behandlung werden auch die Kontraindikationen betont. In drei Absätzen wird die Problematik der Biguanidine dargelegt: »Pharmakologie und Wirkungsmechanismus beim Tier«,»Der Wirkungsmechanismus der Biguanidine aufgrund klinisch-experimenteller Untersuchungen«, und die »Klinische Anwendung der Biguanide«. Die Verwendung der Biguanide bei asymptomatischem und latentem Diabetes wird auch ausführlich diskutiert. Unter den sozialmedizinischen Problemen ist eines der wichtigsten die Berufsberatung von Diabetikern. Die Aufgaben des Rehabilitationsberaters und die Umschulung von Diabetikern, ferner die Bedeutung der Komplikationen in ihrer Berufstätigkeit und die Fragen der Lebensversicherung werden auch besprochen. Das letzte Kapitel ist »Diabetes, Trauma, Begutachtung«. Hier wird über die Fragen der Entwicklung der Krankheit, endogene und exogene Ursachen und die Rolle verschiedener Traumen und das Problem von Diabetes und Verkehrsrecht gesprochen, unter welchen Umständen der Diabetiker fahrtüchtig ist. Für alle Ärzte, die sich mit Diabetes befassen, ist das Studium dieses Buches äußerst wünschenswert.

L. Barta

K. J. Neumärker und M. Neumärker: *Der Hirnstamm und seine Erkrankungen im Kindesalter*. 178 Seiten mit 47 Abbildungen in 72 Einzeldarstellungen. Georg Thieme Verlag, Leipzig 1977. M 75,—

Unter Hirnstamm versteht man das Zwischenhirn, Pons, und die Medulla oblongata; das Dienzephalon wird auch dazu gerechnet. Die Erkennung der komplexen Funktion des Hirnstammes erfordert sorgfältige neurologische und psychopathologische Beobachtungen. Es müssen jedoch auch die Probleme der Entwicklung des Hirnstammes sowie die bezüglichen neuen neurophysiologischen, biochemischen, neu-

ropathologischen und genetischen Fragen in Betracht gezogen werden.

Die Hirnstammerkrankungen des Kindesalters eignen sich vorzüglich zur Beobachtung der Funktion dieses Gebietes. Bei Kindern sieht man Symptome, welche im Erwachsenenalter wegen auf den Hirnstamm einwirkende kortikale Funktionen nicht oder kaum zu ermitteln sind. Außerdem sieht man Offenbarungen und Symptome, die hinsichtlich der Funktion des sich entwickelnden Hirnstammes nur im Säuglings- und Kindesalter charakteristisch sind.

Die Monographie gliedert sich in 22 Kapitel. Von den besprochenen Themen seien nur einige beispielsweise erwähnt: Entwicklungsprobleme des Hirnstammes, Einfluß der Geburt auf den Hirnstamm, Topographie der hinteren Schädelgrube, Hirnstamm und Formatio reticularis aus neurophysiologischer Sicht, apallisches Syndrom im Kindesalter, neurologische Symptomatik und Psychopathologie der Hirnstammtumoren, seltenere raumfordernde Prozesse in der hinteren Schädelgrube mit Hirnstammbeteiligung usw.

Der Wert des vortrefflich ausgestatteten und didaktisch illustrierten Buches wird durch das reiche Schrifttum (1091 Literaturangaben) gefördert.

Es ist erfreulich, daß das Gebiet der Kinderneuropsychiatrie mit einem derartig gründlichen Werk bereichert wurde. Es dürfte aber nicht nur die sich mit Kinderneuropsychiatrie und Neurochirurgie befassenden Spezialisten interessieren, sondern auch für Neurologen, Psychiater und Pädiater von Nutzen sein.

J. Szénásy

W. Plenert und J. Hermann: *Anämien im Kindesalter*. 142 Seiten mit 20 Abbildungen und 19 Tabellen. Georg Thieme Verlag, Leipzig 1977. M 35,—

Diese in der Reihe »Moderne Pädiatrie« veröffentlichte Monographie wendet sich in erster Linie an die in Ambulatorien und Krankenhäuser arbeitenden und in hämatologischen Fragen weniger gewandten Ärzte.

In den einleitenden Kapiteln findet man eine kurze Beschreibung der zur Differentialdiagnostik gebräuchlichen Laboruntersuchungen, mit deren Hilfe sich der praktizierende Arzt die geeignetsten Verfahren zur schnellen Diagnose auswählen kann. Dann werden die Indikationen einer Transfusion, die Eisen-, Vitamin- und Hormontherapie und die Knochenmarktransplantation erörtert. In den weiteren Kapiteln werden die einzelnen Formen der Anämie nach ihrer diagnostischen Erscheinungsart besprochen: z.B. die infolge der gestörten Urzelldifferenzierung auftretenden aplastischen und hypoplastischen Anämien, die Hämoglobinsynthese, die Störungen des Eisenstoffwechsels, die mit Blutverlust oder herabgesetzter Lebensdauer der roten Blutkörperchen einhergehenden Anämien, schließlich der vom pathogenetischen Standpunkt gemischt betrachtete Typ. Bei allen Erkrankungsformen wird auf die Pathogenese, klinische Manifestation und Symptomatik, auf die wichtigeren Abweichungen der Laborwerte und auch auf die Therapie hingewiesen.

Jedem Kapitel schließt sich ein Literaturverzeichnis an, das die bedeutenderen Fachbücher, Monographien zum Thema enthält.

Das leicht verständliche, didaktisch aufgebaute Büchlein faßt alles Wissenswerte über die kindlichen Anämien kurz zusammen und soll dem praktizierenden Arzt als ein nützliches Hilfsmittel empfohlen werden.

G. Kardos

R. Sachsenweger: *Stereo-Sehübungen*. 62 Seiten mit 86 farbigen Abbildungen und 2 Pappbrillen. Georg Thieme Verlag, Leipzig 1977. M 12,—

Der Verfasser dieses für Kinder zusammengestellten Bilderbuches ist der Direktor der Leipziger Augenklinik und eine

Autorität auf dem Gebiet des Stereo-Sehens. Das Büchlein ist für den Augenarzt ein nützliches Hilfsmittel, ähnlich wie die Ishihara-Tafeln. Die Mehrzahl der Bilder dient zur Untersuchung und Übung des räumlichen Sehens, ein Teil eignet sich auch zur Prüfung anderer Funktionen des binokularen Sehens, z. B. Sehschärfe, Heterophorie, simultane Perzeption und Fusion. Die Dissoziation der Bilder des rechten und linken Auges erfolgt mit sich ergänzender blauen und roten Färbung; die Bilder werden erst mit der dem Büchlein beiliegenden blau-roten Pappbrille betrachtet plastisch erscheinen, natürlich ausschließlich bei intaktem beidäugigen Sehen, nicht aber bei Schielfehlern. In dieser einfachen Weise können auch Kinderärzte und Eltern auf das Vorliegen eines Sehfehlers oder Schielens aufmerksam gemacht und die augenärztliche Behandlung frühzeitig eingeleitet werden. Übung des stereoskopischen Sehens und Schulung der Beobachtungsgabe und Konzentrationsfähigkeit der normalsichtigen Kinder sind jedoch die Primäraufgaben des Bilderbuches.

K. Molnár

I. Weigl: *Zum Spracherwerb bei Krippenkindern.* Volk und Gesundheit, Berlin 1977. 84 Seiten mit 19 Abbildungen und 8 Tabellen. M 6,—

Das kleine Buch befaßt sich mit dem vielschichtigen Problem des Spracherwerbs in Kinderkrippen und mit den Möglichkeiten der Erzieher, die Sprachentwicklung der Kinder günstig zu beeinflussen und vor Störungen zu bewahren.

Nach einer kurzen Einleitung mit Erläuterung des Begriffs Psycholinguistik folgen zwei Hauptabschnitte. Im ersten Abschnitt werden die theoretischen Grundlagen, darunter psycholinguistische Aspekte, psychophysische Entwicklungsstadien sowie lernpsychologische Voraussetzungen, detailliert dargestellt. Die gesetzmäßige Abhängigkeit der Sprachentwicklung von der für die jeweilige Altersstufe spezifischen Tätigkeit und von der sprachlichen Kommunikation zwischen Erzieherin und Kind wird hervorgehoben. An Hand anschaulicher Beispiele folgt im zweiten Abschnitt eine eingehende Beschreibung eigener experimenteller Untersuchungen, die sich auf die Gestaltung der Beschäftigungen zur Spracherziehung im zweiten Lebensjahr und auf die sprachliche Kommunikation im Tagesablauf beziehen. Die Ergebnisse von entsprechenden Praxisanalysen, darin konstatierte Mängel und die Möglichkeiten zu deren Überwindung werden übersichtlich dargestellt. Aufgrund ermittelter Unterschiede zwischen Versuchs- und Vergleichsgruppen wird auf die Bedeutung einer möglichst hohen Anzahl von Kommunikationsvorgängen zwischen Erzieherin und Kind sowie auf die Zugehörigkeit der sprachlichen und nichtsprachlichen Reaktionen zum gesamten Kommunikationsgeschehen hingewiesen. Die Förderung der sprachlichen Entwicklung und Aktivität erfolgt im Zusammenhang mit den gegenständlichen Handlungen und dem Niveau der Spieltätigkeit der Kinder. Das Buch wird mit einer zusammenfassenden Darstellung entsprechender Schlußfolgerungen und mit einem umfangreichen Literaturverzeichnis abgeschlossen.

Die Abbildungen und Tabellen sind übersichtlich, klar verständlich und ermöglichen eine gute Orientierung. Die drucktechnische Ausstattung entspricht jedoch nicht dem wertvollen Inhalt des Buches.

I. Puls

N. M. Aksarina: *Die Erziehung der Kinder in der frühen Kindheit.* Verlag Volk und Gesundheit, Berlin 1978. 280 Seiten. M 23,—

Das Buch ist eine etwas verkürzte Übersetzung des Lehrbuches für die Mitarbeiter der Krippen und Säuglingsheime in der Sowjetunion. Die Autorin ist eine

der Bahnbrecher der sowjetischen Kleinkindererziehung und der neuen Ordnung in den Krippen.

Das Buch enthält zehn Hauptkapitel, welche folgende Themen behandeln: I. Wichtigkeit einer entsprechenden Kindererziehung vom ersten Lebensmonat an. II. Allgemeine Aufgaben und Methoden der Kleinkindererziehung. III—IV—V. Entwicklung und Erziehung innerhalb der ersten drei Jahre. VI. Grundprinzipien der Kleinkinder-Pädagogik. VII. Ausbildung der Lebensordnung der Kinder während der ersten Tage in der Institution. VIII. Art der Kontrolle der Entwicklung und des Verhaltens. IX. Charakteristische Zeichen der Erziehung in Krippen, Heimen und in den vereinigten Krippe-Kindergarten Institutionen. X. Arbeit mit den Eltern.

Die Autorin erörtert eingehend die Art und Weise, wie man sich mit den Kindern beschäftigen soll, und betont öfters, daß auch die besten Konzeptionen nur dann für das Kind nützlich sind, wenn ihre Anwendungsart dem Kinde entsprechen.

Außer der Betonung der Wichtigkeit der freundlichen, verständnisvollen Art der Beschäftigung mit dem Kind und der Bildung entsprechender äußeren Umstände, zieht sich durch das ganze Werk die Betonung des didaktischen Lehrens. Zur Ausbildung fast aller Fertigkeiten und Fähigkeiten, die der Säugling während seiner Entwicklung erreicht, findet sie es notwendig diese zu unterrichten, kaum Platz lassend für die Freude der Entdekkung und für selbständige Initiative. Mit dem kann man natürlich nicht einverstanden sein. Die tiefe Humanität und die aufrichtige Kinderliebe, die das Buch durchtränken, mildern die oft detaillierten, das Leben im vorhinein genau bestimmenden, vielfältigen Vorschriften. Die Autorin weist an vielen Stellen des Buches darauf hin, daß man immer Rücksicht nehmen muß auf die individuelle Belastungsfähigkeit und individuelle Eigenart der Kinder. Man darf Verordnungen nur dann durchführen, wenn das Kind bereitwillig gut gelaunt daran teilnimmt, sich leicht an die Verordnung anpaßt.

E. Pikler

Growth and Development. Edited by O. Eiben. Printing House of the Hungarian Academy of Sciences, Budapest 1977. 493 pages, Price S 30.—

This book contains the whole material of an international symposium held at Tihany near Lake Balaton in 1977. The first part of the volume contains data on intrauterine, infantile and childhood development, while the second part analyses physical types and the variations of stature. Among the papers presented, a study by Polish authors will attract special attention; they have made an anthropometric study of 180 children from birth to 7 years of age and of their parents, following a number of their measurements in the beginning monthly and after the second year of life at three months intervals. In agreement with other authors they found that growth and weight development of the offspring was in close correlation with the height and weight of their parents. The closest correlation was observed to exist between maternal height and the height of the children, especially of those of the female sex. Another interesting paper is that of D. F. Roberts who made a study of the appearance of menarche in girls of different social classes living in different geographical areas, in two schools of two towns in England and a school in India. The results showed that the time of menarche depended on social differences rather than geographical ones. On the basis of these and of earlier similar comparisons made in the U. K. the importance of such investigations is emphasized as the time of the first menstruation appear to represent a useful index of the biological condition of a certain population.

All the papers in the book will be interesting for physicians and especially for paediatricians and those engaged in the care of schoolchildren and adolescents.

R. ÁGFALVI

McCLURE BROWNE, J. C., DIXON, G.: *Browne's Antenatal Care.* Churchill Livingstone, London 1978. 450 pages, Price £ 10.—

The first edition of this book appeared in 1935, under the title Antenatal and Postnatal Care; its author was the internationally highly esteemed authority, F. J. Browne who then produced nine editions of the textbook up to 1960. After his death in 1963, the present editors publisheda well-revised edition in 1970 and then the present one. They succeeded in enlarging and reshaping the text in such a way that its original values have not been lost.

The book contains data on maternal and perinatal mortality statistics, the early diagnosis of pregnancy, the practice of pregnant care and a detailed discussion of radiological diagnostics. A somewhat modest part deals with the physiology of the pregnant woman and a somewhat oversize one with cytological diagnostics. There are excellent chapters on multiple birth, bleedings, inherited diseases and malformations as well as on toxaemia, general and special diseases, infections, venereal diseases and also on psychological problems during and after pregnancy. This well-illustrated book is warmly recommended to obstetricians, paediatricians interested in perinatal problems and to every clinician who wishes to obtain adequate information about the modern practice of obstetrics.

L. LAMPÉ

Tactics and Strategy in Cancer Treatment Edited by G. MATHÉ. XV + 219 pages with 75 figures and 92 tables. Springer Verlag, Berlin—Heidelberg—New York 1977. Price DM 68.—

This book discusses some up-to-date therapeutic results of tumours and leukaemias. The first part of the volume deals with general therapeutic and diagnostic principles, while the second part discusses treatment of the individual forms of tumours and leukaemias in adults and children. The authors are mostly well-known experts, their majority from the USA and France.

Mathé in the forword emphasizes that rational therapy and future advances can only be achieved by the closest interdisciplinary collaboration involving specialists of oncology, surgery, radiology, chemotherapy and immunology. Much of the book is devoted to immunotherapy. It is emphasized that this kind of treatment is still in its infancy; there are many experimental data but evaluable clinical experience is scarce. Every specialist who desires to apply immunotherapy must possess adequate knowledge of both experimental and clinical oncological immunology. Namely, as pointed out in several chapters of the book, immunotherapy may sometimes mar the effect of other kinds of treatment. For instance, there are experimental data to show that the results of chemotherapy are poorer than usual in patients under immunosuppression. In connexion with immunology, some chapters deserve special interest. To mention only two, the part of active immunotherapy of acute myeloid leukaemia by means of cells of increased antigenicity achieved by neuraminidase; or that analysing the results of systematic androgen therapy in acute myeloid leukaemia. There are in addition chapters dealing with the treatment of tumours of the breast, bronchi, ovarium, testicles, the stomach and the prostate and those of trophoblast origin. Paediatricians will welcome the paragraphs dealing with acute lymphatic leukaemia, Hodgkin disease, osteosarcoma, rhabdomyosarcoma, neuroblastoma and Wilms tumour. Every chapter ends with a good and up-to-date list of literary references.

D. SCHULER

Essentials of Paediatric Gastroenterology edited by J. T. HARRIES. XII + 367 pages. Churchill Livingstone, Edinburgh—London—New York 1977. Price £ 11.00

This book written by 19 authors and summarizing in a concise manner the field of paediatric gastroenterology, will be useful for paediatricians and even for general practitioners. The work consists of three parts. The first discusses structure and function, their development, and the techniques of investigation. The second deals with the main problems of the gastrointestinal tract. This is an outstanding part of the work and especially so are the chapters on the postresection state, the functional changes caused by malnutrition and that on the symptoms related to psychological disturbances. The chapters on small intestinal enteropathies, infective diarrhoeas and the surgical emergencies and conditions also deserve mentioning. The third part is devoted to the diseases of the liver and the pancreas; it discusses the inborn errors of hepatic metabolism, persistent jaundice, infections and tumours of the liver and its chronic diseases. There are no chapters on immunological problems and the role of gastrointestinal hormones; these are mentioned together with the special diseases. Every chapter ends with a brief list of well-chosen up-to-date references.

The greatest merit of the book is its clear impact and precise style. Its only shortcoming is that although the conditions associated with malabsorption are duly enumerated, no attempt is being made at their classification.

I. KÓSNAI

Das Atemnotsyndrom der Neugeborenen Herausgegeben von C. MIETENS. 126 Seiten mit 71 Abbildungen und 33 Tabellen. G. Thieme Verlag, Stuttgart 1977. DM 34,—

Das Buch, der 5. Band der Schriftenreihe Intensivmedizin — Notfallmedizin — Anästhesiologie, enthält die Vorträge und Diskussionen des in Bochum im November 1975 abgehaltenen Symposiums, welches sich mit sozusagen sämtliche Aspekten der Atemstörungen des Neugeborenen befaßte.

Der erste Vortrag (TIZARD) behandelt die Prognose des Atemnotsyndroms, dessen Mortalität und psychomotorische Entwicklung, wobei das Krankheitsbild definiert und die Frage der Nachuntersuchungen erörtert werden. Sodann folgt ein Beitrag (WIERICH-HARTUNG) in bezug der Pathologie des Syndroms. Außer der klassischen Beschreibung wird auch die funktionelle Bedeutung der pathologischen Veränderungen angeführt. Die Ätiologie und Pathologie des Syndroms sind das Thema des folgenden Vortrages (WENNER); hier wird das komplexe Wesen des Pathomechanismus beschrieben und die pathologische Funktion der kollabierenden Alveolen mit Hilfe einer mathematischen Formel erläutert. Ein Beitrag über die Biochemie und präpartale Diagnostik der Lungenreifung (KUSS) bespricht die Funktion der Pneumozyten Typ II, die Biochemie und Biosynthese der oberflächenaktiven Substanzen, ferner die Möglichkeiten der intrauterinen Diagnostik und pränatalen Prophylaxe. Für den praktizierenden Neonatologen dürfte der Vortrag über die Röntgenbefunde beim Atemnotsyndrom (LASSRICH) am nützlichsten sein; mit gut dokumentiertem Bildmaterial erhält man ein genaues Bild über die einzelnen Phasen des RDS, die Röntgenzeichen der zur Differentialdiagnose in Frage kommenden Erkrankungen und schließlich über die radiologischen Hilfsmittel zur Erkennung der Komplikationen und die Technik der Therapie. Der Vortrag Hirnblutungen beim Atemnotsyndrom (KÜNZER u. Mitarbeiter) befaßt sich mit dem Problemenkomplex RDS — Puffertherapie — Hirnblutung anhand einer statistischen Analyse. Hier bietet sich das lebhafteste und ausführlichste Diskussionsmaterial. Der Vortrag über die Infusionstherapie bei dem Atemnotsyndrom (RIEGEL) bietet einen genauen Wegweiser zur

optimalen täglichen Flüssigkeitszufuhr in qualitativer und quantitativer Hinsicht. Die weiteren Beiträge: LOEWENICH: Indikationen, Durchführung und Komplikationen der künstlichen Beatmung; LEMBURG: Methoden und Überwachung der Sauerstoffapplikation; BRAND-MIETENS Differenzierte Anwendung von Atemhilfen und künstlicher Beatmung, besprechen eingehend die Indikationen, Methoden, Technik, Kontrolle der modernen neonatalen Atemtherapie. Von den Komplikationen befaßt sich ein Vortrag mit jenen im Bereich der Ophthalmologie (KÖRNER), anschließend finden wir ein Referat über die chirurgische Ligatur des offenen Ductus Botalli bei Frühgeborenen ohne vorhergehende Herzkatheteruntersuchung (KEIDEL u. Mitarbeiter), das am Symposium zwar nicht vorgetragen, wegen seiner hochaktuellen Problematik doch in das Material des Bandes aufgenommen wurde.

D. BÉKEFI

J. WENDLER, W. SEIDNER: *Lehrbuch der Phoniatrie* 348 Seiten mit 136 teils farbigen Abbildungen und 18 Tabellen. G. Thieme Verlag, Leipzig 1977. Preis M 56,-

Die Phoniatrie ist ein eigenes medizinisches Fachgebiet, das sich mit der Physiologie und Pathologie der Stimmbildung und Sprache befaßt. Als Aufgabe setzt sie sich die Prophylaxe, Diagnostik und Metaphylaxe der Tonbildungs- und Sprachstörungen, wobei auch psychologische und soziologische Gesichtspunkte in Betracht gezogen werden.

Einleitend werden die Geschichte und interdisziplinäre Lage der Phoniatrie überblickt, sodann die Fragen der Grenzgebiete- und Nachbargebiete (Physik, Sprachphysiologie, Fonetik, klinische Psychologie, Genetik) besprochen. Hiernach folgt die Erläuterung der wichtigsten Untersuchungsverfahren: Atmung, Larynx, die zur Beurteilung der Charakteristika der menschlichen Stimme dienenden instrumentalen und zur objektiven Stimmdiagnostik gebräuchlichen modernen Methoden und Teste. Ferner werden die Entwicklung der menschlichen Stimme, die Probleme der Stimmbildung der sich mit Sprache und Gesang Beschäftigenden erörtert.

Der zweite Teil des Buches befaßt sich mit den wichtigsten phoniatrischen Krankheitsbildern, den Störungen der Stimmbildung und Sprache und deren entsprechenden diagnostischen und therapeutischen Möglichkeiten. Ein Kapitel ist den Fragen der einzelnen Etappen der Sprachentwicklung und der Rehabilitation von Totalexstirpierten gewidmet.

Das Werk weist stets auf das interdisziplinäre Wesen der Forschungs- und Heilarbeit hin. Das Thema wird vielseitig, die Kenntnisse der Grenzgebiete gründlich, die phoniatrischen Definitionen exakt, die Krankheitsbilder und Untersuchungsverfahren klar und überblicklich, die Literatur kritisch behandelt.

Das Buch dürfte nicht nur den Spezialisten, sondern auch Heilpädagogen, Fonetiker, Otolaryngologen und Pädiater empfohlen werden.

J. HIRSCHBERG

Surgical Pediatric Urology edited by H. B. ECKSTEIN, R. HOHENFELLNER and D. I. WILLIAMS. XI + 533 pages with 1120 illustrations. George Thieme Publishers, Stuttgart 1977. Price DM 238.—

In the last twenty years, paediatric urology has made a great progress, especially in its diagnostic and surgical possibilities. This monograph edited by three internationally well-known authorities and written by 35 experts is an outstanding survey of the subject. For each condition, the characteristic pathological and clinical features, the diagnostics, the indications for surgery and the operative techniques are described clearly, and instead of complicated descriptions, the technical details are demonstrated on excellent figures and drawings.

The book begins with a concise chapter on paediatric nephrology, then care, diagnostics, and treatment are discussed. Beside intravenous urography, the angiographic, isotope and ultrasonic tests and their value are described. A special chapter is devoted to the endoscopic techniques. Subsequently, the operations on the adrenals, the kidneys, the uropoetic system and the testicles are described, even several of them if there is no surgical solution surpassing the others. These chapters are followed by one discussing the treatment of urologic injuries and finally a chapter on the principles of kidney transplantation.

The monograph is especially recommended for surgeons and urologists having some experience in the field but also for those who wish to specialize or are interested in urological surgery.

J. Tóth

Printed in Hungary

A kiadásért felel az Akadémiai Kiadó igazgatója Műszaki szerkesztő: Zacsik Annamária

A kézirat nyomdába érkezett: 1978. IX. 27. – Terjedelem 9,10 (A/5) ív, 54 ábra (1 színes)

79. 6363 Akadémiai Nyomda, Budapest – Felelős vezető: Bernát György

ACTA PAEDIATRICA

ТОМ XIX—ВЫП 4

РЕЗЮМЕ

ДЕЯТЕЛЬНОСТЬ МОНИТОРА ВРОЖДЕННЫХ АНОМАЛИЙ В ВЕНГРИИ

А. ЦЕЙЗЕЛ

Венгерский Монитор Врожденных Аномалий действует с 1 января 1973 г. Его целью является скорейшее выявление возможных повышений частот во времени и по районам индикаторных врожденных аномалий. Венгерский Монитор является частью организованного ВОЗом сотрудничества, распространяющегося в настоящее время на 11 стран. До настоящего времени понадобилось установить состояние опасности в 1975 году при повышении редукционных аномалий конечностей. Это повышение лишь в малой мере объяснялось техническими искажениями регистрации. При повышении частоты случаев необходимо организовать ретроспективные эпидемиологические исследования, проводимые на основе личных распросов, по отношению к согласованным с ними контрольном случаям. В настоящее время мониторированe врожденных аномалий может считаться одним из наиважнейших средств для раннего выявления тератогенных и мутагенных вредных воздействий.

СВЯЗЬ ПОЧЕЧНОГО ПОРОГА РЕАБСОРБЦИИ БИКАРБОНАТА С ВЫДЕЛЕНИЕМ НАТРИЯ У НЕДОНОШЕННЫХ ДЕТЕЙ

Э. ШУЙОК и Ф. ВАРГА

Авторы определяли количество выделяемого с мочой натрия и порог реабсорбции бикарбоната почками у 9 здоровых недоношенных мальчиков. Определения производились на 7-й день жизни, затем раз в неделю в продолжение шести недель, всегда после нагрузки хлористым аммонием. Была установлена отрицательная зависимость между порогом реабсорбции бикарбоната и количеством выделенного натрия. Авторы предполагают, что за низкий порог реабсорбции бикарбоната у недоношенныох детей является ответственной слабая способность к выделению натрия.

МЕТАБОЛИЧЕСКИЙ АЦИДОЗ И ВЫДЕЛЕНИЕ НАТРИЯ У НОВОРОЖДЕННЫХ

Э. ШУЙОК, Ф. ВАРГА и Л. КЕРЕКЕШ

На протяжении 6 недель авторы определяли отношения между весом при рождении, возрастом и выделением натрия, имеющиеся в состоянии ацидоза, а) у 43 новорожденных с весом при рождении от 1000 до 4300 г, с гестационным возрастом от 28 до 41 недели, а также б) у 13 новорожденных, у которых вес при рождении колебался между 100 и 1970 г., а гестационный возраст — от 29 до 35 недель. Новорожденные, родившиеся с большим весом, и более старшие по возрасту выделяли гораздо больше натрия, чем новорожденные с низким весом и младшие по возрасту. Из этого можно заключить, что, при определении потребности новорожденных детей в натрии, следует принимать во внимание степень ацидоза.

ОЦЕНКА ДАННЫХ ЭЭГ ПРИ ПОВЕДЕНЧЕСКИХ НАРУШЕНИЯХ ДЕТСКОГО ВОЗРАСТА

О. КОХЛАЙБ и Л. СЕГЁ

Авторы обследовали 732 ребенка, страдающих нарушениями поведения, для определения частоты встречаемости общих изменений и гиперсинхронной активности. Они установили, что общие изменения поведения средней и тяжелой степени одновременно наблюдаются в 11,5% случаев.

Статистически достоверной разницы между отдельными типами поведения отмечено не было. Замедление появлялось, главным образом, в 7—8-летнем возрасте — т. е. тогда же, когда и у здоровых детей.

Таким образом, общие изменения в поведенческих нарушениях встречались не чаще, чем у здоровых детей. Гиперсинхронная активность («судорожный потенциал») наблюдался у 5,2% детей, страдающих нарушениями поведения: здесь тоже

не было статистически достоверной разницы между отдельными группами поведенческих нарушений. Принимая во внимание, что у 4—6% здоровых детей отмечаются сигналы гиперхронизации, авторы считают, что это отклонение у детей с нарушениями поведения тоже встречается не чаще, чем у здоровых.

Авторы подчеркивают, что никогда нельзя диагностировать эпилепсию только на основании одних данных ЭЭГ, так как здесь решающая роль принадлежит данным клинического обследования. Диагнозы «латентной» или «скрытой» эпилепсий следует совершенно игнорировать. В таком случае, —то есть в случае отрицательных результатов клинического обследования и вместе с тем при наличии определенных отклонений на электроэнцефалограмме, — противосудорожную терапию применять нельзя.

ВЛИЯНИЕ ВКУСА И ТЕМПЕРАТУРЫ НА СОСАНИЕ У НОВОРОЖДЕННЫХ ДЕТЕЙ

З. МАКОИ, П. М. ДУНН и Д. ШПЕЙДЕЛЬ

Авторы изучали поведение при сосании у 10 здоровых новорожденных детей при кормлении их пищей разного типа (питательные смеси, чужое сцеженное материнское молоко) и температуры (тела, комнатной). Исследования проводились на 4,5 и 6 дни после рождения и рассматривались как трехратное повторение той же самой серии опытов.

На основе 120 кривых, записанных во время сосания, определялись: общее времья каждого кормления, продолжительностеь перерывов, их количество, полное давлению и число сосательных движений в минуту. Поведение новорожденных, связанное с сосанием, на изменилось прикормлении их различной пищей, но в одном случае из трижды повторенной серии опытов наблюдалось изменение в связи с изменением температуры.

ИЗУЧЕНИЕ РАЗВИТИЯ ИММУНОЛОГИЧЕСКИХ ФУНКЦИЙ И СУБПОПУЛЯЦИЙ ЛИМФОЦИТОВ У ЗРЕЛЫХ И НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ

Л. КАРМАЖИН, А. МАКАИ и Г. БАЛЛА

У здоровых, преждевременно рожденных новорожденных детей (на 22—38 гестационной неделе) авторы определяли в периферической крови объемом 2 мл, на предметном стекле, процентное распределение и динамику Т-, В- и О-лимфоцитарных популяций, в зависимости от возраста и веса новорожденных. В качестве контроля пользовались пробами крови, взятой у детей в возрасте от 1 года до 14 лет. Свои дальнейшие исследования авторы предполагают выполнять, основываясь на полученных в этих экспериментах данных.

ЭЗОФАГО-ГАСТРО-БУЛЬБОСКОПИЯ В ДЕТСКОМ ВОЗРАСТЕ

ДЬ. РУМИ, И. ШОЛТ и П. КАЙТАР

Авторы произвели эзофаго-гастро-бульбоскопию у 5 детей. Исследование выполнялось под общим наркозом, фиброскопом типа *Olympus GIF-D*$_2$. Причины, по которым была произведена эзофаго-гастробульбоскопия: в трех случаях из-за гематемеза и/или мелены, в одном случае по поводу оккультного кровотечения, у одного трехлетнего ребенка с целью извлечения проглоченного обручального кольца. В двух случаях с повторным кровотечением с помощью ранее произведенной эксплоративной лапаротомии не удалось установить прициму кровотечения Результатом фиброскопического исследования был этимологический диагноз: в одном случае обнаружили варикозные узлы пищевода, во втором случае — кровоточащую язву двенадцатиперстной кишки.

Авторы считают, что если другие исследовательские методики не дают возможность поставить диагноз, то и у детей надо производить эзофаго-гастро-бульбоскопию, — особенно в случае желудочного кровотечения, перед решением об операции.

10-ЛЕТНИЕ РЕЗУЛЬТАТЫ ДОБАВЛЕНИЯ ФТОРА В В ПОВАРЕННУЮ СОЛЬ В ВЕНГРИИ

К. ТОТ

Общеизвестно, что длительное употребление поваренной соли с добавлением фтора подавляет развитие кариеса не только постоянных зубов, но и молочных. Добавление фтора в соль оказалось таким же эффективным, как и питье воды, содержащей оптимальные количества фтора. Однако установление оптимального содержания фтора в соли вызывает проблему; это возможно только на основании изучения традиций питания населения. Количество введенного с поваренной солью фтора можно высчитать только на основании ложно-данного количества соли, 60%

которой, как известно, не утилизируется. На этом основании можно судить о количестве введенного фтора на основе проб мочи. Чем больше потребляют заранее приготовленной пищи, тем труднее решить, в какую соль следует добавлять фтор,а также определить их дневное количество.

НОВЫЙ МЕТОД ФИЗИЧЕСКОЙ НАГРУЗКИ ДЛЯ БОЛЬНЫХ С АСТМОЙ ПРЫГАНИЕ ЧЕРЕЗ ВЕРЕВОЧКУ

Я. КЕЛЕМЕН, Г. ПОДЕР и И. РОМХАНИ

Авторы производили сравнительные эксперименты с нагрузкой на 8 детях обоего пола, страдающих астмой и реагирующих на нагрузку спазмом бронхов. Средний возраст детей был 8,5 лет. В качестве нового вида нагрузки применялось прытанье через веревочку. Спазм бронхов, возникавший после прыганья через веревочку, был более сильным и продолжительным, чем спазм у этих же детей после выполнения эргометрического упражнения с велосипедом.

ЛЕЧЕНИЕ ГРЫЖ ПУПОЧНОГО КАНАТИКА И ПАРАУМБИЛИКАЛЬНЫХ ДЕФЕКТОВ БРЮШНОЙ СТЕНКИ

К. ЯННЕК и В. ЭКЕСПАРРЕ

Грыжа пупочного канатика и параумбиликальный дефект брюшной стенки являются результатом ранне-эмбриональных нарушений развития разного происхождения. Однако с терапевтической точки зрения их следует считать едиными. На основании собственных наблюдений кажущееся самым многообещающим лечение мы демонстрируем на материале 72 грудных детей, родившихся с дефектом передней брюшной стенки. Из них у 49 новорожденных была грыжа пуповины, а у 29 параумбикальный дефект брюшной стенки. Для замещения больших дефектов мы рекомендуем свободно трансплантируемый лоскут кориума. Этот метод впервые был применен нами в 1974 году. Хорошие результаты этого лечения демонстрируются на 12 детях.

ЗНАЧЕНИЕ ОБНАРУЖИВАЕМЫХ С ПОМОЩЬЮ ЭНТЕРОБАКТЕРИАЛЬНОГО ОБЩЕГО АНТИГЕНА (ЕСА) АНТИТЕЛ В ПИЕЛОНЕФРИТЕ ДЕТСКОГО ВОЗРАСТА

К. ПУМП и А. ВЕРТЕНИ

Методом непрямой гемагглютинации с помощью сенсибилизированных ЕСА эритроцитов барана нам удалось выявить наличие антител у детей, страдающих пиелонефритом. Эта реакция была отрицательной у 10 здоровых детей. При остром пиелонефрите реакция во всех случаях была положительной. При хроническом пиелонефрите значения титра показали большой разброс и нередко оценивались как отрицательные. В условиях применяемого метода разведение 1 : 64 является диагностическим пограничным значением титра.

ПОПЕРЕЧНЫЙ ДИАМЕТР ГРУДНОЙ КЛЕТКИ И СЕРДЦА ПОСЛЕ РОДОВОЙ АСФИКСИИ У НОВОРОЖДЕННЫХ

Я. ВЕЙЗЕНБАХ, К. ШУЛЬЦ и М. ШМЕЛЬЦЕР

Авторы определили поперечный диаметр грудной клетки и сердца у 745 новорожденных детей, находившихся после рождения в состоянии асфиксии. Оба диаметра показали хорошую корреляцию с весом новорожденного. Причиной больших индивидуальных отклонений была отчасти разная степень тяжести родовой асфиксии и различная компенсаторная реакция новорожденных. «Wet lung» и диаметр грудной клетки, превышающий 90 перцентил, указывал на хороший прогноз, в то время как снижение его ниже 10 давало мало надежды на выживание ребенка. Увеличение размеров сердца обычно проходило после первых 12 часов, хотя в некоторых случаев отмечалось еще спустя 5 дней, в зависимости от тяжести родовой асфиксии.

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10. V. 1979. HU ISSN 0001—6527 Index: 26.021