

ACTA PAEDIATRICA

ACADEMIAE SCIENTIARUM HUNGARICAE

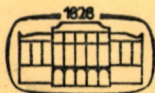
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EDITOR

P. V. VÉGHÉLYI

COMMISSIO REDACTIONIS

D. BODA, P. GEGESI-KISS (Praeses), F. GERLÓCZY, E. KERPEL-FRONIUS,
B. KÖVÉR, L. KULIN, J. MESTYÁN, D. SCHULER, F. VARGA



AKADÉMIAI KIADÓ, BUDAPEST

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A MAGYAR TUDOMÁNYOS AKADÉMIA
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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.

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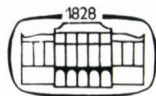
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VOLUME XVIII

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Blood group mythology: present status

ALEXANDER S. WIENER

Serological Laboratory of the Office of Chief Medical Examiner of New York City, and the Department of Forensic Medicine of the New York University College of Medicine, New York

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There are still many myths, incorrect beliefs, in medicine; some pertaining to the field of blood grouping are discussed. Certain fallacious statements are dealt with in detail such as the dependence on the A-B-O blood group of the shape of the retracted clot; the patients with Dupuytren contracture all being type Rh₁Rh₂; the assumption of an association with the blood groups of a number of diseases and even of temperament; the belief in the existence of anti-M-lectin and of little d and thus of anti-d sera; and also of the alleged LW (Landsteiner–Wiener) factor. Finally, Race and Sanger's system of symbols is condemned and the advantages of the author's own nomenclature are pointed out.

The modern world is composed of a society characterized on the one hand by outstanding advances in science and technology, and on the other hand by anachronistic paradoxes, and by superstitious beliefs and mythology. For example, contrasting with the advances in the science of astronomy made possible by advances in radioastronomy, electronics and computer sciences, there has been an increase in the popularity of astrology, such that even in our modern sophisticated society millions of Americans are devotees or believers, as evidenced by the column on the subject which appears in 1300 daily newspapers and which one can consult for one's daily horoscope. The situation has become so serious that a group of 168 scientists, including 18 Nobel prize winners, has recently issued a statement pointing out that it is simply a mistake to imagine that

forces exerted by stars and planets at the moment of birth can in any way shape our future. Despite this, it has been estimated that in the United States today there are 10 000 professional astrologists who make a living by writing, teaching and acting as consultants about the stars, and astrology courses are even being offered in some colleges.

This paradoxical situation is by no means unique for astronomy and astrology, but characteristic of almost all aspects of modern society and science, including blood grouping. In fact, I was confronted with the problem of blood group mythology as long ago as 1928, when while still a medical student I first entered the field of blood grouping. In my very first published paper, when mentioning the discovery of the A-B-O blood groups, I naively cited a report from the current Japanese literature claim-

ing that such tests were in vogue as early as the 12th and 13th century in China and Japan. After my article appeared, at Dr. Landsteiner's suggestion, I consulted a source book from the Surgeon General's library in Washington, D.C., which explained the basis for this fantastic claim. In the book, the following test of blood relationship was described. The fingers of the two individuals in question were punctured, and the blood allowed to fall into a basin of water; if the bloods flowed together the two persons were indeed related, while if the drops flowed apart they were not. This then was how blood grouping was done in ancient China and Japan! It is of interest to note that the same book asserted that if, at the autopsy of a woman, a section of the pubic bone proved to be pure white, the woman in question was a virgin; if a single blue spot was found she was a virtuous woman, but if numerous blue spots were present the woman was a prostitute. No sooner had I completed my study of the source book from the Surgeon General's Office, when I prepared a note of correction which was published in the same journal as my original article. There has been no further mention in any publication of blood grouping tests in ancient Japan or China, so that apparently this was one blood grouping myth that was quickly laid to rest once and for all time.

This early experience alerted me to the danger of relying on secondary sources for information, without consulting the original sources. Also,

during my studies on the science of blood grouping, I have over the years kept a weather eye open for other examples of blood grouping mythology. I regret to report that such examples are numerous and easy to find, and I have therefore made this problem the subject of a number of my publications. Since the matter can be of considerable importance, and has indeed been responsible for serious misconceptions and errors, I decided that the present status of blood group mythology would be a worth while and timely subject for discussion.

To begin with, every journal, even the most distinguished medical and scientific journal, from time to time publishes material that is fallacious, or even absurd. This occurs even in journals which subject every article submitted for publication to the scrutiny of referees, supposedly highly qualified in the field in question. Unfortunately, referees are human and fallible, so that on the one hand they sometimes approve articles containing patent nonsense, while on the other hand they may reject sound reports which contain findings they find difficult to accept because of the novelty of the findings or because they conflict with the referees' own preconceived pet ideas. There is no difficulty in finding even in the most distinguished journals, articles reporting observations that are false or even outrageous. As an example may be cited the article on "Group Specific Appearance of Plasma Clots" — published in *Blood*, in 1950. Accord-

ing to the two authors of that report, recalcified plasma allowed to clot in a bottle retracts and the shape of the retracted clot was claimed by the authors to be group specific. In fact, those authors claimed that the shape of the clot depended on the A-B-O blood group and subgroup of A, and they tabulated 955 plasma clot tests all of which they claimed they had correctly grouped for A-B-O in this way and 140 of group A and group AB, all correctly subgrouped, by their plasma clot test. The authors were unable to suggest any reasonable explanation for the phenomenon they had discovered. Of course, the article and the claims it contain are outrageous, and evidently this was recognized by readers of the journal, because to my knowledge the article has never been cited and never even been referred to, except by me in my search for blood group mythology. This, then, is a curious report containing absurd claims that suffered a neonatal death, so that it did not survive long enough to become a permanent part of blood group mythology.

In the same category as the plasma clot article belongs the claim that every one of 28 patients with Dupuytren contracture proved to be type Rh₁Rh₂. Again this fantastic claim has evidently been ignored by readers of the scientific literature, except by me in my culling of the literature. The author of the article in question is said to have testified in court on the basis of his report that Dupuytren's contracture is not a compensable occupational disease but genetically de-

termined. On the other hand, Dr. R. T. Simmins, who had Dupuytren's contracture, told me some time before his death that he was not type Rh₁Rh₂. At any rate, the report has not been cited to my knowledge, so that this is another fantastic claim that died before it could be permanently incorporated into the body of blood group mythology.

In a different category are the reports claiming associations between the A-B-O blood groups and particular diseases. This aspect of blood group mythology has a long, venerable history, dating back more than 50 years, and it remains viable and healthy even at the present time. Shortly after I first met Dr. Landsteiner, I undertook the preparation of a monograph on blood groups. He encouraged me with this enterprise by reading and correcting the manuscript materials and proofs with me, and I learned a good deal from Dr. Landsteiner as a result. At the time, knowledge of blood grouping was limited mainly to the four A-B-O blood groups, subgroups of A and AB the three M-N types and the agglutinin P. Yet this proved to be a complex undertaking for me and the book finally produced, which was released in 1935, had 18 chapters and 220 pages. One of the chapters dealt with blood groups and disease, at a time when the Rh factor had not yet been discovered, so that the importance of materno-fetal incompatibility, though suspected, had not yet been proved. For attempts to determine associations and disease, in-

investigators used the simplest method possible, they determined the distribution of the four A-B-O groups in series of patients with a particular disease and compared this with the distribution in control series of normal individuals. The diseases for investigation appeared to have been selected without rhyme or reason and included (at the time when the first edition of my book appeared) malaria, syphilis, migraine, dementia precox, epilepsy, feeble-mindedness, general paresis, dental caries, skin diseases, bone and joint tuberculosis, duration of life, etc. Strangely enough no similar attempts were made to study possible associations between diseases and the three M-N types. Though the studies made no sense to me, they were included with reservations in my book (4 pages were devoted to the subject) for the sake of completeness. In the book I pointed out the mutual contradictions among the reports, so that when an association was found by one author this could not be confirmed by others, or this was minimal in degree and readily explained by bias in selection of cases, or to stratification when dealing with a mixed population, or to the fact that the so-called series of controls was not comparable in racial derivation to the series of affected individuals.

Despite these fallacies, investigations on the distribution of the A-B-O blood groups in disease continued, probably because this was an easy kind of "research" for individuals lacking better ideas. However, while great progress was being made regard-

ing other aspects of blood grouping, notably my discovery with Karl Landsteiner of the Rh-Hr blood types, and their role in the pathogenesis of intragroup haemolytic transfusion reactions and of erythroblastosis fetalis, research on blood groups and disease continued without making any real progress. Thus, the discussion of blood groups and disease in the third edition, 1943, of my book on Blood Groups and Transfusion showed virtually no change in the presentation of the subject, except for a table showing that no associations exist between the three M-N types and a variety of diseases. The vacuum that resulted when no further editions of my own book were issued was filled by Race and Sanger's *Blood Groups and Man*. The first two editions of that book made no reference to the topic blood groups and diseases, but this changed after Aird's reports appeared claiming associations between group A and carcinoma of the stomach, group O and duodenal ulcer, gastric ulcer, cancer of the stomach, pernicious anaemia, diabetes mellitus, cancer of the colon and rectum, cancer of the breast, for all but three of which significant associations were claimed (duodenal ulcer $\chi^2 = 192.06$, cancer of the stomach $\chi^2 = 39.6$, pernicious anaemia $\chi^2 = 16.0$ and diabetes mellitus $\chi^2 = 9.2$). This discussion was expanded to 20 pages in the fourth edition (1962) of the Race-Sanger book, but mysteriously was omitted in the fifth edition (1968). It is again omitted in the new sixth edition (1975).

A much more extensive treatment of the studies on blood groups and diseases can be found in Prokop and Uhlenbruck's *Human Blood and Serum Groups*. In that 891 page volume, as many as 34 large pages are devoted to the subject. While the studies on duodenal ulcer are given special prominence, no reasonable mechanism could be suggested why being group O or a non-secretor should predispose one to such a disease. However, rationale apparently has played little or no role in the studies on blood groups and disease, if one may judge from Buckwalter's claim of an association between blood group A and fracture of femur. (This statement must be qualified; I am blood group A and did sustain a fracture of my femur when I undertook to join my grandchildren in ice-skating. Perhaps I should have paid more attention to Buckwalter's report.) However, a plausible rationale has been suggested for possible associations between A-B-O blood groups and particular infectious diseases. As has been shown, notably by Springer and his collaborators, many microorganism have A-like, B-like, and H-like antigens on their surfaces. In view of the canalization of the immune response — i.e. in general, the body does not readily produce antibodies to its own constituents; for example, a group B individual could be expected to be less capable of defense against bacteria which have B-like antigens. Despite the attractive nature of this idea, unfortunately, not a single proved example of association between blood groups and

infectious diseases has yet been established.

The extremes to which the idea of associations between blood groups and disease has been carried are well exemplified by Leone Bourder's 200 page book on "*Groupes Sanguine et Temperaments*". On page 19 of this book, in a table on the relation between blood and temperament, we learn that group A persons are harmonic, group O melodic, group B rhythmic, while group AB persons are H-M-R or complex. The book is also embellished with tables giving the A-B-O blood groups of persons of various professions, namely, creative workers, research investigators, military chiefs, educators, dentists, etc. On a more sophisticated level, associations are worked out for the cephalic index, and even the M-N types and Rh factor come in for discussion. This book, then, is recommended to those who know their A-B-O blood group and wish to know whether they have selected the correct profession for their life-work. Certainly this is more "scientific" than depending on astrology and horoscopes!

Studies on blood groups and diseases appear to have been of particular interest to geneticists, although it is not entirely clear to me how such studies could advance the science of genetics. In fact, R. B. McConnell's "*The Genetics of Gastro-Intestinal Disorders*" (Oxford, 1966) devotes much space and many elaborate tables to that subject. With regard to carcinoma of the stomach, the author remarks (p. 57) "In all, 71 separate

series of carcinoma patients and their controls have been published. In no less than 55 of these series a significant increase in the frequency of group A was found. In 14 series there was little difference from the controls and in only 2 series was there a considerable deficiency of group A". These discrepancies among the reports apparently do not disturb the author of the book who decides there is an association between blood group A and carcinoma of the stomach, thus settling this scientific problem simply by taking a vote. The author fails to explain why, according to the results in the table, for those living in Vienna (patients and controls both 44% group A) one's blood group has no effect at all, while in Cremona the frequency of group A is almost twice as high (84.7%) in the carcinoma patients as in the controls (46.9%). Apparently if one belongs to group A, one can live safely in Vienna, but if one dwells in Cremona, one takes one's life in one's hands.

Interest in studies on blood groups and disease was encouraged by the pronouncement of famous biometricians (Fisher and Ford) that "no gene is neutral in selection". This assertion was made in the face of abundant evidence of the existence of neutral genes, i.e. the multiple alleles of numerous systems of blood and serum groups, eye colour, hair colour, fingerprint patterns, etc. To explain the persistence of such polymorphisms, hybrid vigor, i.e. superiority of of heterozygotes over homozygotes has been invoked. For example, the

prevalence of the semi-lethal sickle cell gene in Africans has been ascribed to the claimed greater resistance to malaria of individuals heterozygous for the gene. In the first edition of their book, Race and Sanger cited the reported excessive proportion (greater than 50%) of type MN children in MN × MN families as a prime example of heterozygous advantage. However, in our own extensive studies on the heredity of the M-N types over several decades, the proportion of type MN children from MN × MN matings did not differ significantly from 50%, so I have pointed out that the excess reported by other workers was probably due to the use of underabsorbed antisera. In a recent publication, Race now accepts my explanation as correct. As for the supposed advantage of heterozygosity, in the case of erythroblastosis fetalis (both in Rh or A-B-O haemolytic disease), the heterozygous baby is at a disadvantage — which is the opposite of what is required by the concept of heterozygous advantage.

The affinity of geneticists for studies on blood groups and disease is evident from the large amount of space that has been devoted to such articles especially in British journals dealing with human heredity, while in December 1964, also the American Journal of Human Genetics found space for an article on "Blood Groups and Personality Traits". This reached its zenith with the appearance in 1972 of Vol. 1/4, Blutgruppen, Humangenetik, Ein kurzes Handbuch (in order to obtain it for my library, I paid \$ 115 for it). More

than half of the book is devoted to the discussion of studies on associations between blood groups and disease. In this very large volume, also, the discussion is again virtually restricted to the four A-B-O blood groups, and the remaining multiplicity of blood groups is ignored. As many as 170 pages are devoted merely to tables, apparently produced on a computer, listing the published findings in detail for disease such as Ca of the stomach, Ca of the pancreas, Ca of the oesophagus, Ca of the cervix, Ca of the body of uterus, Ca of the ovary, mammary carcinoma, choriocarcinoma, Ca of the larynx, Ca of the bronchi, Ca of the urinary bladder, chronic leukaemia, myoma of the uterus, acoustic neuroma, astrocytoma, adenoma of the hypophysis, brain tumours, ependymoma, duodenal ulcer, ulcer of the stomach, ulcerative colitis, pernicious anaemia, diabetes mellitus, coronary artery disease, cholecystitis, eosinophilia, atrophic rhinitis, hepatitis and hepatoma, thromboembolic diseases, toxæmia of pregnancy, chronic eczema, and many other diseases. I leave it to my readers to decide whether the \$ 115 I paid for this book was a worthwhile investment.

While most of the reports of associations between A-B-O blood groups and disease apparently are no longer being taken seriously, the claims that group O persons, especially, A-B-H non-secretors, are more susceptible to duodenal ulcer, while group A persons are more likely to get carcinoma of the stomach, continue to be cited, so that those two assertions appear to

be firmly fixed in the literature of blood group mythology. Nevertheless, for the sake of fairness, it must be pointed out that studies on associations between blood groups and disease are not totally without rationale. To be sure, in general, the genes responsible for the blood group differences appear mainly to be neutral genes. Thus, just as it is immaterial whether one's iris is grey or brown in colour, so it similarly does not appear to matter whether one is group A or group B. However, if the iris is devoid of all pigment, as in albino persons, a genetically determined type, serious damage to one's vision can result from the absence of protective pigment. Similarly, in Rh null individuals the absence of Rh-Hr antigens from the red cell envelope can result in haemolytic anaemia.

A reverse situation exists in the case of the Duffy types. In this case, according to a recent report, the Duffy agglutinogens (Fy^a or Fy^b) act as a receptor for malarial parasites, enabling the microorganisms to invade the red cells, while red cells of type Fy(a-b-) are not readily parasitized. Thus, the type Fy(a-b-), which is absent or rare in whites, is prevalent among blacks in Africa presumably because of the selective advantage of this blood type for resistance against malaria. Another example is provided by the receptors on the red cells to which myxoviruses such as influenza viruses become attached. These receptors appear to be closely associated with, if not identical with, the M-N agglutinogens, as has been shown by

Springer, since enzymes which destroy the receptors for myxoviruses simultaneously destroy the agglutinogens M and N on the red cell surface.

Another important example of the significance of red cell agglutinogens has been found in sheep whose red cells can be divided into two types according to their potassium content, namely, HK (high potassium) and LK (low potassium). The two potassium types are dependent on which of two agglutinogens, transmitted by corresponding allelic genes, is present on the red cell envelope. While a parallel situation apparently does not exist for man, a close correlation has been found in man between A-B-O group and secretor type and the presence in the plasma of alkaline phosphatase isozymes.

Thus, studies on blood groups in disease are in part rational scientifically and in part mythology, so that they can be classified as a kind of "fringe" science comparable to chiropractic, parapsychology (ESP), megavitamin therapy, faddist diets with so-called "organic" foods, reducing diets in which "calories don't count", sightings of U.F.O. (unidentified flying objects) hypnotism, and now acupuncture. With regard to U. F. O., when Einstein was asked his opinion, he said, "No doubt these people are seeing *something*, exactly what I do not know, and I'm not curious to find out." The modern enthusiasm for acupuncture constitutes a step backward instead of forward for medical science. It appears to have been forgotten that at one time, before surgical

anaesthesia had been discovered and perfected, many surgeons made use of the consultative services of hypnotists. In particular, Dr. Mesmer, who was frowned on by other members of the medical profession because they could not duplicate his results, made a good livelihood in this way, since he did succeed in rendering some patients insensible to surgical pain. However, when true anaesthesia was introduced, the less dependable hypnosis was abandoned, so that acupuncture, which appears to be successful only when the operator and the subject are both absolutely convinced it will work, represents a return to the use of mesmerism in a different guise. The precise mapping of acupuncture points appears to be merely mumbo jumbo, since objective study has proved that whether or not acupuncture succeeds is quite independent of the exact points of insertion of the needles.

Another aspect of blood grouping which is plagued by mythology is forensic serology. Once blood has dried, it is difficult or impossible to test it reliably for blood groups other than the four A-B-O blood groups, and not including the subgroups of A. I have been forced to this conclusion by my experience with tests on thousands of dried stains of blood and secretions, from homicide and rape cases, in my capacity as City Serologist in the Office of the Chief Medical Examiner of New York City, since 1938. The reason for this should be apparent — since the red cells are destroyed their agglutinin content

must be determined by indirect absorption or neutralization methods instead of simple, direct agglutination tests, for which the antisera used must be highly diluted (titre only 4 to 6 units, as against 50 to 100 units for ordinary blood grouping), so that the margin of error is very narrow. Moreover, due to incompleteness of absorption when stains are dilute or denatured, all grades of reactions can be encountered instead of the sharp difference between positive and negative reactions characteristic of direct blood grouping to which blood bank technicians are accustomed. Limitations of material, so that tests cannot be repeated and contamination with sweat and bacteria on dirty clothing create additional problems, so that unless adequate control stains of known groups, testing of "unstained" substrate are included, and reading are taken blind, errors are bound to occur. Tests for agglutinogens should be supplemented and complemented by tests for isoagglutinins, but because of limitations of materials this is not always possible. For stains on non-absorbent surfaces like knives and glasses, the most sensitive and rewarding method is Lattes' coverslip method for isoagglutinins in blood crusts, while tests for isoagglutinins on extracts of stains on cloth give the most sensitive results by my acacia method. Even so, the majority of dried blood stains give ambiguous reactions, so that a reliable definitive A-B-O grouping result is possible for only a minority of dried blood stains submitted for examination.

This situation is of course far from ideal, and many newcomers to the field have attempted to introduce new methods of testing that they claim can always determine the A-B-O blood group of dried blood stains. Among these, the most widely used are the mixed agglutination method and the absorption-elution method. While both of these methods appear to be sound in theory, and both are valuable research tools, they do not lend themselves to the blind techniques and often give false results. The results in practice are erratic, and while some sort of reaction is obtained in every test, more often than not this result is wrong or misleading. Obviously, therefore, the mixed agglutination and absorption-elution methods are not sufficiently reliable for use by forensic serologists. Unfortunately, the methods are nevertheless being widely used, with disastrous results as in the following case which occurred in Washington, D. C.

A young woman was found in her apartment, suspended from a curtain rod, and an apparent suicide. However, investigation by the F. B. I. and by the medical examiner showed no evidence of the strangulation by rope, but with finger marks instead, and sperm in the vagina indicating rape. Finger prints found in the apartment proved to be those of the janitor, who had a bad criminal record of previous rapes and murder, so the janitor was arrested. The defense attorney, a public defender, consulted with a forensic serologist who claimed that a stain of semen on a towel found at the scene

of the crime came from a group AB, or group A or group B individuals, based on tests carried out by the absorption-elution method. This finding, if correct, would tend to exonerate the prisoner because he belonged to group O. However, when I was consulted by the District Attorney, I found not only that the stain indeed contained semen but also strongly inhibited anti-H lectin, but not anti-A and anti-B sera, so that it clearly had to come from a group O man. The defense's serology expert testified to her false findings, but her testimony was overcome by my own results, and the janitor was convicted. However, later the other "expert" had saliva of the prisoner mailed to her in her laboratory in Texas and reported the man to be a non-secretor. It turned out that the so-called expert was so ignorant of the elements of forensic serology that she had failed to caution the shipper of the saliva to boil it immediately after collection to destroy blood group enzymes and bacteria. My own test on a properly collected and shipped boiled saliva sample proved that the prisoner to be a group O secretor, as expected, and the criminal is now in prison paying the penalty for the crime he committed.

Despite this and similar blunders, the absorption-elution method continues to be used. Apparently it is attractive because it always *seems* to give a result, though the result is wrong more often than not. The so-called expert for the defense in the case above has been teaching the absorption-elution test and has even been included

on the program of this AABB meeting, proving that the myth of the absorption-elution test still survives. In fact, in a recent issue of a Japanese Journal of Forensic Medicine, an investigator reported his application of the absorption-elution method for determining the blood group of very small pieces of hair, nails, teeth and cancellous bone. As in the report on plasma clot blood grouping already described, this worker claims to have grouped correctly hundreds of fragments of hair, nail, etc. — without, however, any mention of the use of the blind test. — Thus, the myth of the absorption-elution test for forensic serology appears to be a hardy one, unless my presentation here is more effective than I expect it will be, judging from the reception given to my previous articles on blood group mythology.

As another example of the perseverance of blood grouping myths I mention the claimed anti-M lectin from *Iberis amara* seeds. Since lectins of anti-N specificity have actually been found, it seemed plausible that anti-M lectins could also exist. However, when the discoverer of anti-M lectin sent me first extracts of the seeds, and then later the seeds themselves, I was unable to detect any evidence of any anti-M activity. My experience has been shared by other workers, but despite this the myth of anti-M lectin survives and can be found cited even in books published in 1975.

Here we cite also the claim by workers in Bulgaria that by injecting over the period of several years

Rh-positive red cells into a plant, *Begonia punctata* they had succeeded in inducing the production by the plant of anti-Rh (titre 16 units) that could be used for typing human blood. This report was excitedly quoted in the literature until Jenkins et al. tested extracts of the injected plant and found them to contain human serum, which evidently was the source of the anti-Rh antibodies in the plant extracts.

Another myth with more serious repercussion is that of little d. Even at the present time that hardy myth survives. On forms released by the U. S. Department of Immigration for reporting the results of blood grouping tests, the serologist is required to place check marks in one of a series of four small boxes marked O, A, B and AB, in one of a series of three boxes marked, M, N and MN, and check marks also in as many boxes as necessary among six boxes marked C, D, E, c, d, and e. Thus, this scheme makes no provision for reporting type MN_2 , which is not uncommon among Chinese. In addition, it presumes the existence of anti-d sera, and renders impossible the reporting of any of the niceties of the Rh-Hr system, especially for carriers of the genes R^z and r^y .

The many myths involving the Rh-Hr system have been discussed in detail in my previous articles, so that only the highlights need be mentioned here. At the basis of all these myths is a blood grouping myth that few recognize as such, namely, that there exists only a single comprehensive

and up-to-date text on the subject, one which need not be named because it is so well-known and is now in its sixth edition. This book is used and cited like a bible, even though blood grouping is not a religion but a science. Unfortunately, the book is characterized by its failure to present basic principles of the subject correctly, by its misquotations of the literature and by distortions of fact. It therefore remains a mystery why it still continues to be cited as if it were the sole reliable reference on blood grouping, when other books which are free from blood grouping myths are available. Judging from the way the misinformation and myths contained in this blood group "bible" are quoted over and over again, and even further elaborated and embellished, the bible earned the appellation as the *Source Book of Blood Mythology*, because it is responsible for many of the myths that I have discussed, and which continue to hamper progress in the thorough understanding of the subject of blood grouping.

A major cause for the myths to be found in the notorious blood group bible, is the failure to recognize the difference between agglutinogens (intrinsic attributes of the red cell envelope) and their serological specificities (extrinsic attributes of the agglutinin molecule); the latter are conveniently also known as blood factors. The CDEcde notations are based on the simple (actually, naive) assumption of a one-to-one-to-one correspondence among antibodies, agglutinogens and genes. Thus each serologi-

cal specificity becomes a gene so that, for example, what I interpret as an agglutinin Rh_1 determined by a corresponding allelic gene R^1 , and having the serological specificities $RH_0(D)$, $RH'(C)$, and $HR''(e)$ is interpreted instead as representing a complex of three agglutinin molecules C, D and e, or three separate determinants on the red cell surface determined by a tightly linked triplet of genes DCE , and the concept of so-called gene cistrons with subloci in a specific order is invoked. As more Rh-Hr specificities were discovered these were readily absorbed under my own concept of serological specificities as additional extrinsic attributes of the agglutinin molecule; in fact, the number of serological specificities corresponding to a single agglutinin is theoretically *unlimited* or *infinite*. At the same time, in contrast, the C-D-E mythologists have been compelled to postulate more and more determinants, so that eventually an infinite number of them will have to be crowded into a single agglutinin molecule of finite size. Simultaneously, the number of subloci on the gene cistron had to be increased, and one ambitious and imaginative investigator has even drawn a figure of the Rh-Hr gene complex with as many as 20 subloci arranged in a particular order. (Unfortunately, using my own microscope I continue to discern only a single gene locus for the Hr-Hr alleles.)

An essential characteristic of blood group mythologists and other mythologists is their ability to disregard

facts which conflict with their preconceived idea. Thus, when new facts are unearthed that do not match established dogma, true scientists invent new hypotheses to match the facts; not so, for mythologists—they simply distort or ignore the facts to match their ideas which are kept intact. A case in point is little d. Based on the demonstrated existence of $rh'(C)$ and its contrasting factor $hr'(c)$, Fisher predicted the existence of contrasting factors for $Rh_0(D)$, namely, little d, and for $rh''(C)$, namely, little e(hr''). The discovery of little e was actually reported, and there have also been reports by impressionable workers of the discovery of little d. These latter claims I proved to be wrong, and I also pointed out that not merely a single kind of little e existed since there are multiple cognate specificities of HR'' , such as HR^S and HR^B , as described by M. Shapiro. Thus, of Fisher's two predictions, one—little d—has never been fulfilled, while the other prediction did not go far enough since at least three antibodies, not merely one, have been found, any of which could fit the requirements for Fisher's single anti-e. The fact that Fisher's predictions were thus totally incorrect, however, has caused his antagonists no apparent embarrassment. In fact, Race and Sanger continue to write even in the sixth, 1975, edition of their book, "Now that the groups seem so clear, it must be difficult to realize how obscure they appeared before Fisher illuminated them. Such successful prediction must be rare in

biology". This citation demonstrates that, unlike scientists who modify their theories when new facts are unearthed which do not conform with their previous ideas, mythologists do the opposite — they alter the facts to make them fit their preconceived ideas. The facts here are that R. A. Fisher was a distinguished mathematician who never did a blood grouping test in his life, and that may be why not one of his ideas about Rh-Hr was original or correct, as proved by the experience and findings of the past three decades.

As for the assertion that the facts regarding Rh-Hr appeared "obscure" before Fisher "illuminated" them, that is totally false. The serology, genetics and nomenclature of the Rh-Hr types were all worked out by me in detail, as early as 1943. In particular, my theory of inheritance by multiple allelic genes, each allele determining a corresponding agglutinin with multiple (theoretically unlimited in number) serological specificities, has stood the test of time, and is being more and more widely accepted and used. My concept of an unlimited number of Rh-Hr specificities is being constantly confirmed as more and more of the Rh-Hr antisera thus anticipated by me of different specificities are found, 35 by the latest count, while Fisher's much more modest prediction of only two such antibodies, anti-d and anti-e, has proved to be entirely incorrect. Yet the blood group mythologists continue to cite the so-called Fisher predictions and synthesis, and in one recent book (1975) even appears

the claim, "So far, five of the six antibodies predicted by Fisher have been discovered, the exception being anti-d." In this way the blood group mythology regarding Fisher's predictions and synthesis continues to be promulgated and even improved upon by raising the number of antibodies said to be predicted by him from two to six.

Another myth to which the Race-Sanger book devotes considerable space is the so-called LW factor — for which more than four pages are used as compared with the five pages in the same book for the complete discussion of the real, clinically and genetically important Kidd blood group system. The antibody anti-LW was first reported by Levine in 1967, who said he found it in the serum of guinea pigs immunized with the red cells of rhesus monkeys. The LW agglutinin was described as a very high frequency antigen, and LW negative individuals who can be either Rh positive or Rh negative, are extremely rare. Thus, LW has nothing to do with Rh, but since it was discovered by the same method by which Landsteiner and Wiener discovered the Rh factor, Levine named the agglutinin he had discovered as LW, in "honour of" Landsteiner and Wiener. Later, paralleling the history of Landsteiner and Wiener's Rh (or rhesus) factor, human LW negative individuals were encountered whose sera contained antibodies similar in specificity to Levine's rhesus LW antiserum. In their book, Race and Sanger pointed out that tests by deVeber et al. on 10 552

unselected Canadian donors showed *not one* to be LW negative, indicating that LW is indeed a very high frequency antigen. In contrast to this as many as 6 of 45 individuals mentioned in Landsteiner and Wiener's first report of their discovery of the Rh (or rhesus factor) were negative. It seems impossible therefore to confuse Levine's LW with Landsteiner's and Wiener's Rh, but Race and Sanger manage to do so anyhow in their book, thus contributing another myth to the already overburdened field of blood group mythology. Interested readers can find a clear and detailed explanation of the reactions of Levine's anti-LW sera produced in guinea pigs in the excellent book of A. G. Erskine.

The nomenclature which I have developed for the Rh-Hr system is simple and compact — all the Rh-Hr symbols are meaningful and, as all scientific symbols should be, are terse mnemonics. Thus, the nomenclature is easy to understand and master — because, like a silent teacher, good scientific symbols give their users insight into the subject. Moreover, by the use of this nomenclature, all the findings regarding the Rh-Hr types are readily and neatly tabulated because the symbols for phenotypes and genotypes, and the symbols for agglutinogens and their serological specificities are sharply distinguished, and most important, the symbols for the phenotypes and genotypes lend themselves to a natural, logical arrangement in tables. Thus the seemingly very complex tables synthesising all the

facts regarding the Rh-Hr phenotypes and genotypes are readily understood and mastered when my nomenclature is used, and need not be memorized, because all the tables can readily be reconstructed by simple logic as each reaction and symbol falls into its natural place in the tables.

Not so for the Fisher synthesis—The C-D-E symbols do not distinguish clearly between phenotypes and genotypes or between antigens and their specificities. Worse they do not lend themselves to a natural, logical order, so that tables of the Rh-Hr types in terms of C-D-E in different editions of the Race-Sanger book all have different unsystematic arrangements, with resulting errors of commission and omission. While my own tables of Rh-Hr can be compared to an English dictionary where each symbol or work is easily located, the Fisher-Race tables of C-D-E are comparable to Chinese or Japanese dictionaries, which lacking an alphabet, have no systematic arrangement of their symbols or "words". For examples of the errors that result from the use of the Fisher-Race CDE symbols, the reader may consult Table 32 on page 186 of the 6th edition of the Race-Sanger book. Red cells having the specificities $\text{RH}'(\text{C})$, $\text{RH}''(\text{E})$, $\text{HR}'(\text{c})$ and $\text{HR}''(\text{e})$, but lacking $\text{HR}_0(\text{D})$, are said to be of phenotype rh_yrh in my Rh-Hr terminology, with two possible genotypes, $r'r''$ and $r^y r$, which are both quite rare. The table in the Race-Sanger book, however, gives for this Rh-Hr blood type only the

single genotype $r'r''$ and omits $r^y r$, even though my family studies have proved that $r'r''$ and $r^y r$ are about equal in frequency. It is noteworthy that Race and Sanger in their book themselves apparently find the C-D-E appellation unequal to the task of representing phenotypes and genotypes, so that they are forced to resort to so-called "shorthand symbols" which are nothing more than transparent, trivial modifications of my own genotype Rh-Hr symbols, and which, of course, have nothing at all to do with the C-D-E notations.

I shall conclude this review by pointing out again the myth, which, in my opinion, is at the basis of almost all other blood grouping myths. It is noteworthy that when the author of a scientific paper in the field of blood grouping wishes to cite a source book on the subject, the book selected is almost invariably the Race-Sanger *Blood Groups in Man*, now in its sixth edition. Thus, other important sources, such as the encyclopaedic book of Prokop and Uhlenbruck, *Human Blood and Serum Groups*, are generally ignored or slighted. The result is that there has arisen the myth that the only reliable and complete text on blood groups is the Race-Sanger book, which is used

like a bible, even though blood grouping is a science and not a religion. Unfortunately, the Race-Sanger book is not dependable, because, as has been shown, it distorts and misrepresents important facts, so that it has become instead a sourcebook of blood group mythology. There is however no doubt that the Race-Sanger book is useful because it contains information not otherwise readily available. Therefore, my purpose here is not to condemn the book, but only to caution those who must use the book, and to point out that for learning the fundamental principles of blood grouping, one can do better by referring to other sources, notably, the book by Erskine. If this message of mine has been successfully transmitted, the further progress of the science of blood grouping will benefit therefrom, and the effort that I have expended in preparing this review will not have been in vain.

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Alexander S. WIENER, M. D.
64 Rutland Road
Brooklyn, N.Y. 11225
USA

Quantitative Renographie bei Pyelonephritis im Kindesalter

Von

S. KÖVES und K. PUMP

Urologische Klinik der Medizinischen Universität und Komitats-Kinderkrankenhaus,
Pécs

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Anhand der quantitativen Bewertung der Ergebnisse der bei 32 an Pyelonephritis leidenden Kindern durchgeführten Radiorenographie konnten Folgerungen in bezug auf die Nierenfunktion gezogen werden. Die quantitative Bewertung der Radiorenographie erwies sich als ein brauchbares und empfindliches Verfahren, welches über die Anwesenheit der Pyelonephritis orientiert und auch zur Aufstellung des therapeutischen Planes eine Hilfe bietet.

Die Entwicklung der morphologischen und Funktionsuntersuchungen der Nieren sowie die Anwendung von bakteriologischen und serologischen Verfahren trugen in bedeutendem Maße zur Erleichterung der Diagnose der im Kindesalter auftretenden Pyelonephritis bei [1, 2]. Eine wesentliche Hilfe auf diesem Gebiet bietet unter anderem auch die Radiographie, die in bezug auf die Entwicklung der juvenilen Pyelonephritis frühe Informationen liefert [3, 4].

Die Bewertung der Radiorenographie erfolgt im allgemeinen semiquantitativ; die quantitative Bewertungsmethode bietet indessen Möglichkeiten zur Selbstkontrolle, indem die Parameter der homolateralen Niere mit der der kontralateralen bzw. die Parameter derselben Niere mit den früher gewonnenen Werten verglichen werden können.

Die Radiorenographie wurde quan-

titativ bewertet, die Aufnahmeportion zahlenmäßig festgestellt, um daraus Folgerungen in bezug auf die Nierenfunktion zu ziehen.

METHODIK

Die Untersuchungen und die anschließende Bewertung der Daten erfolgten bei 32 an Pyelonephritis leidenden Patienten; es wurden insgesamt 79 Radiorenogramme gefertigt (in 18 Fällen 2mal, in 13 3mal und in einem Fall 4mal).

Es wurde die zweite Phase des Radiorenogramms bewertet, da diese eng mit der Nierenfunktion zusammenhängt und die Akkumulation der markierten Substanz sich in dieser Phase abspielt [5]. Die Aufnahmeportion ist von der angewandten Dosis unabhängig. Von den 3minütigen Werten wurden die Initialwerte der zweiten Phase subtrahiert (A) und dieser Wert mit dem Initialwert dividiert. Diesen Vorgang veranschaulicht Abbildung 1.

Die Untersuchung erfolgte bei liegenden Kindern mit einem 4kanäligen EFKI Apparat Typ Nephrograph MB 7104,

nach Verabreichung von 0,5 μCi ^{131}I -Hippuran/kg Körpergewicht. Registrierung: Zeitkonstante: 3 sek, Papiergeschwindigkeit: 1 cm/min, Registrierungsdauer 30 min. Die Nierenlokalisation wurde anhand der Urographie bestimmt.

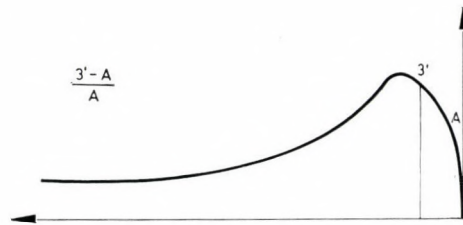


ABB. 1 Radiorenogramm mit Parametern für die quantitative Auswertung

ERGEBNISSE

Vorerst wurde die Aufnahmeportion der zweiten Phase ausgerechnet und diese Angabe mit den früheren Werten des betreffenden Kindes verglichen. Die Ergebnisse sprachen dafür, daß sich die Funktion in 9 Fällen (in 3 Fällen beiderseits, in 2 Fällen links und in 4 Fällen rechts) verschlechterte. In 23 Fällen ließ sich keine Funktionsverschlechterung erkennen, in 13 dieser Fälle wies die Aufnahmeportion auf unveränderte Funktion und in 10 auf eine gebesserte Funktion hin. In 6 der 9 Fälle mit einer Funktionsverschlechterung zeigte das klinische Bild eine Aktivität, während sich in 3 Fällen keine Aktivitätszeichen des klinischen Bildes widerspiegeln.

Andererseits lag bei 4 der 23 Kindern, bei denen eine Funktionsverschlechterung zu verzeichnen war, eine schwer beeinflussbare chronische Infektion vor, in 6 dieser Fälle meldete sich die

Infektion intermittierend. In 13 Fällen war der Befund dauernd negativ.

FALLDARSTELLUNGEN

Fall Nr. 1. Radiorenogramm eines 8jährigen, an Pyelonephritis leidenden Mädchens. (Abb. 2).

Kontrolluntersuchung nach 7 Monaten; der Parameter zeigt die durch die aktive Pyelonephritis bedingte Funktionsverschlechterung deutlich.

Fall Nr. 2. Radiorenogramm eines 7jährigen, an Pyelonephritis leidenden Mädchens. (Abb. 3).

Kontrolluntersuchung nach 4 Monaten. Die Aufnahmeportion weist auf mäßige Funktionsverschlechterung hin.

Fall Nr. 3. Radiorenogramm eines 8jährigen, an Pyelonephritis leidenden Knabens. (Abb. 4).

Gebesserte Nierenfunktion.

Fall Nr. 4. Radiorenogramm eines 11jährigen Mädchens; Pyelonephritis und beiderseitiger vesikorenalereflux. Das Radiorenogramm zeigt auf der rechten Seite stark eingengte Nierenfunktion. (Abb. 5).

Links wurde an dem ureterovesikalischen Abschnitt eine plastische Operation *sec. Gregoir* vorgenommen. Nach 7 Monaten besserte sich auf der linken Seite die Aufnahmeportion, rechts konnte jedoch der Parameter nicht ermittelt werden. Rechtseitige Nephrektomie. Kontrolluntersuchung: mäßige funktionelle Entleerungsstörung der Solitärniere, weitere Besserung der Aufnahmeportion.

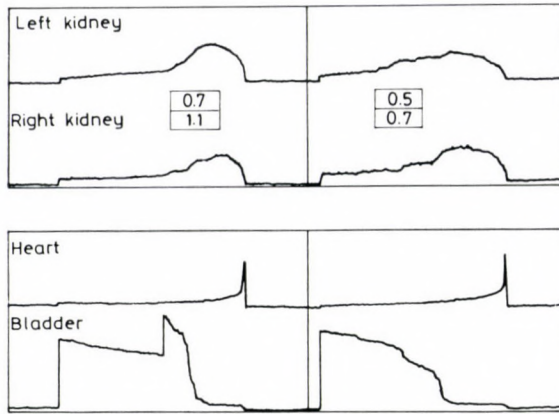


ABB. 2

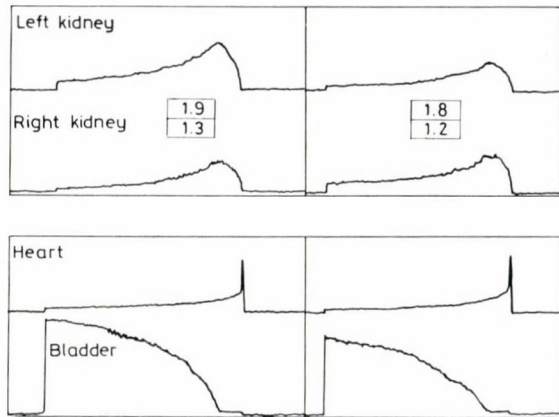


ABB. 3

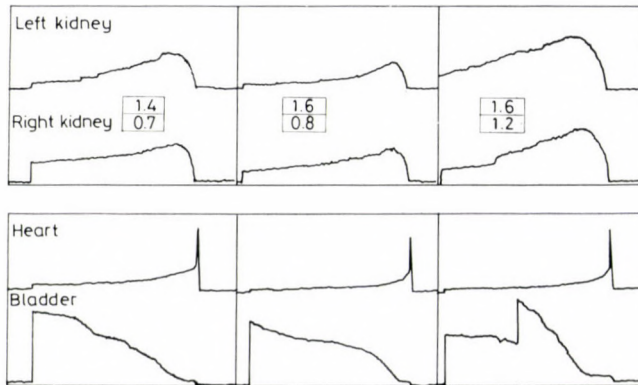


ABB. 4

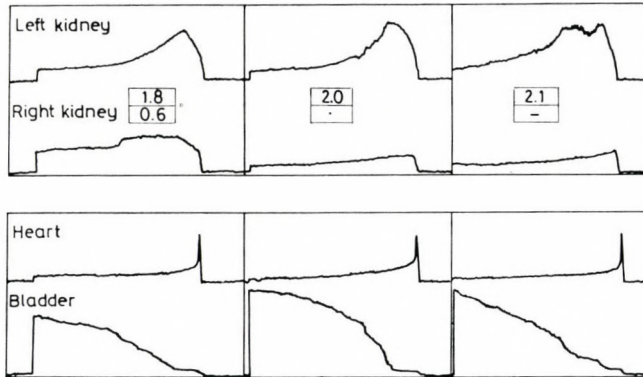


ABB. 5

BESPRECHUNG

Mittels Bewertung der zweiten Phase des Radiorenogramms wurden bei an akuter und chronischer, primärer und sekundärer Pyelonephritis leidenden Kindern gewisse, die Nierenfunktion charakterisierende Parameter bestimmt. In dieser — d. h. in der zweiten — Phase spielt sich die Akkumulation der markierten Substanz in der Niere ab. Die Aufnahme des ^{131}I -Hippurans hängt eng mit der tubulären Nierenfunktion zusammen. Anhand unserer Ergebnisse vertreten wir die Ansicht, daß die quantitative Bewertung der zweiten Phase des Radiorenogramms ausführlichere Informationen bietet, als die semiquantitative Auswertung. Die Methode liefert zuverlässige Da-

ten in bezug auf das Bestehen bzw. den Verlauf der Pyelonephritis und anschließend auch über die Wirksamkeit oder die Unwirksamkeit der Therapie.

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Dr. S. KÖVES
Urologische Klinik
Munkácsy M. út 2
H-7621 Pécs, Ungarn

Distribution of serum amylase isoenzymes in cystic fibrosis homozygotes and heterozygotes

By

Ö. TAKÁCS, I. SOHÁR, Aranka LÁSZLÓ, P. PÉNZES, and K. GYURKOVITS

Institute of Biochemistry and Department of Paediatrics,
University Medical School, Szeged, Hungary

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A simple method has been elaborated for the routine separation and quantitative determination of amylase isoenzymes. The ratio P/S, the quotient of the activity values obtained by densitometric evaluation of the pancreatic and salivary isoenzymes, is used to characterize their distribution. In healthy adults and children the value for P/S is above 1 in 80% of the cases, with a mean of 1.87 ± 0.23 . In 90% of heterozygote CF gene-carriers, the P/S is below 1 with a mean of 0.68 ± 0.13 . In addition to the higher total amylase activity, in MV homozygote patients P/S is less than 0.1, and even 0.001. The phenomenon is explained by a compensatory enhancement of salivary activity.

The method is a suitable diagnostic test of the exocrine function of the pancreas and for evaluation of the serum amylase isoenzymes. The P/S value allows to differentiate heterozygote CF gene-carriers from homozygotes and healthy individuals.

It was shown earlier [4] that the total amylase activity in saliva and serum is significantly increased in cystic fibrosis (CF) patients. The phenomenon can be explained by a compensatory increase of salivary amylase activity. The CF heterozygotes could not be distinguished from the normal individuals on the basis of the total amylase activity in serum and saliva. Alpha-amylase has been assumed to have a pathogenetic role in CF [2] but this has been refuted by Nikolajek and Emrich [6] who found no difference in alpha-amylase in the serum and sweat of CF patients and healthy controls.

It has therefore been attempted to utilize the distribution of amylase

isoenzymes as a diagnostic method for the differentiation of MV homozygotes and heterozygotes from each other and from the healthy population.

MATERIAL AND METHODS

Three groups were examined.

(1) A normal group of healthy blood donors, healthy children and adults free from CF.

(2) Heterozygotes originating from CF families identified by the modified Szczepanski bromide test [3]. The average bromide index for the group was 27 ± 10 . Data from 27 confirmed CF heterozygotes were used for statistical evaluation.

(3) The homozygote group consisted of 8 complete CF homozygote children with a bromide index of 76 ± 20 .

Distribution of amylase isoenzymes

(a) 0.2 ml 40% saccharose and 0.1 ml buffer containing 0.01% bromophenol blue is added to 0.1 ml serum. If the total amylase activity is below 100 U/l, 1–2 crystals of bromophenol blue and saccharose at a final concentration of 10% (0.10 g/ml) are added to the undiluted serum, and the samples are mixed. In the case of a total amylase activity above 500 U/l, or of saliva or duodenal juice examination, the sample is diluted to an amylase value of 6–8 mU in 20 μ l. Total amylase activity was estimated with the Phadebas kit (Pharmacia, Uppsala).

(b) Electrophoresis was carried out in 5.6% polyacrylamide gel prepared essentially according to Davis [1]. Gel buffer: Tris–hydrochloric acid, pH 8.9. Electrode buffer: Tris–glycine (0.005 M Tris, 0.4 M glycine), pH 8.3. A vertical plate electrophoretic apparatus was used; the system has the advantage that 48 parallel examinations can be performed on the same gel. At a potential of 300 V the separation requires 4 hours. Optimum temperature: 10 °C. It is advantageous to carry out the separation in the cold-room.

(c) For detection of amylase activity and determination of the isoenzyme pattern the gel plates are incubated in 0.02 M phosphate buffer pH 6.9 containing 0.0067 M NaCl and 1% water-soluble starch at 37 °C for 60 min.

After thorough rinsing with distilled water, the gel plates are incubated in a wet-chamber, at 37 °C for 2 hours, and stained with 0.1 N iodine solution until the activity-free gel background has turned an intense blue. The subsequent decrease of the colour intensity may be inhibited if the gel plates are placed in iodine solution diluted 10-fold with 20% ethanol. Evaluation should take place within 16 hours.

A densitometer fitted with a Kipp integrator is used for quantitative evaluation of the isoenzyme pattern. Visual

evaluation may be attempted by a practised observer: detection of the homozygote isoenzyme pattern is simple, and establishment of the normal distribution does not cause a problem either, but recognition of the isoenzyme pattern characteristic of the heterozygote phenotype requires great practice. The data measured with the integrator are evaluated statistically, with Student's *t* test.

RESULTS

(1) *Normal group.* In the vast majority of cases the amylase of normal serum contains one major salivary (S_1) and one major pancreatic (P_2) isoenzyme. In addition one minor component from each pheno-

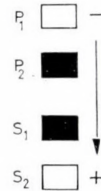


FIG. 1. Amylase isoenzyme patterns in serum after polyacrylamide gel electrophoresis. +: Anode; -: Cathode; Abbreviations: P_1 , P_2 , pancreatic isoamylases. S_1 , S_2 , salivary isoamylases.

type (P_1 and S_1) was present in negligible amounts.

The distribution of isoenzymes was characterized by the quotient of the sums of the major and minor components, in pancreatic juice and saliva, respectively,

$$\frac{P_1 + P_2}{S_1 + S_2}$$

For the 23 normal subjects the P/S values was 1.8 ± 0.23 (range, 0.62 to 5.3).

TABLE I
Distribution of isoamylases (P/S ratio) in serum, bromide index and total amylase activity.
Mean \pm S. D.

	P/S ratio	Significance		Bromide index, per cent	Total amylase activity U/L
		versus normal group	versus heterozygotes		
Normal subjects N = 23	1.87 \pm 0.23	—	+	8 \pm 6	201 \pm 62.3
CF heterozygotes N = 27	0.68 \pm 0.13	$\begin{matrix} + \\ p < 0.001 \end{matrix}$	—	27 \pm 10	203 \pm 79.5
CF homozygotes N = 8	x < 0.1	$\begin{matrix} + \\ p < 0.001 \end{matrix}$	p < 0.02	76 \pm 20	269 \pm 113.7

+ = significant
— = non-significant

In 50% of the normal subjects the P/S value lay between 1 and 2, and in 80% it was above 1. A representative isoenzyme pattern of the normal group is shown in Fig. 3.

(2) *Heterozygote group.* Twenty-four of the 27 cases examined exhibited a P/S value below 1, the mean being

0.68 \pm 0.13. This means that in heterozygotes the activity of salivary isoenzymes predominates. There was a significant difference against the normal group: p < 0.001. A representative electrophoretic picture of the heterozygote group is given in Fig. 4.

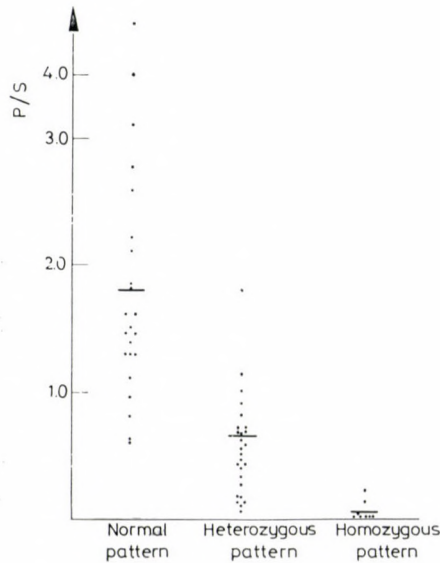


FIG. 2. P/S ratios in the sera

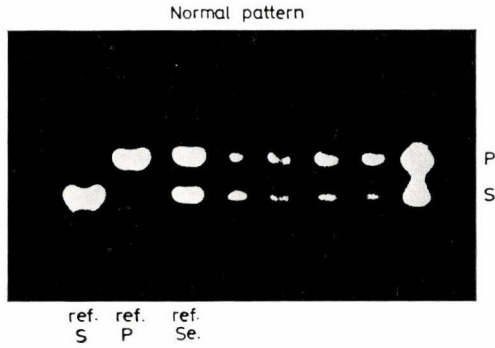


FIG. 3. Representative serum isoamylase pattern in normal persons. Abbreviations: Ref. S., Ref. P., Ref. Se.: Reference saliva and pancreatic juice, reference serum obtained from healthy subjects.

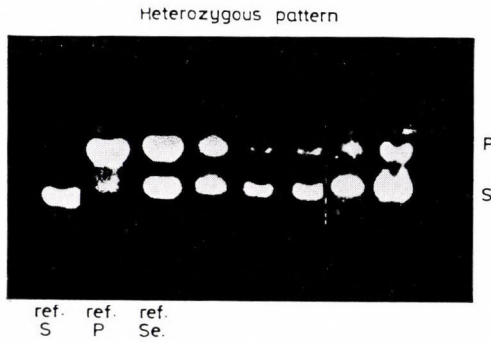


FIG. 4. Amylase patterns of CF heterozygotes. Abbreviations as in Fig. 3.

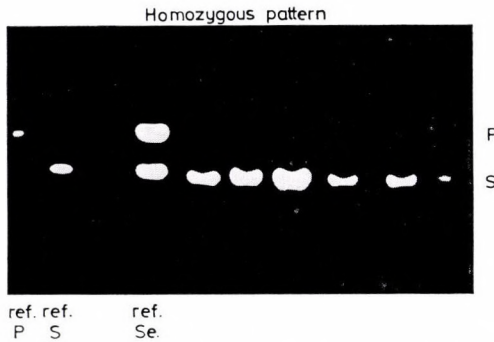


FIG. 5. Amylase patterns of CF homozygotes. Abbreviations as in Fig. 3.

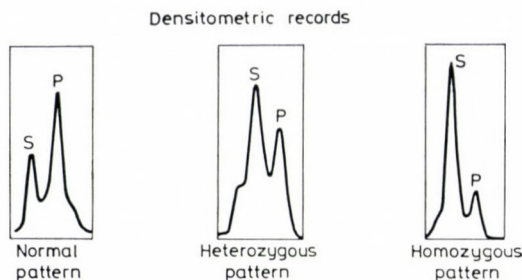


FIG. 6. Representative densitometric records from sera of normal subjects, CF heterozygotes and homozygotes.

(3) *Homozygote group*. In homozygotes the serum total amylase activity was higher than in heterozygotes or normal individuals. The ratio of isoenzyme distribution shows the dominance of the salivary phenotype. In most cases only the major salivary component (S_1) could be detected, with a barely perceptible activity in the P_1 zone. The P/S ratio was less than 0.1, sometimes as low as 10^{-3} – 10^{-4} . The homozygote enzyme pattern is seen in Fig. 5.

Figure 6 illustrates representative densitometric curves for the amylase isoenzyme distribution in normal individuals, heterozygotes and homozygotes.

DISCUSSION

In a study of the salivary amylase isoenzymes of 700 patients, Ward et al. [12] obtained 8 different bands. On the basis of about 1000 samples, Wolf and Taylor [13, 14] reported on result which did not agree in all respects with the former. The exact pattern is still unelucidated. For example, Merritt et al. [5]

described 6 more salivary and further 4 pancreatic isoamylases. Several of these exhibited an identical mobility on polyacrylamide gel; it may be assumed that artifacts were involved. In 1974, Takeuchi et al. [10] described the use after electrophoresis of a blue starch preparation (Phadebas) for the detection of amylase activity. With this method, one pancreatic and one salivary type isoenzyme could be detected on cellulose acetate membrane. Our studies, however, showed that acrylamide gel electrophoresis combined with Phadebas can be used only in the case of very high amylase activities. Recent investigations [7] agree in that two variants of the anodic salivary isoenzymes exist, with similarly 2 variants of the cathodic pancreatic isoenzymes (see Fig. 1), although Skude [9] stated that at high enzymatic activities 5 salivary isoenzymes and 4 pancreatic isoenzymes can be detected. On the other hand Otsuki et al. [8] made a quantitative study of the distribution of amylase isoenzymes in 3036 samples of normal serum and urine. The result was the

same as that of our present study: activities of the P₁ and S₁ amylase isoenzymes predominated in the serum of 98% of healthy subjects with P₂ in excess of S₁. Thus, the amylase isoenzyme problem has not been solved satisfactorily.

As to the amylase isoenzymes of CF patients, Taussig et al. [11] observed that the P-type isoenzyme was absent or significantly decreased in two-thirds of the cases. In agreement with our results, these authors too found an identical proportion of P and S isoenzymes in the serum of normal subjects.

A low serum total amylase activity has never been observed in CF patients. In the cases of Taussig et al. [11] it was the duodenal amylase activity which was absent or low. Study of the serum isoenzyme patterns is therefore suitable for the reliable differentiation between MV homozygotes and heterozygotes. Since, however, the P/S ratio for our healthy controls and MV heterozygotes showed an overlap in the range from 0.8 to 1.1, it is advisable to consider heterozygosity only below a P/S value of 0.8.

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Dr. Ö. TAKÁCS
 POB 471
 H-6701 Szeged, Hungary

Cystic fibrosis: a HLA associated hereditary disease?

By

Gabriella I. KAISER, Aranka LÁSZLÓ and K. GYURKOVITS

Blood Transfusion Centre and Department of Paediatrics, University Medical School, Szeged

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Twelve homozygote patients and thirty-two heterozygote gene carriers from families with cystic fibrosis were HLA-typed. Diagnostic criteria were sweat electrolyte concentration, pancreatic enzyme levels from duodenal juice and stool, Szczepanski's bromide test in the group of homozygotes, and the latter only in the cases of heterozygotes.

In comparison with 130 healthy blood donors typed for 29 HLA antigens, B18 proved to be more frequent in the group of patients and gene carriers, with 50 and 31%, respectively, and 14% in the normal population. The association seems to be stronger in the homozygotes than in the heterozygotes ($p < 0.005$ and $p < 0.02$, respectively).

With growing knowledge concerning tissue antigens, a search has begun for their correlation with diseases [1, 2]. The first success was the demonstration of a correlation between the susceptibility to oncogenic viruses and H-2, the main histocompatibility system in mice, which corresponds to the HLA system in man [7]; and then their relation with human leukaemia [2].

The pioneer work was followed by many clinical observations [3, 6, 8, 10]. Some of the correlations between a disease and the presence of certain HLA antigen(s) are so strong, e. g. ankylosing spondylitis with B27 or gluten enteropathy with B8, that persons negative for these antigens are affected only exceptionally. There are now other examples, in which an

association found with a HLA-B series antigen was followed by finding another, but stronger, association with a HLA-D antigen in linkage disequilibrium with the former, e. g. 7 and 7a (the present B7 and Dw2) in multiple sclerosis. (The nomenclature used in this paper corresponds to the latest decisions of the WHO-IUIS Terminology Committee, see ref. [12].) It seems certain that as soon as HLA-D typing becomes a routine procedure, further disease associations will be found.

The next step would be the elucidation of the mechanism through which these effects are brought about. It is, however, impossible to find a common explanation for the different malignancies, immunopathological diseases, or bacterial and viral in-

fections. The most plausible explanation for most disease groups is perhaps the theory that certain disease genes not localized as yet may be in linkage disequilibrium with some HLA antigens.

Cystic fibrosis (CF) has so far been involved in a single study and this brought a negative result, showing no deviation from normal HLA antigen frequencies [4, 5]. A slight association with B5 was considered insignificant [5].

MATERIAL AND RESULTS

Twelve homozygote patients and 32 heterozygote gene carriers from families with CF were HLA-typed. The diagnostic criteria were sweat electrolyte concentrations, pancreatic enzyme levels (lipase, amylase) from duodenal juice and stool, Szczepanski's bromide test [9] in the group of homozygotes, and the latter only in the cases of heterozygotes. Of the latter, 18 were parents of homozygous children, with a bromide index corresponding to the level of heterozygotes.

In comparison with 130 healthy blood donors typed with microlymphocytotoxicity test (by NIH technique) during the same period with the same typing sera for 29 HLA antigens, HLA-B18 proved to

be more frequent in the group of homozygotes and heterozygous gene carriers (50 and 31%, respectively, and 14% in the normal control group (Table I)).

DISCUSSION

Cystic fibrosis is a genetically well-defined condition with severe clinical consequences. To offer an explanation for the observed correlation with B18, which might hold true only if confirmed on a greater number of patients, we believe that linkage disequilibrium with the disease gene(s) should be assumed in this particular case too. There seems to be room for many genes in the region where those coding for the antigens of the main histocompatibility complex are situated [3, 6]. One or more of these genes might regulate a certain metabolism necessary to the normal development of cell membranes.

ACKNOWLEDGEMENT

The authors are indebted to Miss Ella Trummer for excellent technical assistance.

TABLE I
Incidence of HLA-B18 in 44 CF patients

Patients	Number of cases	HLA-B18 positive per cent	Chi square	p	p (corrected)
Homozygotes	12	50	8.164	< 0.005	0.116
Heterozygotes	32	31	5.440	< 0.02	
Control blood donors	130	14			

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Dr. Gabriella I. KAISER,
Blood Transfusion Centre,
P. O. Box 464.
H-6701 Szeged, Hungary

Paraneoplastic syndrome in childhood

By

D. SCHULER, Rosalie KOÓS, Isabelle KRAUZE, Ágnes PÉTER

Second Department of Paediatrics and Department of Neurology, Semmelweis University Medical School, Budapest

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The case of a five-year old boy is reported who at the age of 18 months had successfully been operated upon for neuroblastoma and who had subsequently signs of cerebellar encephalopathy. The paraneoplastic conditions of childhood are discussed in connection with the reported case. Opsoclonus was not observed in the patient, and symptoms showed rapid improvement on methotrexate, carmustine and CCNU treatment. Six months later the child was free of neurological disturbances and only displayed a slight mental retardation (IQ: 88). Cytological alterations observed in the CSF during the cerebellar encephalopathy are described in detail. At present, 41 months after the operation the child is well and free of symptoms.

The symptoms constituting the so-called paraneoplastic syndrome are related to the presence of a malignant tumour but do not arise under its direct effects such as its mechanical action, metabolic or hormonal activity. The syndrome is of differential diagnostic value as it may monitor the appearance of relapses and help in predicting the prognosis. In the present study, the main features of the paraneoplastic syndrome of childhood are outlined on the basis of data in the literature and of clinical studies carried out in a 5-year-old child with sympathicoblastoma.

REPORT OF A CASE

The patient now is a 5-year old boy, who had started walking and talking at the age of 14 months and it was at that time that he had first been admitted for

high temperatures, a cough and occasional vomiting. Chest X-rays revealed a tumour in the posterior mediastinum. A tumour mass was removed, but some tumorous tissue remained attached to the ribs. Histological diagnosis was sympathicoblastoma. Treatment was carried out according to the schedule outlined in Fig. 1. Following discharge the child was controlled regularly. He developed well, but his speech was somewhat delayed. Laboratory findings remained normal until 14 months after the operation when he began to show signs of faltering walk. He was afebrile and received no drugs at that time. Physical examination showed normal conditions.

Neurological findings. Normal retina. Clear consciousness, no meningeal signs. Normal oculo-motor function. Slight dysphagia. Normal proprioceptive reflexes. Trunk ataxia with deviation to the right. Tremor of head, and on reaching for objects, of the hands.

Laboratory studies. ESR, 10 mm/hr. Haemoglobin, 12.8 g per 100 ml. WBC, 5400. Differential count, normal. Serum

protein concentration, 6.8 g per 100 ml. Serum electrophoresis: slight increase in alpha globulin level. Urine analysis: normal. Vanillin-mandelic acid excretion, 4 $\mu\text{g}/\text{mg}$ creatinine. In CSF: cell count, 28/3; protein, 180 mg per 100 ml; sugar, 97 mg per 100 ml; bacteriology negative. EEG: 2.5–3/sec slow waves interrupted by sharp peaks mainly temporo-parietally. CNS scintillography failed to show signs of intracranial relapse.

One week after the onset of symptoms, the patient was unable to walk. Intravenous feeding was introduced because of frequent vomitings and swallowing difficulties. On the 7th day intrathecal methotrexate (MTX) therapy was started with a dose of 10 mg/m^2 . A total of eight injections was given during the following 3 months. This was followed two weeks later by two injections of carmustine (BCNU) in a dose of 70 mg at two weekly intervals. Another four weeks later chloroethylcyclohexyl-nitrosourea (CCNU) in a dose of 100 mg was given orally and repeated two weeks later.

Cytological examination of the CSF was carried out regularly. Data are seen in Table II. Four distinct periods could be distinguished on the basis of qualitative differences in the cell count.

1. Before treatment and 72 hours after the second MTX injection, intact red blood cells and activated monocytes were found in the CSF. These latter cells contained vacuoles which failed to stain with oil-red.

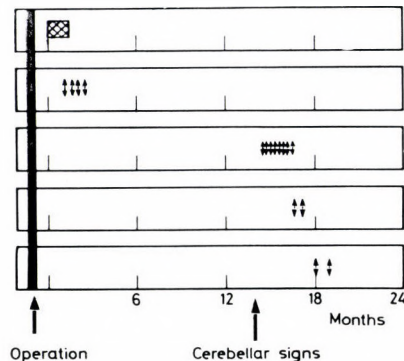
2. During the course of further MTX injections, lymphocytes, plasma cells and monocytes with deformed nuclei appeared (Figs 1 and 2).

Following the 7th MTX injection, lymphocytes and plasma cells increased in size (Figs 3 and 4) and number. Toluidine blue staining demonstrated 2–5 compact nucleoli in the basophilic cells (Fig. 5).

3. After the second BCNU injection, monocytes and lymphocytes resembling Rieder cells dominated the picture. Herniation of the nucleus was observed in some of the blast-like basophils reaching a size

TABLE I

Treatment protocol		
X-ray therapy		2850 r
Vincristine	1.5. mg/m^2 intravenously	
MTX	10 mg/m^2 intrathecally	
BCNU		70 mg
CCNU		100 mg orally



of 30–50 μ (Fig. 6). Multinucleated plasma cells were also observed (Fig. 7). Nuclear fragmentation was demonstrated by Stockinger's stain (Fig. 8).

Some of the cells exhibited hydropic desintegration, a swollen oedematous cytoplasm with metachromatic nucleus (Fig. 9). In some cells the cytoplasm and nucleus showed nearly identical staining (Fig. 10). Drop-like structures could also be found in some degenerated cells; the cytochemical properties of these cells could not be established (Fig. 10).

4. 9 days after the second BCNU injection only small lymphocytes and

monocytes were found in the CSF.

The child showed considerable improvement after the third MTX injection. Following the 7th MTX dose he could walk unaided, but still exhibited trunk ataxia, slight tremor of the arms and hands and minimal central facial palsy. CSF and EEG tests gave normal results.

At present, 41 months after removal of the neuroblastoma, and 25 months after the regression of symptoms of cerebellar encephalopathy, the child is well and free of symptoms. His IQ is 88. Neurological findings are normal except for a minimal facial asymmetry.

TABLE II

Treatment before i.p.	Time of i.p.	Cell count	Ly	Monoc. Histoc.	Lymphoid cell	Plasma cell	Eos.	Blast.	Degen. Ly	Phagocyte
	1974. IV. 11	6/3	8	59	6	Artificial bleeding erythrocytes, neutrophils				
I. thec. II. MTX IV. 23	IV. 26.	28/3	1	75	5					
IV. MTX IV. 29.	V. 27.	12/3	36	29	12	16	4	1		2
V. MTX V. 7.	V. 14.	13/3	38	21	14	20	4	1		2
VIII. MTX V. 21.	V. 29.	?	24	20	18	22	6	2		8
I. v. II. BCNU VI. 15.	VI. 20.	10/3	35	25	10	17	1	8	3	1
—	VI. 24.	12/3	53	30	8	8			1	

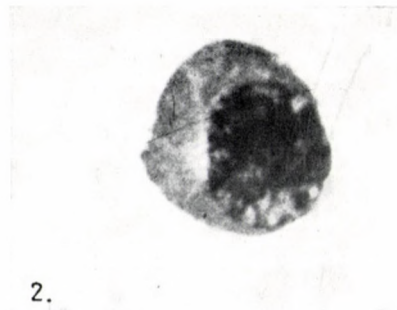
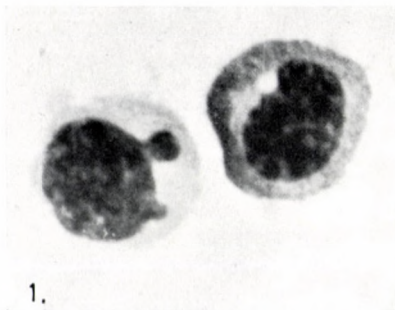


FIG. 1. Lymphoid cells with light and with basophilic cytoplasm, 72 hr after the 4th MTX dose. (MGG, $\times 1000$)

FIG. 2. Immature plasma cell one week after the 5th MTX dose (MGG, $\times 1000$)

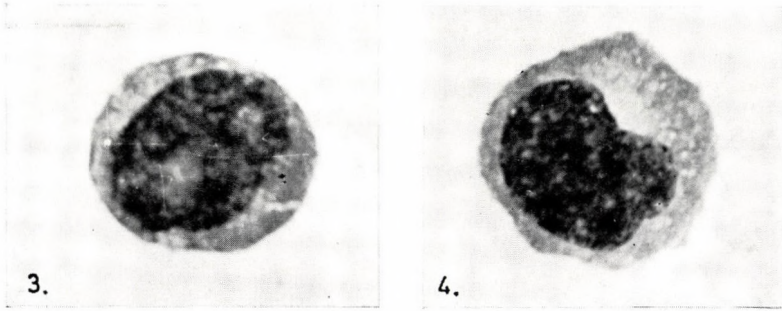


FIG. 3. Giant basophil (blast-like) with large nucleoli 8 days after the 7th MTX dose (MGG, $\times 1000$)
 FIG. 4. Giant plasma cell (MGG, $\times 1000$)

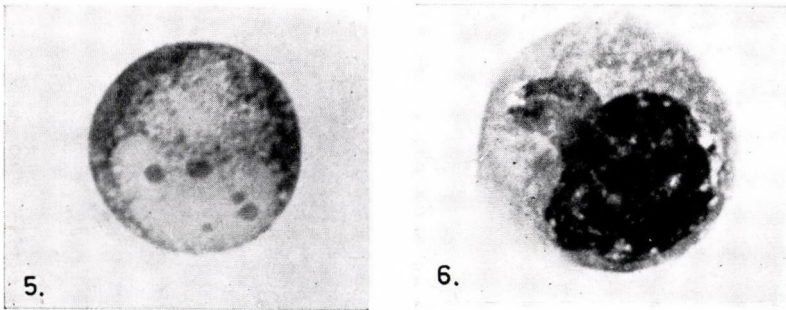


FIG. 5. Large basophilic cell with compact nucleoli of various sizes (Toluidin blue, $\times 1000$)
 FIG. 6. Giant basophilic cell with herniation of nucleus, 5 days after 2nd BCNU injection (MGG, $\times 1000$)

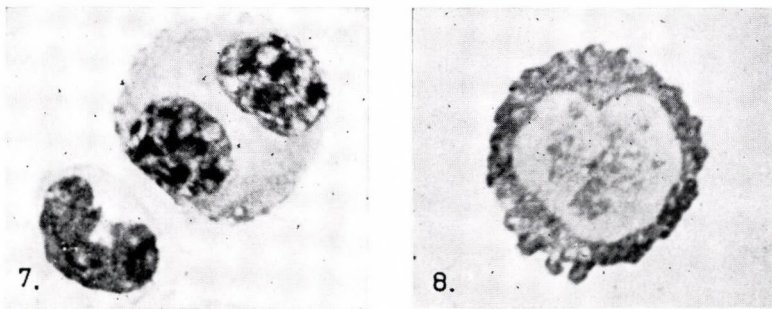


FIG. 7. Large binucleated plasma cell and monocyte (MGG, $\times 1000$)
 FIG. 8. Large basophilic cell with split nucleoli (Stockinger staining, $\times 1000$)

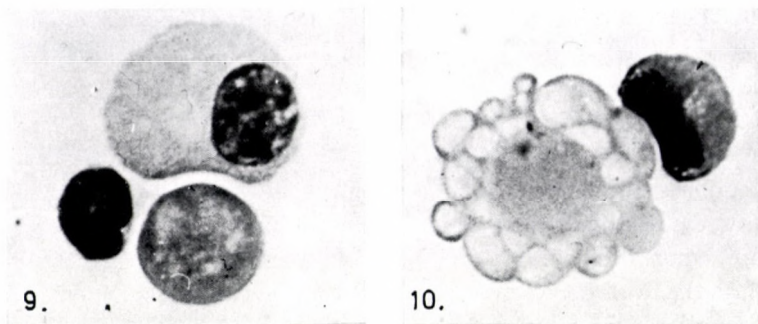


FIG. 9. Cells with signs of hydropic desintegration (MGG, $\times 1000$)

FIG. 10. Cells with cytoplasm and nucleus

DISCUSSION

The symptoms of the paraneoplastic syndrome in childhood can be divided into two categories: (i) ectopic hormone syndromes; (ii) symptoms not directly related to the effect of the tumour. They may be reversible, irreversible or partially reversible [12, 19].

(i) In the ectopic hormone syndromes, the tumour produces a hormone which does not correspond to the origin or histological type of the neoplasm. The criteria are that the hormone should resemble one of the physiologically produced hormones, should be demonstrable in the tumour and its production should disappear after removal of the tumour. This unusual, inappropriate hormone production is thought to be the result of a structural gene de-repression. If the structural gene responsible for synthesis of the given hormone is de-repressed, the hormone will be produced by the tumour cell in spite of its cells not being programmed for such a secretion. Thus, a mechanism similar as that of alpha-fetoprotein

or other carcino-embryonic antigen production can be held responsible for the hormone production.

A number of paraneoplastic endocrinopathies are well recognized in adults, but only some of these occur in childhood [17]. Ectopic ACTH production was noted in tumours of the thymus, lungs, adrenals. Langerhans islets, in phaeochromocytoma, neuroblastoma and ganglioneuroblastoma, resulting in typical signs of Cushing's syndrome [11, 12]. ACTH was demonstrable in the tumours by immunological methods. Post mortem the adrenals were found hypertrophic due to the ectopic hormone production, but the hypophysial basophilic cells showed no abnormality. The ectopic origin of ACTH can be demonstrated by the dexamethasone test, which fails to reduce the serum concentration of cortisol under paraneoplastic conditions. Removal of the tumour results in the disappearance of the Cushingoid symptoms. If surgical removal is impossible, symptoms can be alleviated by o-, p-DDD administration.

Among the tumours that do not

arise from the gonads, hepatoblastoma was shown to produce ectopic gonadotropin, resulting in elevated levels of the hormone in serum and urine [14, 19]. Structurally the hormone closely resembled the luteinizing hormone (LH) or the interstitial cell stimulating hormone (ISCH). Accordingly, the hormone overproduction resulted in elevated testosterone production and thus induced precocious puberty, without affecting the tubuli of the testes. After puberty, testosterone and androstenedione levels remain unchanged in spite of the Leydig cell hyperplasia, and as a result no virilization will occur. In girls precocious puberty will not develop since FSH production has not yet started. Administration of high doses of oestrogen for a short period will help to distinguish between hypophyseal or tumorous production of gonadotropin. If it is hypophyseal in origin, oestrogen treatment will reduce the hormone level by a feedback mechanism [11].

Ectopic parathormone production was reported in hepatoblastoma and anaplastic carcinoma of the testes [17, 25]. The condition is characterized by hypercalcaemia and hypophosphataemia. Clinical signs are those of hypercalcaemia, namely nausea, anorexia, constipation, polyuria or even oliguria, sensory disturbances. Bone metastases leading to osteolysis are also accompanied by hypercalcaemia, but the serum phosphorus level is also elevated in these cases.

Phaeochromocytoma may sometimes occur with increased erythro-

poietin production, which leads to erythroid hyperplasia in the bone marrow and high haematocrit values in peripheral blood [24, 27]. Erythropoietin production was demonstrable in the tumour by immunological methods.

It is unclear whether the protracted hypoglycaemia sometimes observed with large, usually abdominal, tumours of mesenchymal origin is a true paraneoplastic endocrinopathy. Certain studies suggest that these tumours produce an insulin-like substance, perhaps pro-insulin, but this is not generally accepted [13]. Immunological methods failed to identify insulin in the tumour. As hypoglycaemia was only observed with large tumours, it is possible that the sugar consumption of the tumour may be responsible for the effect [16]. Clinical signs appear on fasting and can be counteracted by intravenous injection of sugar. The symptoms do not arise suddenly and lead to headache, loss of vision, confusion and various neurological complaints.

Ectopic production of somato-matotropin was also reported in connection with childhood tumours, but it did not cause any clinically detectable signs.

(ii) Of the other reversible paraneoplastic symptoms fever, diarrhoea, hypotonia (ptosis, myasthenia) and hypertension should be mentioned. These too disappear on removal of the tumour.

Voute et al. [26] described a paraneoplastic syndrome in the mothers of fetuses who later developed

neuroblastoma. The transplacentally induced syndrome was characterized by sweating, headache, palpitation, paleness, paraesthesia of the fingers and, in some cases, hypertension.

In contrast to the reversible symptoms, cerebellar encephalopathy is an irreversible paraneoplastic syndrome. On rare occasions, however, this form too can show improvement. Cerebellar encephalopathy, also referred to as encephalopathy with opsoclonus and myoclonus, usually begins several months or even years before the tumor is diagnosed. Apart from our patient, whose cerebellar symptoms began 14 months after the operation only one case has been reported where symptoms appeared 19 months after removal of the tumour.

As to the cause of the myoclonus cerebellar encephalopathy, it is as obscure as with the other paraneoplastic syndromes. It was suggested that a toxic metabolite of the tumour may be responsible for the symptoms. There seems to be no correlation with vanillin-mandelic acid excretion, as the level of this substance was normal in approximately 50% of the patients affected by the syndrome [23]. The role of a tumour metabolite is also unlikely, since cases arising after removal of the tumour cannot be explained on this basis. It is possible that both the tumour and the paraneoplastic syndrome is caused by the same, as yet unidentified agent (neurotropic virus?). Finally, the role of an antigen-antibody cross-

reaction cannot be ruled out either. This would occur between antibodies produced against the tumour and the cerebellum. The good antigenicity of neuroblastomas seems to support the latter hypothesis [9, 10], along with the observed tendency to spontaneous regression [22]. A further point in favour of the immunological pathomechanism is the reported serum immunoglobulin abnormality and plasmocytosis in some cases [6].

Myoclonus encephalopathy is characterized by cerebellar ataxia, intention tremor, myoclonus and mental retardation. Opsoclonus, an irregular, clonic movement of the eyes, is also present. In rare cases, as in the present one, the opsoclonus may be missing or manifest only later, following removal of the tumour [15, 18]. Ataxia and tremor can reach such a degree that the patient will be unable to walk.

The symptoms of myoclonus encephalopathy disappear only on rare occasions, irrespective of whether or not the tumour has been removed. Of the 31 cases reported in the literature, only 5 have recovered from the paraneoplastic syndrome [1, 3, 5, 18, 21, 23] and two of these children later succumbed to the progression of the tumour. Opsoclonus and ataxia disappeared in 9 out of the 31 patients, but mental retardation persisted. In one of the 5 patients with favourable prognosis, encephalopathy began after eradication of the neuroblastoma [5]. This case along with our observation where the mental retardation was slight, indicates a

better prognosis for cases with late onset of symptoms. It is an interesting observation that the overall prognosis of neuroblastoma patients affected by myoclonus encephalopathy is better than the average. According to Altman and Baehner [1] two year survival in these patients was 89% as opposed to the expected value of 30–34%; it may be related to the fact that this type of paraneoplastic syndrome usually accompanies neuroblastomas with mediastinal localization. Of the 28 cases described by Berg et al. [3,] and Nissan et al [16] were mediastinal, and 12 retroperitoneal. The mediastinal form is thought to have a better prognosis than the abdominal one [7].

In myoclonus cerebellar encephalopathy, as opposed to inflammatory encephalopathies, the CSF shows no abnormality. A few cases have only been described with lymphocytosis and increased protein levels. Dyken and Kolar [6] observed plasmocytosis in the CSF. In our patient an increased protein level was found with a slightly elevated cell count. These values, however, returned to normal with a few weeks. Before treatment, activated monocytes with vacuolated cytoplasm dominated the cytogram. The vacuoles failed to stain with oil red.

As mentioned above, removal of the neuroblastoma causing the paraneoplastic syndrome will inhibit the progression of the encephalopathy, but will not lead to cure. There are no therapeutic means to achieve a cure. Although some authors ob-

served improvement after the administration of ACTH and cortisone in opsoclonus-myoclonus encephalopathy [8, 21], the improvement may have been spontaneous. Treatment with MTX, BCNU and CCNU was carried out in spite of the lack of signs indicating cerebral metastases. The intentional tremor improved after the 2nd injection, and trunk ataxia improved after the 5th dose of MTX.

Following MTX and BCNU treatment, qualitative changes occurred in the cytogram. Lymphocytes and plasma cells appeared. With the improvement of the condition, the cytological reaction became more pronounced, the immune-active cells became enlarged and their number increased. It is difficult to correlate the proliferation of lymphocytes and plasma cells with the immune-suppressive effect of MTX. Experimental data indicate, however, that in certain conditions cytostatic drugs exert a paradoxical effect [2, 4, 20, 22]. The time factor, the concentration of the drug and the quantity of antigen are considered important in this paradoxical reaction. MTX for example, given in vitro and in small doses may inhibit lymphocyte proliferation when given early after antigenic stimulation and stimulate the reaction when given later. In our patient, MTX may have acted under peculiar immunopathological conditions, and resulted therefore in stimulating rather than inhibiting immunocyte proliferation.

Six months after the cessation of treatment all neurological disturb-

ances disappeared in our patient and now only a slight mental retardation persists (IQ: 88.) This outcome of the illness seems very favourable as compared to that reported in the literature. This points to the possibility that our treatment schedule may be beneficial in the therapy of the paraneoplastic condition. To confirm this assumption, analysis of further cases is required.

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PROF. D. SCHULER

Tűzoltó u. 7

H-1094 Budapest IX, Hungary

Das Nicolau-Syndrom — eine Komplikation der Depot-Penicillin-Therapie

G. WEINMANN, L. SCHAEFER

Kinderklinik der Medizinischen Akademie Erfurt

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Es wird über 2 Patienten mit Nicolau-Syndrom berichtet, das nach zufälliger intraarterieller Injektion von Depot-Penicillin entstanden war. Diese bedrohliche Komplikation, die mit Schocksymptomatik, livider Verfärbung der Haut, anschließender Blasenbildung und Hautnekrosen sowie Querschnittslähmung oder Lähmung peripherer Nerven einhergeht, bedarf einer baldmöglichsten thrombolytischen Behandlung. Also Sofortmaßnahmen sind Schocktherapie und Heparinisierung angezeigt. Durch strenge Indikationstellung, besonders bei Säuglingen und Kleinkindern und Injektionen in den *M. vastus fibularis* unter entsprechenden Vorsichtsmaßnahmen ist die Gefahr des Auftretens dieser Nebenwirkung gering zu halten.

Neben häufigen allergischen Reaktionen werden bei der Behandlung mit Depot-Penicillin gelegentlich auch schwere, nicht allergische Komplikationen beobachtet. Letztere entstehen infolge unbeabsichtigter intravasaler Applikation bei der intramuskulären Anwendung von Depot-Penicillinen.

Nach intravenöser Injektion kommt es besonders beim Erwachsenen zum sogenannten Hoigné-Syndrom (Übersicht bei [7]), das charakterisiert ist durch zentralnervöse Erscheinungen wie Angst und Beklemmungsgefühl, akustische und optische Sensationen sowie motorische Unruhe und Bewußtseinstäubung, und das besonders bei schweren Herzleiden nicht selten zum Tod des Patienten führt. HOIGNÉ und KREBS [6] deuteten dieses Krankheitsbild als temporäre Hirnembolie.

Gelangt Depot-Penicillin in ein arterielles Gefäß, so führt dies zum

embolischen Verschluß der arteriellen Endstrombahn mit schwerer Schocksymptomatik. Wir fanden in der Literatur bisher 26 Fälle dieses als Nicolau-Syndrom bezeichneten Krankheitsbildes, das ausschließlich im Kindesalter, vor allem bei Säuglingen und Kleinkindern beobachtet wurde [2, 4, 9, 13, 14, Übersicht 3, 12]. Wegen der weit verbreiteten Anwendung von Depot-Penicillinen erschien es uns wichtig, an Hand von Erfahrungen bei zwei eigenen Patienten über diese ernststen Komplikationen bei der Penicillin-Therapie zu berichten.

I. Pat. R., H., 2 Mon., erhielt wegen eines Infektes der oberen Luftwege 600 000 E Depot-Penicillin links intragluteal injiziert. Eine Stunde später weißliche, dann livide Verfärbung beider Beine. Bei der Aufnahme in einem auswärtigen Kran-

kenhaus Schockzustand, nach erfolgreicher Schockbehandlung und Heparinisierung Weiterbehandlung in unserer Klinik.

Aufnahmebefund: Linke Gesäßhälfte und linkes Bein des Säuglings ödematös geschwollen und livide verfärbt. Livid-fleckige Verfärbungen auch am rechten Bein, am Skrotum und am Unterbauch bis in Nabelhöhe. Blutauflagerungen auf dem Stuhl. Fußpulse beiderseits tastbar; Sehnenreflexe seitengleich auslösbar, Fibularisparesis links.

Leukozytose von $13\,900/\text{mm}^3$ mit Linksverschiebung. Keine Hinweiszeichen für Verbrauchskoagulopathie. EMG*: Die Ableitung aus dem M. tibialis und M. fibularis links und dem M. gastrocnemius zeigte Veränderungen im Sinne von »Riesenspotentialen« mit einer Amplitude von 1000 Mikrovolt und einer Verlängerung der Aktionspotentialdauer auf 8–11 ms.

Diese Befunde sprechen für eine periphere neurogene Paresis im Bereich des M. fibularis.

Unter thrombolytischer Therapie mit Streptokinase Besserung der Befunde, kleinere nekrotische Hautbezirke heilten später nach Blasenbildung narbig ab. Nach einem halben Jahr Paresis des M. fibularis zurückgebildet.

2. Pat. H., M., 3 Mon., erhielt wegen Angina catarrhalis 600 000 E Depot-Penicillin rechts intragluteal. Nach 30 Minuten weißliche Verfä-

rbung des rechten Beines, das linke Bein livide verfärbt. In auswärtigem Krankenhaus Schockprophylaxe und Heparinisierung.

Bei Aufnahme in die Klinik war der Säugling blaß und berührungsempfindlich. Beide Beine, Gesäß und Unterbauch waren livid-fleckig verfärbt (Abb. 1). Rechter Fuß kühler als der linke. Fußpulse beiderseits tastbar. Schonhaltung beider Beine.

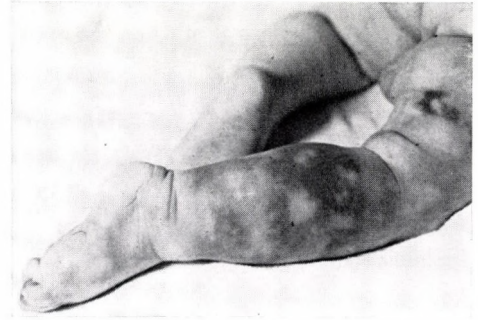


ABB. 1. Fall 2: 18 Stunden nach Injektion unregelmäßig livid verfärbte Hautbezirke mit girlandenförmiger Begrenzung.

Harnträufeln, klaffender Sphinkter ani.

EMG: Neuropathologische Veränderungen wie Lichtung des Musters, erhöhte Amplitude und Verlängerung der Aktionspotentialdauer, besonders im M. quadriceps links und rechts und im M. fibularis links und rechts vorhanden. Dabei Veränderungen im rechten M. fibularis am deutlichsten.

Leukozytose von $11\,100/\text{mm}^3$ mit Linksverschiebung. Kein Anhalt für Verbrauchskoagulopathie.

Nach 5-tägiger thrombolytischer Therapie vollständige Rückbildung

* Für die Überlassung der EMG-Befunde sei an dieser Stelle Herrn MR Doz. Dr. sc. med. W. HOFFMANN, Leiter der Abteilung für Entwicklungsfragen an der Kinderklinik der Medizinischen Akademie Erfurt gedankt.

der lividen Verfärbung des linken Beines und des Unterbauches. Am rechten Bein zunächst Blasenbildung (Abb. 2), dann allmählich narbige Abheilung nekrotischer Hautbezirke, nach einem Monat trockene Mumifizierung und Demarkierung der Zehen (Abb. 3). Nach 7 Wochen Spontanamputation der End- und Mittelfalangen im Bereich der 1. bis 3. Zehe und der Endphalangen der 4. bis 5. Zehe (Abb. 4). Bei Entlassung unverändert Blasen- und Mastdarm-lähmung sowie neurogene Parese beider Beine. Die Kontrolle des EMG-Befundes nach $2\frac{1}{2}$ Jahren ließ bei weitgehender Rückbildung der Pare-

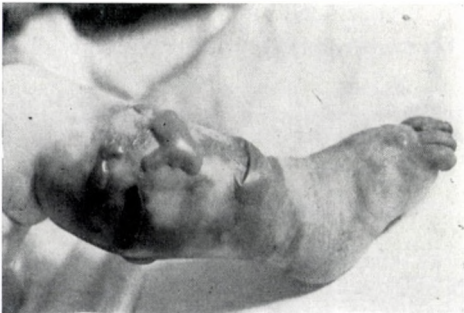


ABB. 2. Nach 2 Tagen Blasenbildung und Demarkierung im Zehenbereich



ABB. 3. Nach einem Monat Mumifizierung der Zehen und Spontanamputation, zunächst der 2. Zehe.



ABB. 4. Nach 7 Wochen Minderdurchblutung der Haut, narbige Abheilung, Spontanamputation der Grund- bzw. Mittelfalangen 1-5.

sen beider Beine keine Rarifizierung des Musters im M. quadriceps beiderseits erkennen. Es lag lediglich eine geringe Verlängerung der Aktionspotentialdauer vor. Im Bereich des M. tibialis und fibularis waren rechts deutliche Veränderungen mit eingestreuten Fibrillationen und verlängerter Aktionspotentialdauer vorhanden. Die Bestimmung der motorischen Nervenleitgeschwindigkeit des N. tibialis ergab links einen Normalwert von 65 m/s und rechts einen verminderten Wert von 35 m/s. Hier war das neuropathologische Bild, besonders im Bereich des rechten N. tibialis vorhanden.

Beide Patienten wiesen die unverwechselbaren Symptome des Nicolau-Syndroms auf [11]:

1. Plötzlich auftretende Ischaemie im Bereich der Injektionsstelle;
2. Anschließend schmerzhaftes, unregelmäßiges, bläulich-rotes Erythem mit Blasenbildung und Nekrosen;
3. in einigen Fällen schlaffe Lähmung der Extremität, in die injiziert wurde (Pat. 1), auch Querschnittslähmung (Pat. 2);

4. Blutstühle (Pat. I) und Makrohaematurie (nicht beobachtet);
5. Leukozytose.

DISKUSSION

Pathologisch-anatomische Untersuchungen [8, 16] haben ergeben, daß das Nicolau-Syndrom durch intraarterielle Medikamenteninjektion ausgelöst wird. Um die Penicillin-Kristalle, deren Größe dabei eine Rolle spielen soll, bilden sich Thromben, die den Gefäßverschluß bewirken. Die Ausdehnung der Hautveränderungen bis zum Nabel und zur Gegenseite kann so erklärt werden, daß durch einen hohen Injektionsdruck das Medikament entgegen dem Blutstrom bis in die Bauchorta und von dort in beide Beinarterien gelangt. Die neurologischen Ausfälle sind Folge der Embolisierung der Aortae lumbales und ihrer Spinaläste.

Das Auftreten des Nicolau-Syndroms erfordert sofortiges Handeln. Neben der Schocktherapie mit niedermolekularen Dextranen ist eine sofortige Heparinisierung angezeigt, um ein Fortschreiten der Thrombosierung zu verhindern. Wir schließen uns den Empfehlungen von DOMULA und Mitarbeitern [3] an, sofort Heparin in einer Dosierung von 300 IE/kg KG intravenös zu verabfolgen; dies sollte bereits durch den ambulant tätigen Arzt geschehen. Daraufhin ist das Kind in eine Klinik zu verlegen, in der eine thrombolytische Therapie möglich ist. Sollte sich die Verlegung aus irgendwelchen Gründen verzö-

gern, so ist die Heparinbehandlung durch i. v. Dauertropfinfusion in einer Dosierung von 25 E/kg KG/h fortzuführen.

Als wichtigste Gerinnungsuntersuchungen sind die Bestimmung der Thrombozyten, des Fibrinogens, der Thrombinzeit, des Quickwertes und der partiellen Thromboplastinzeit zu nennen. Eine Behandlung mit gefäßerweiternden Mitteln, die nicht während des Schockzustandes erfolgen sollte, versuchten wir bei einem der beiden Patienten, ohne einen Einfluß auf das Krankheitsgeschehen zu sehen.

Es wäre verfehlt, die Benzathin-Penicilline grundsätzlich in Mißkredit zu bringen, zumal das Nicolau-Syndrom vereinzelt auch nach Injektionen von wäßrigen [1] und öligen [10] Penicillinen beobachtet wurde. Andererseits stellt das Depot-Penicillin in der ambulanten Praxis ein wichtiges injizierbares Antibiotikum dar, das man gern dort anwendet, wo die zuverlässige orale Behandlung nicht gewährleistet ist.

Zur Vermeidung der beschriebenen Komplikationen möchten wir — in Übereinstimmung mit einigen Autoren — folgende Empfehlungen geben:

1. Strenge Indikationstellung, besonders im Säuglings- und Kleinkindalter;
2. der Arzt sollte die Injektion nach Möglichkeit selbst vornehmen; wenn in Ausnahmefällen eine erfahrene Schwester damit beauftragt wird, sollte sie über die Komplikationen informiert sein;
3. auf einen Aspirationsversuch darf nicht verzichtet werden; eine intravasale Injektion wird dadurch jedoch

nicht sicher vermieden, zumal sich während der Injektion besonders bei unruhigen Kinder die Lage der Kanüle verändern kann.

4. Nach VON HOCHSTETTER [5] empfiehlt sich, als Injektionsort der mittlere Abschnitt des M. vastus fibularis (lateraler Teil des M. quadriceps femoris); dort fehlen größere Gefäße, und außerdem wurde in diesem Bereich eine geringe Komplikationsrate ermittelt.

5. Bei wiederholten Injektionen ist der Injektionsort zu wechseln, da sich stark vascularisiertes Granulationsgewebe entwickeln kann (Injektionskarte nach SCHRÖTER [15]).

6. Um nachträgliche Kristalleinlagerungen zu vermeiden, ist ein »Verreiben« nach der Injektion zu unterlassen.

7. Da Komplikationen innerhalb der ersten 30 Minuten erkennbar werden, ist zu fordern, daß die Patienten in der ersten halben Stunde nach einer Depot-Penicillin-Injektion in der Nähe des Arztes gut beobachtet werden.

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Dr. med. G. WEINMANN
 Kinderklinik der Medizinischen
 Akademie
 DDR-50 Erfurt
 Am Schwemmbach 32a

Die Bedeutung des Serum-(Lysozym-) Spiegels im Kindesalter

Von

L. KARMAZSIN, Anikó MAKAY, F. ROZGONYI, Margit SZÖVETES und
Mária BALOGH

Kinderklinik und Mikrobiologisches Institut der Medizinischen Universität Debrecen

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Bei an verschiedenen Krankheiten leidenden Kindern im Alter zwischen 1 und 14 Jahren wurde die Serum-Lysozymaktivität registriert und mit Werten gesunder Kontrollpersonen verglichen. Leukämiekranken wurden ins Untersuchungsmaterial nicht aufgenommen. Die Erfahrungen sprechen dafür, daß sich die Enzymbestimmung: 1. zur Feststellung bzw. Ausschließung des bakteriellen Ursprungs von Prozessen mit ungeklärter Ätiologie, 2. zur Beurteilung des therapeutischen Effekts der Immunosuppressivbehandlung und 3. zur frühen Erkennung der während der Immunosuppressivtherapie auftretenden bakteriellen Infektionen eignet.

Dem von FLEMING [6, 7] vor mehr als 50 Jahren (1922) entdeckten Enzym Muramidase wurde nur neustens, im Laufe der mit dem komplexen Immunsystem des Organismus verbundenen Forschungen — und zwar angesichts seiner bakteriolytischen Aktivität — eine besondere Aufmerksamkeit gewidmet. Auf Empfehlung des Enzym-Komitees der Internationalen Gesellschaft für Biochemie wird das Enzym jetzt Lysozym genannt [5]. Durch das Enzym, ein Eiweiß mit 14–15 000 Molekulargewicht, werden die Mukopolysacchariden der Bakterienzellwand hydrolysiert und die Bakterien so mittels osmotischem Schock *in situ* abgetötet. Es beteiligt sich auch an der Verdauung von Bakterien, die durch ein anderes System bereits abgetötet worden sind, und spielt mitsamt anderen Enzymen seine wichtigste

Rolle in der letzten, entscheidenden, sog. »killing«-Phase der Phagozytose, in der das Abtöten der inkorporierten Bakterien stattfindet. Das Lysozym ist ein wichtiger Faktor der bakteriziden Plasmakapazität und übt auch auf die Granulopoese einen beschleunigenden Effekt aus [11].

Das Enzym kann in größeren Mengen in den Azurgranula, d. h. in den Lysosomen und Monozyten der neutrophilen Granulozyten und nach den neuesten Literaturangaben auch in den zur Ultraphagozytose fähigen Lymphozyten vorgefunden werden [1, 3, 13]. Das Freiwerden der lysosomalen Enzyme im Zytoplasma wirkt als ein stimulierender Faktor auf die Lymphozytentransformation ein. Die Lysosome der Granulozyten liegen tief im Zytoplasma. Das Freiwerden des Enzyms erfolgt nur im Falle der Schädigung, der

Zerstörung bzw. der funktionellen Stimulation der Zelle. Durch die Monozyten, deren Lysosome in der Nähe der Zelloberfläche liegen, wird das Enzym nicht nur produziert, sondern wahrscheinlich auch sekretiert [2]. Durch gewisse Agentien und Medikamente so z. B. Steroide, die auf die Membranstabilisation der Lysosome einwirken, wird das Eindringen der Lysosomwirkstoffe in die Phagozyten-Vakuolen verhindert. In diesen Fällen kann sich aber die intrazelluläre Bakterizidie (killing) nicht abspielen und die Bakterien persistieren an von den Antibiotika sicher geschützten Stellen [18]. Das Lysozym kann in niedrigen Konzentrationen im Normalserum und -plasma, in den Gewebemakrophagen, renalen tubulären Zellen, im Speichel, in den Tränen und in äußerst geringen Mengen auch im Harn nachgewiesen werden. Das Enzym gelangt vor allem dem Zerfall der Granulozyten und Monozyten zufolge in das Serum [10], so daß man in sämtlichen Fällen, in denen der Granulozytenumsatz beschleunigt ist, oder verletzbar Zellen in den Kreislauf gelangen oder sich die Phagozytentätigkeit der Mikroorganismen steigert, mit der Erhöhung der Enzymkonzentration im Serum rechnen kann.

Es ist seit einiger Zeit bekannt, daß der Kenntnis der Lysozym-Aktivität der Zellen, des Serums bzw. des Harns in der Diagnostik der Hämoblastosen, bei der Differenzierung der einzelnen Leukämietypen und auch bei der Beurteilung der Prognose sowie des Remissions-

grades dieser Krankheit eine nicht zu unterschätzende Bedeutung zukommt [2, 14]. Neuere Literaturdaten weisen auf die während der immunsuppressiven Therapie zustandekommenen Änderungen der Enzymaktivität hin [17].

Angesichts des Gesagten trachteten wir mittels enzymkinetischer Untersuchungen einen Parameter zu ermitteln, der sich zur Beurteilung der Wirksamkeit bzw. des membranstabilisierenden Effekts der immunsuppressiven Therapie sowie zur frühen Erkennung der während der Therapie auftretenden bakteriellen Infektionen eignet.

MATERIAL UND METHODIK

Die 96 Serumproben — die unser Untersuchungsmaterial bildeten — stammten von an verschiedenen Krankheiten leidenden Kindern im Alter zwischen 1 und 14 Jahren. Als gesunde Kontrolle wählten wir Kinder, die an unseren chirurgischen und endokrinologischen Abteilungen unter Behandlung standen.

Die akute bakterielle Infektion wurde mittels Bakterienzüchtung (Rachensekret, Blut, Harn) verifiziert; das Züchtungsergebnis war in der Mehrzahl der Fälle ein grampositiver Krankheitserreger. Bei Virusinfektionen stützten wir uns auf die klinischen Symptome, das Blutbild und auf die negativen bakteriellen Befunde. Unter den einer immunsuppressiven Therapie unterworfenen Patienten kamen keine Leukämiekranken vor. Die Nierenfunktionswerte der untersuchten Kinder waren normal.

Zur Untersuchung der Serum-Lysozymaktivität diente die von LITWACK [13] beschriebene turbidimetrische Methode. Angesichts der auffallenden Empfind-

lichkeit des *Micrococcus lysodeieticus* gegenüber die hydrolytische Aktivität des Lysozyms kam als Substrat dieser Organismus zur Anwendung.

Den zu unseren Untersuchungen verwendeten *Micrococcus lysodeieticus*-Stamm (M 15/65 ATCC No. 4968; Czechoslovak Collection of Microorganisms No. 169) stellte uns das Tschechoslowakische Stammzentrum zur Verfügung. Die Bewertung erfolgte mit dem Photometer Spectromom 202. Die der Transmission entsprechende Lysozymkonzentration wurde mit Hilfe von Standardkurven ausgerechnet und die Werte in $\mu\text{g/ml}$ Serum angegeben. Um eine dem optimalen Meßbereich entsprechende Transmission — zwischen 55% und 70% — zu erhalten, wurden die Verdünnungen unter Berücksichtigung dieses Parameters verfertigt. Das venöse Blut wurde in silikonierete sterile Röhren entnommen und das Serum, falls es nicht unverzüglich aufgearbeitet wurde, bei -20°C aufbewahrt. Lyphämische, hämolytische Seren ergeben kein zuverlässiges Ergebnis.

ERGEBNISSE, BESPRECHUNG

Die Ergebnisse (Durchschnittswerte, Standarddeviation, Signifikanz) veranschaulicht Tabelle I.

Im Laufe unsere Untersuchungen

wurden vor allem die als Grundlage dienenden Normalwerte bestimmt. Bei akuter bakterieller Infektion ließ sich eine signifikante Erhöhung der Serum-Lysozymaktivität feststellen. Der hohe Wert der SD (22,09) kann mit den extremen Streuungen erklärt werden.

Bei einem unserer an akuter Osteomyelitis leidenden Patienten betrug der Serum-Lysozymwert $126 \mu\text{g/ml}$. Durch Virusinfektionen wurde die Enzymaktivität nicht beeinflusst.

In der Gruppe der mit Immunsuppressiver Dauertherapie behandelten Patienten lag die Enzymaktivität erwartungsgemäß signifikant niedriger. Eine, nebst unveränderter immunsuppressiven Therapie zustandgekommene Steigerung der Serumaktivität — als Zeichen der bakteriellen Infektion — konnte nur in 5 Fällen registriert werden; die Angaben dieser 5 Kinder sind in Tabelle II dargestellt. Die Serumuntersuchungen fanden kurz nach Krankheitsbeginn statt, der Unterschied zwischen den Normalwerten und diesen Werten war aber auch dann augen-

TABELLE I
Ergebnisse
(Gesamtmaterial)

	Gruppierung des Krankmaterials	Anzahl der Fälle	Lysozym Durchschnittswert $\mu\text{g/ml}$	SD	P
1.	Normalkontrollen	20	25,07	7,05	—
2.	Akute bakterielle Infektion	36	42,21	22,09	<0,1 %
3.	Virusinfektion	10	25,46	7,27	—
4.	Steroid-Dauerbehandlung	20	16,43	4,86	<0,1 %

Vergleich mit Gruppe 1.

TABELLE II
5 Angaben von 5 Kindern

Name, Geschlecht	Diagnose	Therapie	Lysozym µg/ml	Bakterielle Infektion	Lysozym µg/ml
G. M. ♀	R. A.	Prednisolon	9,2	Sinusitis maxillaris	24,2
J. K. ♀	R. A.	Prednisolon	16,0	Tonsillitis catarrhalis	34,2
E. F. ♀	Sarkoidose	Prednisolon	13,8	Paronychia	43,8
E. N. ♂	R. A.	Tetracosactid Penicillamin	17,6	Abscessus regionis humeri	38,6
Zs. H. ♀	R. A.	Cyclophosphamid	16,0	Tonsillitis lacunaris	41,2
Durchschnitts- werte			14,5		36,4

fällig. Unsere Ergebnisse stimmen mit den Literaturdaten überein.

Unsere bisherigen Ergebnisse sprechen eindeutig dafür, daß sich die Untersuchung der Serum-Lysozymaktivität zur Feststellung bzw. Ausschließung des bakteriellen Hintergrunds von mit unsicheren Symptomen einhergehenden Prozessen ungeklärter Ätiologie eignet. Ihre Nützlichkeit beweisen auch unsere geringzahligen Fälle, da wir damit in den Besitz eines Parameters gelangen, welcher als ein Frühindikator der im Laufe der immunosuppressiven Behandlung auftretenden bakteriellen Infektionen eine nicht zu unterschätzende diagnostische Hilfe bietet.

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PROF. DR. L. KARMAZSIN
H-4012 Debrecen Pf. 32.

Oxygen therapy and massive pulmonary haemorrhage in newborn infants

M. FEKETE, M. HORVÁTH, L. BÁRDOSI, J. MESTYÁN

Department of Paediatrics and Institute of Pathology, University Medical School, Pécs

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A significant rise in the frequency of neonatal pulmonary haemorrhage was observed in the year when intensive oxygen therapy by CPAP and IPPV ventilation was started. To clarify the role of oxygen therapy the neonatal deaths occurring in two periods of different oxygen treatment were analysed and compared in respect of all clinical features which may be involved in the pathogenesis of pulmonary haemorrhage. In conclusion it is suggested that the local effect of oxygen is probably an additional but significant pathogenetic factor in the condition.

Massive pulmonary haemorrhage (MPH) is in general thought to be the cause of 1–10% of neonatal deaths. The pathogenesis of MPH is still controversial. Diagnosis *in vivo* can rarely be achieved in due time and no successful treatment has yet been reported. Perinatal asphyxia [4, 15, 17, 22, 27], hyaline membrane disease [27], lesions of the central nervous system [4, 14, 15], aspiration [11, 25], pneumonia [10, 21], hypothermia [6, 9], septicaemia [3, 17], congenital heart malformations [3, 4, 16, 22], coagulation defects [1, 12, 26], transfusion and infusion therapy [22], oxygen- and respirator therapy [7, 20, 23, 24, 28] had all been suggested as causative or at least predisposing factors. Despite the obvious interrelationships existing between suspected mechanisms, the long list truly reflects the lack of solid knowledge. Nevertheless the recent theory of Adamson et al. [2] and Cole et al. [13] seems to

synthesize all the former explanations by suggesting that hypoxia and acidosis trigger a vicious circle leading to haemorrhagic pulmonary oedema.

The average frequency of MPH in our patient material was 4.5% (range, 1.0–9.2) in the six-year period 1967 to 1972 [17]. A frequency of 8.2% (14 out of 170 neonatal deaths) was recorded in 1973, and in 1974, when CPAP and respirator (IPPV) therapy attained wide use in our special care baby unit, a significant ($\chi^2 = 4.66$; $p < 0.05$) rise was noted (17.3%, i.e. 28 out of 162 deaths). As the role of high FiO_2 in causing MPH had been suggested [7, 20, 23, 28] we have tested this possibility in a retrospective clinical study.

METHODS

Newborn infants who died during two different periods of oxygen therapy, i. e. from 1st January to 31st December,

1973, and from 1st January to 31st December, 1974, were studied. All data which may have been related to the frequency of MPH were analysed and compared in the two groups of neonates (170/1973 and 162/1974). Postmortem examination was performed on all babies who succumbed. Autopsy reports were reviewed and MPH cases selected on the basis of gross and histologic findings. No distinction was made between interstitial and intraalveolar haemorrhage.

Clinical data listed below were compared in the two populations of patients: 1) pathologic pregnancy; 2) delivery by Caesarean section or breech presentation and/or forceps; 3) perinatal asphyxia; 4) hypothermia on admission; 5) birth weight; 6) gestational age; 7) intrauterine nutrition (dysmaturity); 8) infusion therapy; 9) blood transfusion therapy; 10) oxygen therapy; 11) postmortem finding. For statistical analysis, the 2K contingency tables were used with χ^2 test, except for comparing oxygen therapy.

Definitions. *Perinatal asphyxia:* the baby needed resuscitation at birth; the five minute Apgar score was less than 7; on admission IRDS or postasphyxic syndrome was diagnosed on the basis of the acid-base status, X-ray and/or clinical signs.

Hypothermia: rectal temperature below 36 °C on admission.

Infusion therapy: 5–10% glucose +4.2% sodium bicarbonate infusion by Braun–Melsungen perfusor, maintenance volume per day.

Blood transfusion therapy: 10–15 ml/kg ACD blood not older than 72 hours, by Braun–Melsungen perfusor.

Oxygen therapy: $\text{FiO}_2 \geq 40\%$ via head-box; CPAP breathing $\text{FiO}_2 \geq 40\%$ with a pressure of 5–12 H_2O cm; IPPV ventilation with 60–100% oxygen by Bennett PR-2 respirator. Duration of oxygen therapy was expressed in days.

Postmortem finding: gross finding which was thought to be the primary cause of death.

RESULTS

Results are shown on Figs 1 and 2, and in Tables I to III. It can be seen that the two populations studied were remarkably similar ($p > 0.05$ — $p > 0.3$) in respect of all data compared except for oxygen therapy (Table II). Whilst in 1973, 140 patients received oxygen therapy via head-box for 1.9 days, in 1974, 120 babies were treated in the same way for 2.5 days on the average, 80 infants received CPAP ventilation and 23 babies had IPPV for 1.6 and 1.3 days, respectively. The difference in intensity and duration of oxygen therapy during the two periods is obvious.

In 1973, 7.6% (13 infants) and in 1974, 12.9% (21 infants) of the cases had blood transfusions within 24 hours prior to death. The difference was significant statistically ($p < 0.05$). Furthermore, nearly two thirds of the infants could only be classified from the point of view of intrauterine nutrition and development. This was due partly to the gestational age of a number of patients being unknown and partly to the considerable number of infants with a gestational age of less than 28 weeks (33 in 1973 and 30 in 1974).

In 1974, the number of those with subtotal pulmonary atelectasis as a single autopsy finding decreased considerably, while the number of infants with atelectasis associated with intraventricular or subependymal haemorrhage increased significantly ($p < 0.05$). The frequency of other kinds

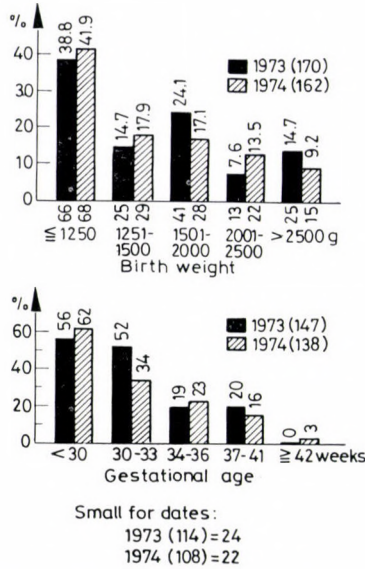


FIG. 1 Birth weight and gestational age of newborn infants who died in 1973 and 1974. Top: percentage values; bottom: number of babies. Only the number of infants is given in the lower part of the figure (gestational age distribution).

of extracranial and extrapulmonary haemorrhage remained unchanged (14 in 1973 and 16 in 1974).

On Table III, clinical data of MPH cases are shown. It can be seen that except oxygen therapy, the various parameters showed a

similar frequency in the two groups of infants. The duration of oxygen therapy calculated per patient was significantly ($\chi^2 = 5.64$; $p < 0.02$) longer in 1974 than in 1973. Similarly as that for all deaths in the two test periods, a relative rise in the frequency

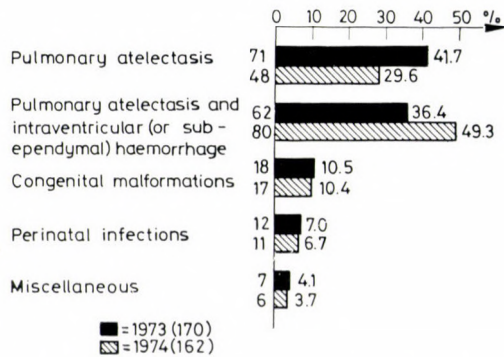


FIG. 2 Gross postmortem findings in newborn infants who died during the two periods. Right: percentage values; left: number of infants.

TABLE I
Clinical data of newborn infants who died in 1973/1974

	1973		1974	
	No.	per cent	No.	per cent
<i>Number of patients</i>	170	100	162	100
<i>Pathological pregnancy</i>	74	43.6	63	38.9
<i>Delivery by Caesarean section, or breech presentation or forceps</i>	34	20.0	31	19.2
<i>Perinatal asphyxia</i>	121	71.1	118	72.8
<i>Hypothermia on admission</i>				
< 34 °C	87	51.1	84	51.8
34.0–35.0 °C	15	8.8	23	14.1
35.1–36.0 °C	37	21.7	31	19.1
<i>Infusion therapy</i>	151	88.8	149	91.9
within 24 hours prior to death	142	83.5	142	87.6
<i>Blood transfusion therapy</i>	39	22.9	55	33.9
within 24 hours prior to death (*)	13	7.6	21	12.9

*p < 0.05

TABLE II
Oxygen therapy in newborn infants who died in 1973/1974

Duration of oxygen therapy (day)	Head-box — $\text{FiO}_2 \geq 40\%$		CPAP — $\text{FiO}_2 \geq 40\%$		IPPV — 60–100% oxygen	
	1973	1974	1973	1974	1973	1974
1	82	54	—	50	—	18
2	29	20	—	21	—	7
3	10	11	—	10	—	3
4	6	14	—	2	—	—
5	6	7	—	2	—	—
6	7	14	—	—	—	—

1973 — 1.9 days/patient — Head-box (140 patients)
 1974 — 2.5 days/patient — Head-box (120 patients)
 1.6 days/patient — CPAP (85 patients)
 1.3 days/patient — IPPV (23 patients)

TABLE III
Clinical data of newborn infants who died of MPH

	1973	1974
Number of patients	14/170	28/162
Perinatal asphyxia	9/14	20/28
Prematurity	12/14	27/28
Small for dates	3/14	5/28
Hypothermia	11/14	23/28
Respiratory distress syndrome	6/14	15/28
Postasphyxial syndrome	4/14	8/28
Perinatal infection, septicaemia	1/14	1/28
Rhesus haemolytic disease	1/14	1/28
Congenital heart malformation	0/14	0/28
Infusion therapy	14/14	27/28
Blood transfusion therapy	4/14	10/28
Oxygen therapy		
Head-box $\text{FiO}_2 \geq 40\%$ (days)	30/14	40/28
CPAP $\text{FiO}_2 \geq 40\%$ (days)	0/14	38/28
IPPV 60–100 O_2 (days)	0/14	11/28
<i>Postmortem findings</i>		
Pulmonary atelectasis	8/14	7/28
Pulmonary atelectasis associated with intraventricular or subependymal haemorrhage	4/14	19/28
Septicaemia	1/14	1/28
Rhesus haemolytic disease	1/14	1/28
Hyaline membrane (histology)	3/14	5/28

of intraventricular and subependymal haemorrhage could be observed in 1974 among MPH patients too.

DISCUSSION

A causal relationship between oxygen therapy and MPH had first been suggested by Shanklin and Wolfson [28] on the basis of clinical observations. Kistler et al. [19] observed damage of pulmonary capillary endothelium in subjects breathing high concentration oxygen which favours transudation and oedema formation. Increased capillary pressure due to left ventricular failure has also been suggested to have a role in the capillary endothelial damage and disseminated intravascular coagulation

was found in rats kept in 100% oxygen [31]. Boothby and deSa [7] concluded that the increased frequency of pulmonary haemorrhage was probably related to the use of oxygen at high concentration and $\text{FiO}_2 > 80\%$ for longer than 24 hours may be dangerous. Recently Kotas et al. [20] have reported on extensive intra-alveolar and interstitial pulmonary haemorrhage in newborn animals evoked by high environmental oxygen concentrations. They emphasized the role of reduced alveolar collateral ventilation due to pulmonary immaturity and also of the higher absorption coefficient of oxygen in comparison with that of air.

In spite of evidence of the role of oxygen in causing or predisposing to MPH, the argument could not be

rejected that the grave pathological condition *per se* would lead to MPH. If this is correct, MPH should be considered a 'preterminal syndrome'. After all, in the light of the work of Adamson et al. [2] and Cole et al. [13] it seems much more likely that cardiorespiratory and circulatory changes caused by asphyxia play the primary role and the local effect of oxygen is probably only one, though not an insignificant, additional factor.

The results of the present study support the probability of a causal relationship of intensive oxygen therapy and pulmonary haemorrhage. The two compared populations of newborn infants were closely similar in respect of all parameters but oxygen therapy. The fact should, however, be emphasized that the severity and duration of asphyxia and the effect of treatment could not be evaluated in this study. For this reason the pathogenetic role of oxygen therapy can only be assumed but not regarded as proven.

The rise in frequency of intraventricular and subependymal haemorrhages in the total population studied and among babies with MPH in the year of intensive oxygen therapy is puzzling. The effect on cerebral circulation of a hyperoxyemia or of CPAP and IPPV has not so far been elucidated. It may, however, be supposed that CPAP with a pressure of less than 12 H₂O cm does not reduce cardiac output in general, but can be dangerous in patients with hypovolaemia and/or heart failure [18].

The risks of oxygen therapy are well known. The present results draw attention to the possibility of a less widely known complication and emphasize the need for a strict indication and control of oxygen administration.

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DR. M. FEKETE

József A. u. 11.

H-7623 Pécs, Hungary

A simple score to facilitate detection of congenital disorders

K. MÉHES

County Hospital, Győr, Hungary

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A simple score has been constructed to facilitate the selection of apparently normal newborns at risk of hidden congenital disorders. Components of the score are family history of previous malformations, stillbirth or infantile death of unknown origin, intrauterine growth retardation (2 points each), and six minor malformations: antimongoloid palpebral slant, hypertelorism, preauricular fistula, simian crease, mammillary and hallucal abnormality (1 point each).

Out of 1000 consecutive neonates screened with the method 28 scored 3 or more, in 6 of whom hidden congenital abnormalities were discovered at later reexamination. At the same time only 2 hidden defects were found in the children with a neonatal score of 2 or less. Although the follow-up was incomplete, the results suggest that the score is useful in selecting infants for more complicated clinical and genetic investigations.

About 5 to 6% of live-born neonates are affected by congenital abnormalities with completely or partly genetic background [21]. Half of them show major malformations or characteristic symptoms, which makes early diagnosis easy. In about 2 to 3% of newborn infants there are, however, no obvious signs of an anomaly, and the hidden morphological or functional disorder cannot be suspected. The most effective method to prevent irreversible somatic and mental damage in such cases is the screening of unselected neonatal populations. Indeed, biochemical mass screening has saved, for example, hundreds of phenylketonuric and galactosaemic children all over the world, and serial cytogenetic investigations of unselected newborn infants

are of great scientific value. In spite of this considerable progress the available biochemical and cytogenetic screening methods can detect only a limited number of abnormal conditions, and except for phenylketonuria screening, the cost of the required technical and financial investment makes these methods impracticable for mass screening purposes.

Hence, there is still need to refine the physical examination of the newborn infant. Careful observation of minor malformations offers a possibility to increase the effectiveness of early diagnosis of congenital disorders. These small morphological anomalies are in themselves clinically insignificant, but many studies suggest that they are positively correlated with significant fetal pathology [9, 23].

Marden et al. in 1964 [13] concluded that 'the detection of multiple minor anomalies may be of value alerting the physician to the existence of an obscure major abnormality or the recognition of a specific multiple anomaly syndrome'. Since then this idea has been firmly established but the principles of utilizing the minor birth defects in clinical diagnosis has not yet been put into practice.

In the last few years we have attempted to elaborate an effective but simple screening method for selected minor malformations.

The incidence of minor malformations was on the average 0.21 per neonate in full-term, well-nourished infants, and 0.76 in small-for-gestational age (SGA) newborns [16]. This high frequency of some minor defects in SGA-infants was also observed by Drillien (4), Crichton et al. [3], and Hook et al. [11].

Multiple minor malformations represent a high risk of hidden major anomalies or pathological conditions [16]. Out of 110 apparently healthy newborns with two or more minor malformations, 10 proved to have severe disorders at reexamination after the age of 1 year [14]. Since multiple minor anomalies are more common in SGA-babies, who are also known to be frequently affected by major malformations [2, 4, 14], the intrauterine malnourished newborn is considered to be at high risk for congenital abnormalities.

As to single minor malformations, several features such as a peculiar face and deformity of the ears, cannot

be defined precisely, which makes the diagnosis rather subjective, as shown by a Hungarian collaborative study of 10 203 newborn infants. Some other features tend to disappear with age. For example, in a follow-up study we observed that 74% of low-set ears and 79% of high arched palate found in the newborn could not be seen after the age of 1 year [19]. These anomalies may be typical of certain syndromes, but are in themselves of little diagnostic value. In addition, some minor defects, previously regarded as important signs, are not closely correlated with any congenital disorder. This seems to be the case with the single umbilical artery [1, 6], etc. At the same time, there are some well-defined minor malformations which in themselves may indicate a certain risk of further hidden abnormalities.

Ocular hypertelorism is a characteristic symptom of at least 30 syndromes. Its recognition by inspection is often unreliable; exact measurement is necessary to avoid a false positive scoring [5, 18].

Antimongoloid (downward) slant of palpebral fissures proved to be a fairly consistent feature throughout childhood. Its distinct form occurs in 1% of neonates, and it often determines the peculiar appearance of the face and is characteristic of some special conditions.

Preauricular fistulae may be inherited in some families. They are rare in normal newborns. For example, no preauricular fistula was seen in 11 203 normal neonates. Its

appearance is often associated with other disorders.

Mammillary abnormality. Widely set, too small, absent or accessory nipples may call attention to several syndromes, and especially to disorders of the kidneys and the urinary tract [7, 8].

The *simian crease* shows a fairly close correlation with a variety of congenital anomalies. This is valid for both genetically determined [15] and environmental diseases [10].

Abnormalities of the hallux should make one to look for several malformation syndromes and for some disorders of mineral metabolism.

On the basis of these earlier observations we constructed a simple scoring system. The score is based besides six important and easily recognizable minor malformations, on intrauterine growth retardation and the family history. The first experiences with the score are presented in this study.

MATERIAL AND METHODS

A total of 1019 newborn infants were examined within the first 48 hours after birth. Neonates with major malformations were excluded, and only 1000 apparently normal babies were involved, irrespective of birth weight. The examinations were carried out by doctors not trained in genetics. They only received a list of the following scoring criteria.

Family history: malformation, known hereditary disease, infantile death or stillbirth of unknown origin among the siblings and parents of the index subject.

Intrauterine growth retardation: birth

weight and length under the 10-percentile curve of the Hungarian standard.

Antimongoloid slant: the outer canthi fall below the line of the inner ones, as judged by the edge of a plastic ruler laid across the two inner canthi.

Hypertelorism of the eyes: the distance of the inner canthi is longer than 8% of the head circumference measured at the same level [18].

Preauricular fistula can be detected by mere inspection.

Mammillary abnormalities: accessory, hypoplastic or absent nipples, or those lying widely apart, at a distance measuring 28% or more of the chest circumference [18, 20].

Simian crease: only classic, uninterrupted lines qualified without bridge formation.

Hallucal abnormalities: broad, dorso-flected and short halluces, unusually wide gap between the 1st and 2nd toes.

Quantitation of the score was given as follows:

Positive family history . . .	2 points
SGA-infant	2 points
Antimongoloid slant	1 point
Ocular hypertelorism . . .	1 point
Preauricular fistula	1 point
Mammillary abnormality . .	1 point
Simian crease	1 point
Hallucal abnormality	1 point

All the infants who scored 3 or more were controlled at home by a district nurse, and invited to a reexamination at the age of 3 to 12 months. On this occasion a detailed paediatric examination was supplemented with cardiologic, radiologic, metabolic and karyotype investigations.

The infants with a score under 3 were observed at home, and in case of any illness were referred to our department. A detailed reexamination could, however, be carried out only in a representative sample of 58 babies with a score of 2, and 130 with a score 1 or 0.

RESULTS

Of the 1000 newborns 747 had a normal family history, and no intrauterine malnutrition or any minor malformation. One minor anomaly occurred in 59 cases (Table I). 166 infants scored 2 points mainly because of a positive family history or intrauterine malnutrition. In 28 babies the score was 3 or more. As demonstrated by the figures, a pos-

itive family history and intrauterine growth retardation were the commonest features. The frequency of the six minor malformations examined was in accordance with data of previous studies.

The findings at reexamination are summarized in Table II. In spite of the small number of positive cases, the figures demonstrate a significantly higher frequency of hidden congenital disorders in infants scoring

TABLE I

Score values and distribution of symptoms in 1000 apparently normal infants at birth

	Score value						Total frequency	
	0	1	2	3	4	5	No.	Per cent
Number of infants	747	59	166	17	9	2	1000	100.0
Positive family history			85	13	8	1	107	10.7
Small-for-gestational age			78	6	3	2	89	8.9
Antimongoloid palpebral slant		1	0	1	2	1	5	0.5
Hypertelorism		20	2	4	4	1	31	3.1
Preauricular fistula		0	0	0	0	1	1	0.1
Mamillary abnormality		15	1	3	4	0	23	2.3
Simian crease		22	5	4	4	1	36	3.6
Hallucal abnormality		1	0	1	0	0	2	0.2

TABLE II

Results of reexamination of children with different neonatal score values

Score value	No. of infants	Reexamined No.	Congenital disorder No.
3 or more	28	27	6
			$p < 0.01$
2	166	58	1
1	59	28	0
0	747	102	1
Total	1000	215	8

3 or more. The small number of hidden major defects in children with 2 and 1 score values suggests that a positive family history, intrauterine malnutrition or a single minor malformation alone is of little alerting value, but the combination of these should carefully be considered. A low proportion of unaffected children with a score of 0 could be reexamined. Still, all the children seen as newborns live in the district of our hospital, and more of them has been referred to us with a congenital disorder.

The reexamination revealed a congenital defect in 8 infants who at birth seemed to be normal. The following 6 infants scored 3 or more at neonatal screening.

Case 1. A boy born after 40 weeks of gestation. Birth weight, 2010 g; length, 46 cm. Both halluces were conspicuously small and dorsoflexed. Score: 3. No problem had arisen until the age of 6 weeks, thereafter he failed to thrive, signs of rickets developed. Reexamination at the age of 4 months revealed a late infantile type hypophosphatasia.

Case 2. Male infant. Birth weight, 3300 g, length, 53 cm. Fifth pregnancy of the mother, the fourth resulted in stillbirth of unknown cause. The newborn had bilateral simian creases and hypertelorism. Score: 4. He was symptomless and thrived well until the age of 1 year, when a 47, XXY karyotype (Klinefelter's syndrome) was discovered.

Case 3. In a SGA male neonate (gestational age, 39 weeks; birth weight, 2100 g; length, 45 cm) anti-

mongoloid slant of the palpebral fissures and a simian crease were noticed. Score: 4. From the fifth week of life he had been admitted several times due to recurrent pneumonias and failure to thrive. Mucoviscidosis was diagnosed and confirmed by autopsy when he died at the age of 6 months.

Case 4. Male neonate. Gestational age, 41 weeks; birth weight, 2350 g; length, 46 cm. He had antimongoloid palpebral slant, hypertelorism and a preauricular fistula on the left side. Score: 5. He was symptomless in the first weeks, but later jaundice developed. Congenital biliary aplasia was detected.

Case 5. Full-term, well-nourished male infant. He was the third child of his parents, the first died of meningococce. He had a small accessory nipple on the right side. Score: 3. At reexamination, pyuria was found. Radiologic investigation revealed bilateral dilatation of the ureters and vesicorenal reflux at the age of 7 months.

Case 6. SGA newborn girl. Gestational age, about 37 weeks. Birth weight, 1800 g; length 43 cm. She had wide set nipples (intermammary index = 30.1%). Score: 3. She thrived well. At the age of 3 months she was referred to our department with a history of prolonged fever. Pyelonephritis and hydronephrosis on the right side were diagnosed.

Two infants with neonatal scores 2 and 0 respectively, appeared to have hidden malformations.

Case 7. SGA female newborn (gestational age, 39 weeks; birth weight,

2360 g; length, 47 cm). Score: 2. Symptomless at birth. A systolic murmur was noticed in the third week; later a ventricular septal defect was diagnosed.

Case 8. Well-nourished female neonate. Score: 0. At the age of 10 months she had prolonged fever and pyuria. X-rays revealed bilateral vesicoureteral reflux and hypoplastic left kidney.

Since this study deals with apparently healthy newborn infants, only the frequency of hidden disorders is reported. However, while screening the 1000 apparently normal neonates, 19 infants were found with various congenital diseases diagnosed in the early neonatal period. These included 2 chromosome abnormalities (Down syndrome), 1 enzymopathy (histidinemia) and 16 gross malformations. Thus, the sum of congenital disorders was 27 in 1019 neonates, i. e. 2.65%, which is in good agreement with the international statistics excluding blood group incompatibilities and mental retardation.

DISCUSSION

The aim of the present study was to design a simple score system to facilitate the early detection of congenital disorders in an apparently normal newborn population. A basic requirement was that unskilled observers should be able to carry out the screening quickly and without extra cost in every neonatal unit. On the basis of previous studies six minor but distinct malformations were thought to be important clues

in the detection of major defects. In addition, the family history and intrauterine growth rate were chosen to contribute to the scoring system. Selection of these criteria and their relative value expressed in points was arbitrary. Previous malformations or infantile death in the family and immaturity seemed, however, to be so strongly correlated with genetic disorders that they deserved special consideration. Combination of these phenomena with minor malformations and multiple minor malformations in themselves were also supposed to indicate a high risk for hidden major abnormalities. Babies with a score of 3 or more were regarded as high risk, and an effort was made to re-examine infants with 3 or more points. Only part of the babies scoring 2, 1 and 0 could be re-examined; the absolute number of infants followed-up in this group was, however, still 188, i.e. six times that of the children scoring 3 or more.

The results clearly suggest that newborn infants with a score of 3 or more are at high risk for hidden abnormalities. At reexamination 6 out of 27 with scores 3 or more were found to be affected by some congenital disorder, while this ratio was only 2 out of 188 among the children scoring 2 or less. Since only about 3% of all the apparently normal neonates scored 3 or more, the scoring system seems to be suitable for the selection of infants at risk.

We do not know exactly how many cases with congenital abnormalities have been overlooked, yet based on

the present results the number of such infants was probably negligible.

The individual minor malformations included in the score are by no means pathognomonic for a given group of abnormalities or syndromes. Chromosome anomalies, inborn errors of metabolism and organ malformations were all represented among the disorders discovered. The majority was clearly of genetic origin, but teratogenic abnormalities might have also been involved.

In some of the children scoring 3 or more, certain disorders may not have been recognized. Long term follow-up of such patients seems therefore justified. This is all the more warranted since in earlier studies the number of minor birth defects was positively correlated with idiopathic mental retardation [22], with hyperkinetic, aggressive and intractable behaviour [24] and even with leukaemia [12].

An advantage of the score is its simplicity. It can easily be combined with the first routine examination of the newborn, thus practically all neonates can be screened. The efficiency of the programme was 100%, the quality of the work of the different observers could be checked only indirectly, but in a previous study the frequency of clinically recognizable autosomal anomalies observed by doctors not specially trained correlated well with the data of cytogenetic screening programmes [17].

A further advantage of the screening was that it stimulated the observers to carry out a more careful physical examination of the infants.

This resulted in more exact recording of major abnormalities and also helped to detect some more minor malformations not included in the score.

If our results will be confirmed by a larger prospective study, this or a similar simple score might help in selecting the newborns at risk. This would be especially beneficial in countries where facilities for mass screening employing sophisticated genetical and biochemical investigations are not available.

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Dr. K. MÉHESES
 County Hospital
 Pf. 92.
 H-9002 Győr, Hungary

Geburtstraumatische Parese des Nervus Phrenicus

Von

K. MENZEL, W. GENSSLER, E. GOTTSCHALK, M. LINKE, B. TÖPKE

Kinderklinik und Chirurgische Klinik der Medizinischen Akademie Erfurt

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Geburtstraumatische Zwerchfellparesen bei Neugeborenen treten vorzugsweise nach komplizierten Geburten auf. In der Mehrzahl der Fälle sind sie mit einer oberen bzw. totalen Plexuslähmung kombiniert. Im Gegensatz zu pleuroperitonealen Hernien und kongenitalen Zwerchfellmuskelhypoplasien wird die rechte Seite bevorzugt. In schweren Fällen gilt heute der frühzeitige Entschluß zur transthorakalen Zwerchfellraffung als *Conditio sine qua non*. Hierbei geben die Autoren der offenen Zwerchfellplifikation gegenüber der geschlossenen Faltung den Vorzug. Fünf eigene Beobachtungen werden dargestellt.

Die geburtstraumatische Phrenicusparese tritt vorzugsweise nach komplizierten Geburten (Forceps, Steißlage) auf. Erstmals beschrieben wurde diese seltene, auf einer mechanischen Läsion oder einem Ausriß der Nervenwurzeln C3–C5 beruhende Geburtsschädigung 1921 durch KOFFERATH [8]. RICHARD und Mitarb. [10] fanden bei Zusammenstellung der bis 1957 publizierten 74 Fälle bei 53 eine Kombination der Phrenicusparese mit einer oberen bzw. totalen Plexuslähmung; bei 21 Erkrankten wurde die Zwerchfell-Lähmung isoliert beobachtet. Im Gegensatz zu pleuroperitonealen Hernien und kongenitalen Muskelhypoplasien des Diaphragmas tritt die geburtstraumatische Phrenicusparese vorwiegend rechtsseitig auf [6, 10, 12].

Die ersten Symptome der Phrenicusparese, zumeist Dys- und Tachy-

pnoe sowie Cyanose sind in 54% der Fälle bereits am 1., bei 19% der Patienten jedoch erst nach dem 10. Lebenstag zu beobachten [10]. Bei ausschließlich konservativ behandelten Zwerchfell-Lähmungen liegt die Mortalität zwischen 20 und 25% [7, 10]. Eine wesentliche Senkung der Sterblichkeit wurde durch die operative Zwerchfellraffung erreicht [2, 11, 12].

Anhand der Darstellung von 5 eigenen Beobachtungen sei nachfolgend auf die Problematik der geburtstraumatischen Phrenicusparese eingegangen.

EIGENE BEOBACHTUNGEN

Im Zeitraum vom 1. 3. 1974 bis zum 29. 2. 1976 konnten an der Kinderklinik der Medizinischen Akademie Erfurt unter 1365 behandelten Neugeborenen 5 Patienten mit einer

Zwerchfell-Lähmung beobachtet werden. Bei 3 dieser Kinder bestand gleichzeitig eine obere Plexusparese vom Typ Erb-Duchenne, die bereits unmittelbar postnatal diagnostiziert wurde. Die bei 4 Patienten rechtsseitige und in einem Fall linksseitige Lähmung des Diaphragmas wurde in der Postnatalperiode jeweils durch frühzeitig durchgeführte Röntgenuntersuchungen erkannt. Während sich die Plexusparese bereits bis zum Ende des ersten Lebensmonats zurückgebildet hatte, dauerte die Reparation der Phrenicusparese bei 3 Säuglingen mehrere Monate. Bei 2 Patienten war auf Grund zunehmender respiratorischer Insuffizienz die operative Zwerchfellraffung erforderlich.

Fall 1: M. H., geb. 31. 3. 74. Erstes Kind gesunder Eltern. Geburt aus II. hinterer Hinterhauptslage durch Forceps aus Beckeneingang. Geburtsgewicht 3250 g, Länge 53 cm. Post partum leicht verzögertes Einsetzen der Atmung. Leichte schlaaffe Parese der linken Schulter und Oberarmmuskulatur. Pulmo und Cor klinisch o. B.

Röntgenaufnahme des Thorax (2. Lebenstag): Linkes Zwerchfell $1\frac{1}{2}$ ICR höher stehend als rechtes (Abb. 1). Mediastinum, Herz und Lunge unauffällig.

Ab 8. Lebenstag zunehmende Cyanose bei Nahrungsaufnahme und Belastung. Röntgenologisch linkes Diaphragma $2\frac{1}{2}$ ICR höher stehend als

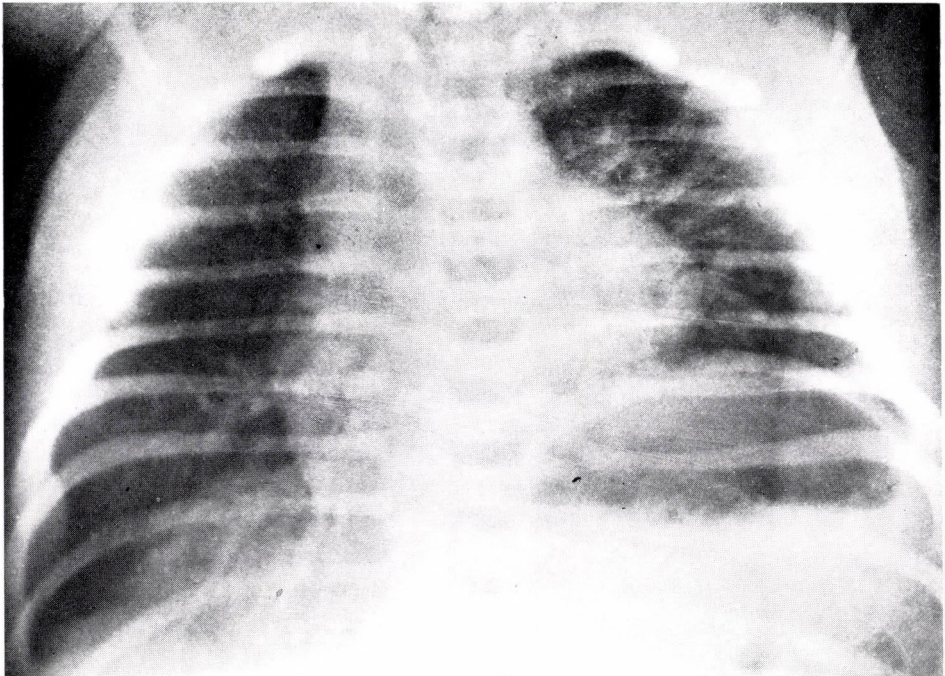


ABB. 1. Röntgen-Aufnahme des Thorax im a. p.-Strahlengang. 2. Lebenstag. Zwerchfellhochstand links

rechtes; vermehrt streifig-retikuläre Zeichnung der linken Lunge.

Bis 24. Lebenstag zunehmende respiratorische Insuffizienz mit paradoxer Atmung, Nahrungsaufnahme nur noch über Sonde möglich. Thorax-Röntgenbefund: Unveränderter Zwerchfellstand, Dystelektase im linken Oberlappen (Abb. 2). 34. Lebenstag: Röntgenologische Zunahme der Relaxation und der paradoxen Beweglichkeit des Zwerchfells (Abb. 3), Verlagerung des Herzens nach rechts, Dystelektasen beiderseits. Säure-Basen-Status während des gesamten stationären Aufenthaltes ausgeglichen.

Aufgrund der progredienten respiratorischen Insuffizienz und der pulmonalen Veränderungen ist die Indi-

kation zum operativen Vorgehen gegeben. Der Eingriff erfolgt durch postero-laterale Thorakotomie im Sinne der von REITTER und KONRAD [9] empfohlenen offenen Doppelung des, weit relaxierten Diaphragmas. Nach Abschluß des Eingriffes kommt es zur raschen Stabilisierung des Gesamtzustandes und zu völliger Rückbildung der respiratorischen Insuffizienz innerhalb der nächsten 48 Stunden. Atemphasengesteuerte Röntgenaufnahmen des Thorax schließen bei mittelständigem Mediastinum und guter Lungenbelüftung paradoxe Zwerchfellbewegungen aus.

Eine ambulante Kontrolle im Alter von 10 Monaten zeigt völlig altersgerechte statische und geistige Entwick-

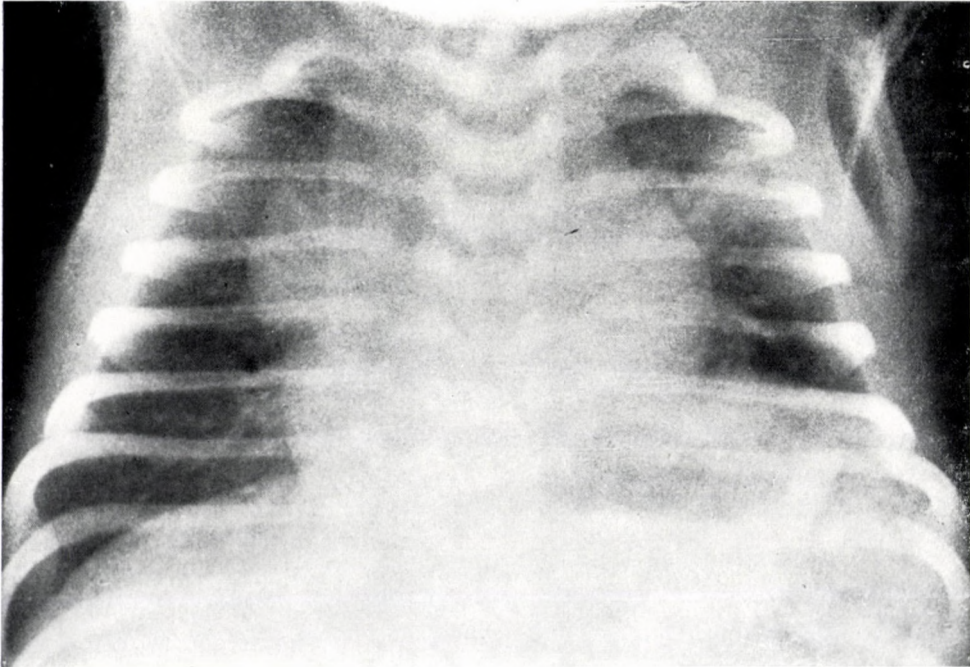


ABB. 2. Thoraxaufnahme 24. Lebenstag. Zwerchfellhochstand links unverändert. Dystelektase des linken Oberfeldes. Zunehmende Thymushyperplasie.

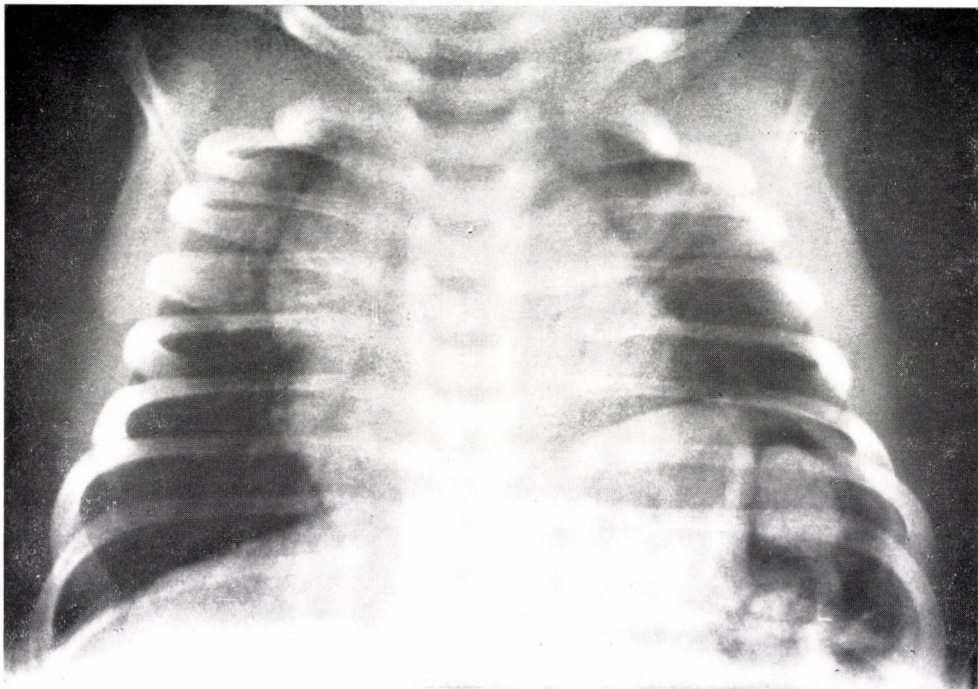


ABB. 3. Thoraxaufnahme 34. Lebenstag. Zwerchfell auf der linken Seite jetzt nahezu 3 ICR höher stehend als rechts. Zunahme der Dystelektase des linken Oberfelds. Ange deutete Dystelektase des rechten Oberfeldes. Beginnende Verlagerung des Herzens nach rechts.

lung bei einem röntgenologisch normalen Thoraxbefund (Abb. 4). Die Erbsche Parese hatte sich bereits bis zum Ende der 4. Lebenswoche zurückgebildet.

Fall 2: N. L., geb. 13. 2. 1976. Erstes Kind gesunder Eltern, Geburt durch Forceps aus Beckeneingang bei hinterer Hinterhauptslage wegen Hydrops gravidarum, Präeklampsie und protrahierten Geburtsverlaufes. Postpartal klinisch unauffällig.

Röntgenaufnahme des Thorax (1. Lebenstag): Zwerchfellhochstand rechts (Abb. 5). Säure-Basen-Haushalt während der ersten Lebenswoche ausgeglichen.

11. Lebenstag: Zunahme des Zwerchfellhochstandes (rechte Zwerchfellkuppel in Höhe des 5. ICR, paradoxe Beweglichkeit des rechten Zwerchfells). Röntgenologisch deutliche Strukturvermehrung der Lunge. Ab 11. Lebenstag zunehmende Ruhedyspnoe, bei Belastung generalisiert Cyanose.

22. Lebenstag: Röntgenologisch ausgedehnte Dystelektasen im Bereich der rechten Lunge bei unverändertem Zwerchfellhochstand. Säure-Basen-Haushalt: Erstmals kompen sierte respiratorische Azidose (pH 7,35; $p\text{CO}_2$ 67 Torr, BE + 4,5 mval/l).

33. Lebenstag: Zunehmende Belastungsinsuffizienz. Röntgenologisch

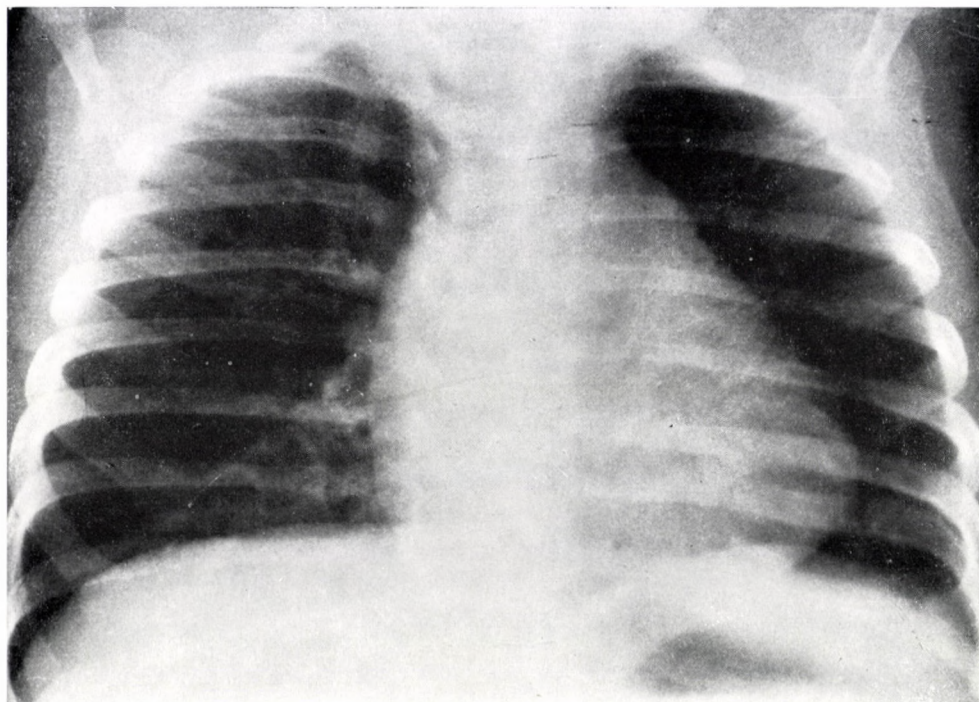


ABB. 4. Thoraxaufnahme im 10. Lebensmonat. Seitengleicher Zwerchfellstand mit postoperativen Residuen links basal. Kein pathologischer Herz- und Lungenbefund.

ausgeprägte Dystelektasen im Bereich beider Lungen (Abb. 6). Säure-Basen-Status: Hochgradig dekompensierte respiratorische Azidose (pH 7,135; $p\text{CO}_2$ 100 Torr, BE + 18,0 mval/l). Aufgrund der oben genannten klinischen, röntgenologischen und laborchemischen Befunde war die Indikation zum sofortigen operativen Eingreifen gegeben. Nach rechtsseitiger Thorakotomie wurde die offene Zwerchfelldoppelung durchgeführt.

Der postoperative Verlauf war durch das Auftreten eines doppelseitigen Spannungspneumothorax kompliziert. Nach Anlegen einer beiderseitigen Saugdrainage besserte sich das Befinden des Kindes rasch, und

die Atmung stabilisierte sich kontinuierlich. Die in den ersten Tagen nach der Operation vorhandene Atelektase der rechten Lunge (Abb. 7) bildete sich innerhalb von 6 Tagen zurück. Bis zum 10. postoperativen Tag hatte sich röntgenologisch der Thoraxbefund (Abb. 8) ebenso wie der Säure-Basen-Status weitgehend normalisiert.

Fall 3: S. S., geb. 22. 9. 1974. Erstes Kind gesunder Eltern, Geburt durch Forceps aus II. vorderer Hinterhauptslage, Geburtsgewicht 3870 g, Länge 54 cm. Wegen knorksender Atmung, Anschwellung und Haematom im Bereich der rechten Halsseite sowie oberer Plexusparese rechts Auf-

nahme im Alter von 24 Stunden. Röntgenaufnahme des Thorax: Zwerchfellhochstand rechts (Abb. 9). Thorax-Durchleuchtung: Paradoxe Zwerchfellbewegung. Befinden nicht beeinträchtigt.

37. Lebenstag: Keine Cyanose, keine Ateminsuffizienz. Plexusparese inzwischen vollständig zurückgebildet. Thorax-Röntgen: Zwerchfell rechts ca. 3 ICR höherstehend als links. Zwerchfellbuckel medio-ventralrechts. Thoraxorgane im übrigen röntgenologisch unauffällig. Da während der weiteren stationären Beobachtungszeit sowohl klinisch als auch

röntgenologisch Hinweise auf eine Progredienz fehlen, wird auf einen operativen Eingriff verzichtet.

Bei mehrfachen ambulanten Kontrollen zeigte sich bei unverändertem Wohlbefinden bis zum Alter von 3 Monaten eine weitgehende Rückbildung der röntgenologischen Veränderungen (Abb. 10).

Fall 4: A. M., geb. 5. 12. 1974. Erstes Kind gesunder Eltern, Geburt durch ganze Extraktion aus I. reiner Steißlage. Geburtsgewicht 2950 g, Länge 49 cm. Postpartal blaß, geringe Spontanmotorik, keine Dyspnoe, keine Cyanose. Obere Plexusparenese

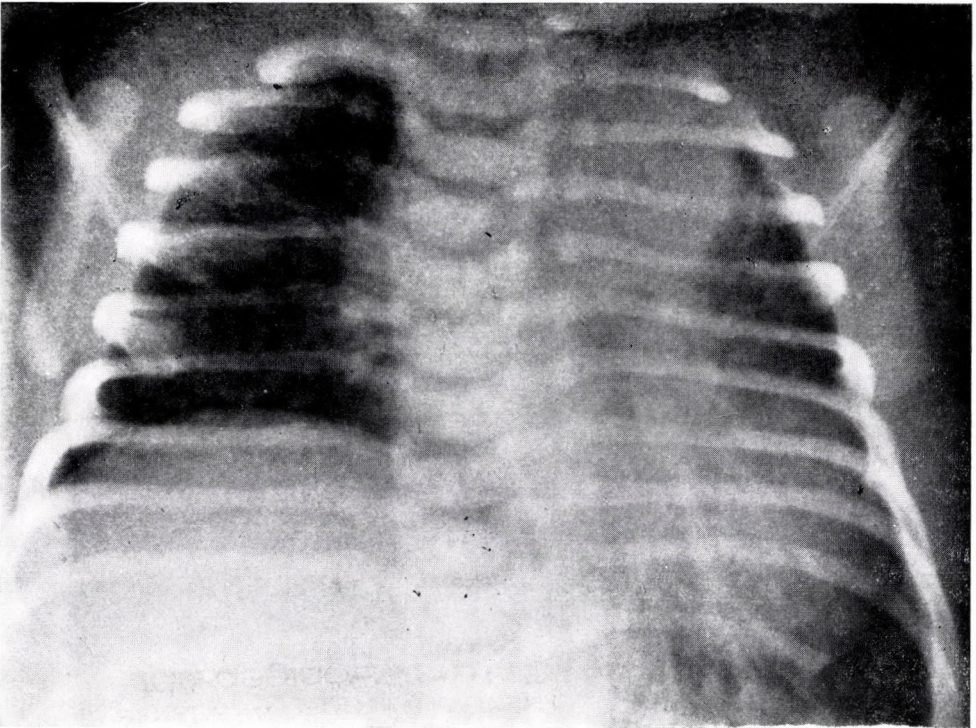


ABB. 5. Röntgenaufnahme des Thorax im a.p.-Strahlengang. 1. Lebenstag. Zwerchfellstand rechts in Höhe der 7. Rippe, links Unterrand der 10. Rippe. Strukturvermehrung beider Lungen. Herzvergrößerung.

rechts. Atemexkursion des Thorax rechts schwächer als links.

Röntgen (2. Lebenstag): Rechts Zwerchfell um 2 ICR höherstehend als links. Herz und Mediastinum mäßig nach links verlagert (Abb. 11). Atemphasengesteuerte Röntgenaufnahmen: Paradoxe Zwerchfellbewegungen rechts. Klinisch sind Hinweise auf eine respiratorische Insuffizienz im weiteren Verlauf nicht gegeben. Bis zum 18. Lebenstag bildet sich die Plexusparese zurück.

Am 74. Lebenstag zeigt die Röntgenuntersuchung des Thorax bis auf geringe Zwerchfellbuckelung rechts eine nahezu vollständige Normalisierung des Thoraxbefundes (Abb. 12).

Fall 5: N. P., geb. 25. I. 1976. Erstes Kind gesunder Eltern. Spontan- geburt aus I. vorderer Hinterhauptslage, Geburtsgewicht 3600 g, Länge 52 cm. Postpartal deutliche Akrocyanose. Klinisch und röntgenologisch Claviculafraktur rechts. Kephalhämatom rechts parietal. Röntgenaufnahme des Thorax: Zwerchfellohochstand rechts (Abb. 13). Thorax-Durchleuchtung: Synchroner Atemtätigkeit des Zwerchfelles, keine paradoxe Beweglichkeit.

Kontrolle des Thoraxbefundes am 12. Lebenstag: Keine Progredienz der Zwerchfellparese.

Während einer 2-wöchigen stationären Beobachtung war das Kind

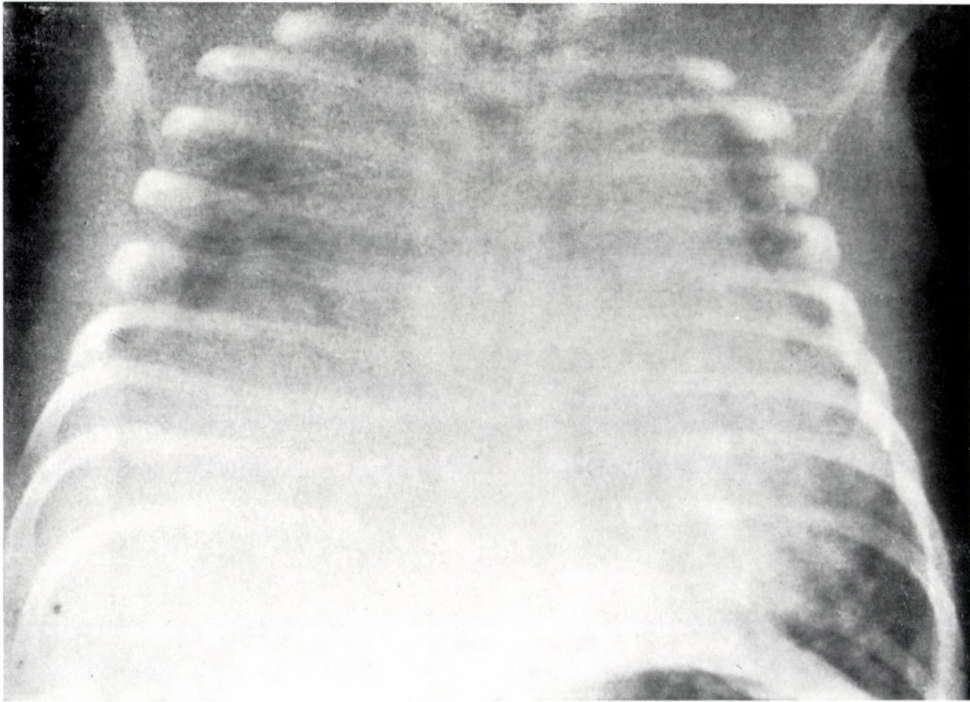


ABB. 6. Thoraxaufnahme 33. Lebenstag. Dystelektase der gesamten re. Lunge. Dystelektase im linken Unter- bis Mittelfeld. Zunehmende Strukturverdichtung der linken Lunge.

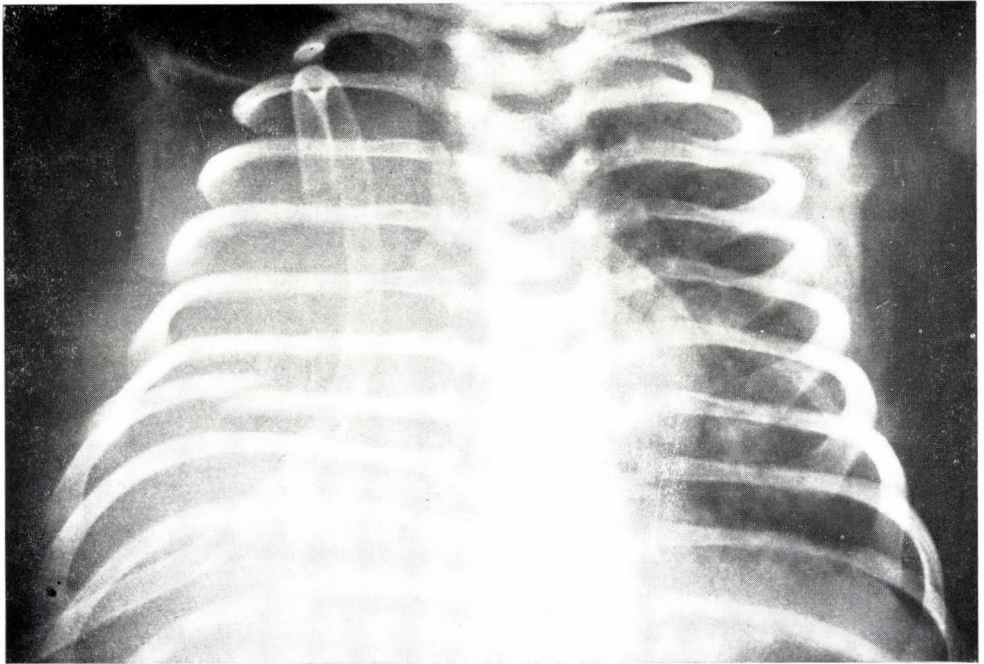


ABB. 7. Thoraxaufnahme 34. Lebenstag. Ein Tag nach Operation. Atektase der rechten Lunge. Verlagerung von Herz und Trachea nach rechts. Liegende Saugdrainage rechts. Fraktur der 7. Rippe.

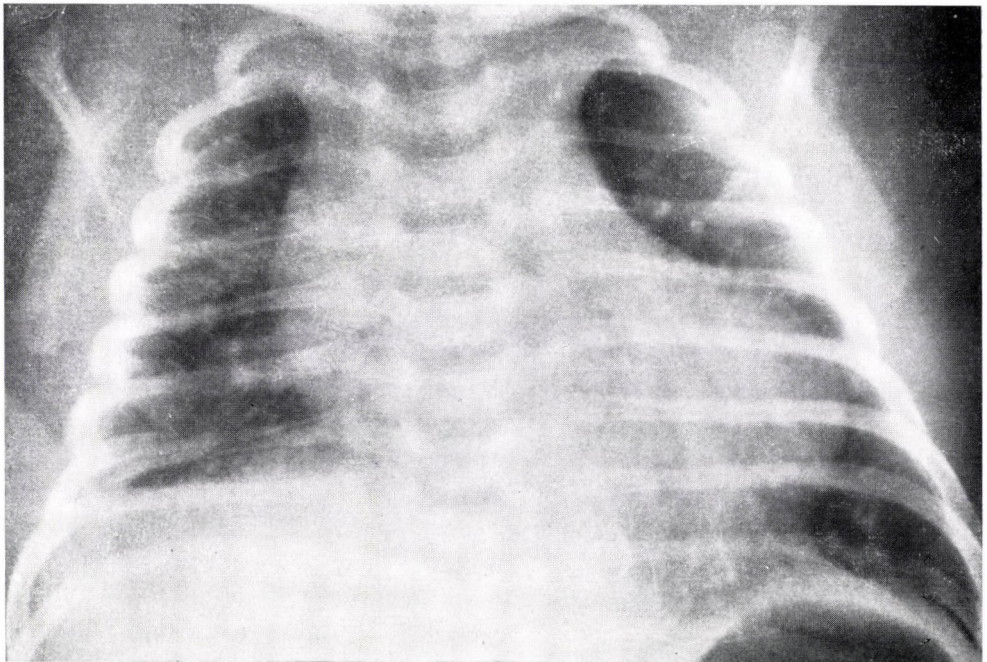


ABB. 8. Thoraxaufnahme am 10. postoperativen Tag. Lungen seitengleich belüftet. Mediastinum und Trachea mittelständig. Zwerchfell rechts. $1\frac{1}{2}$ ICR höher stehend als links.

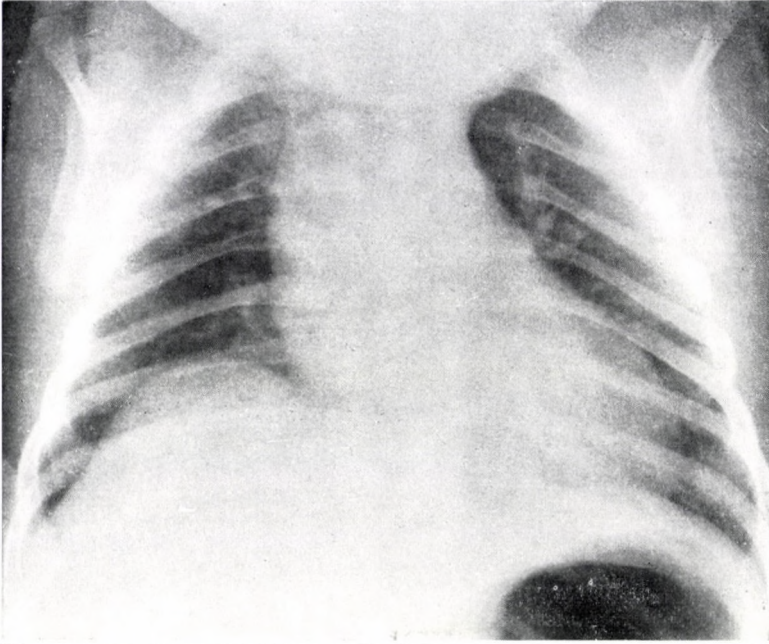


ABB. 9. Röntgenaufnahme des Thorax. 7. Lebensstag. Zwerchfellbuckel rechts medial und Zwerchfellhochstand rechts. Kein pathologischer Herz- und Lungenbefund.

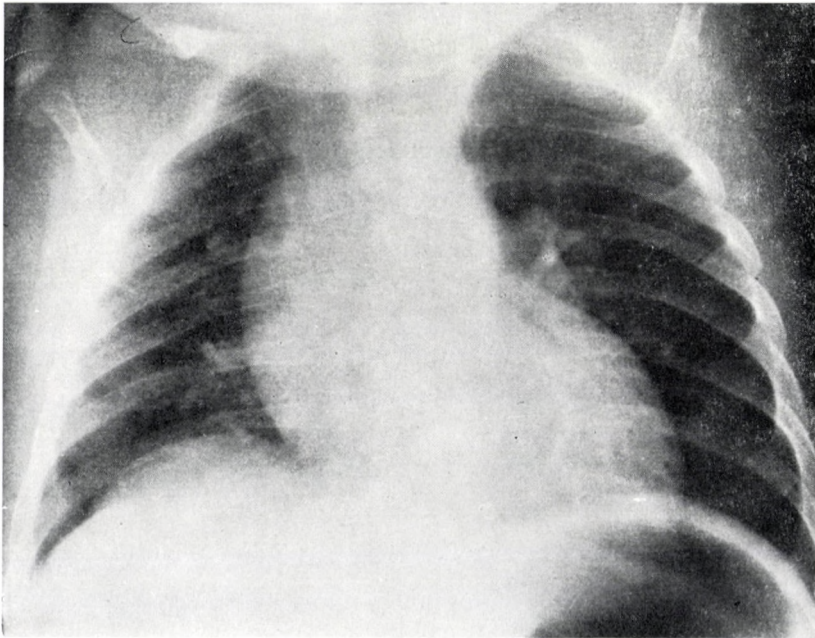


ABB. 10. Röntgenaufnahme des Thorax im 3. Lebensmonat. Noch geringer Zwerchfellhochstand rechts. Angedeuteter Zwerchfellbuckel rechts.

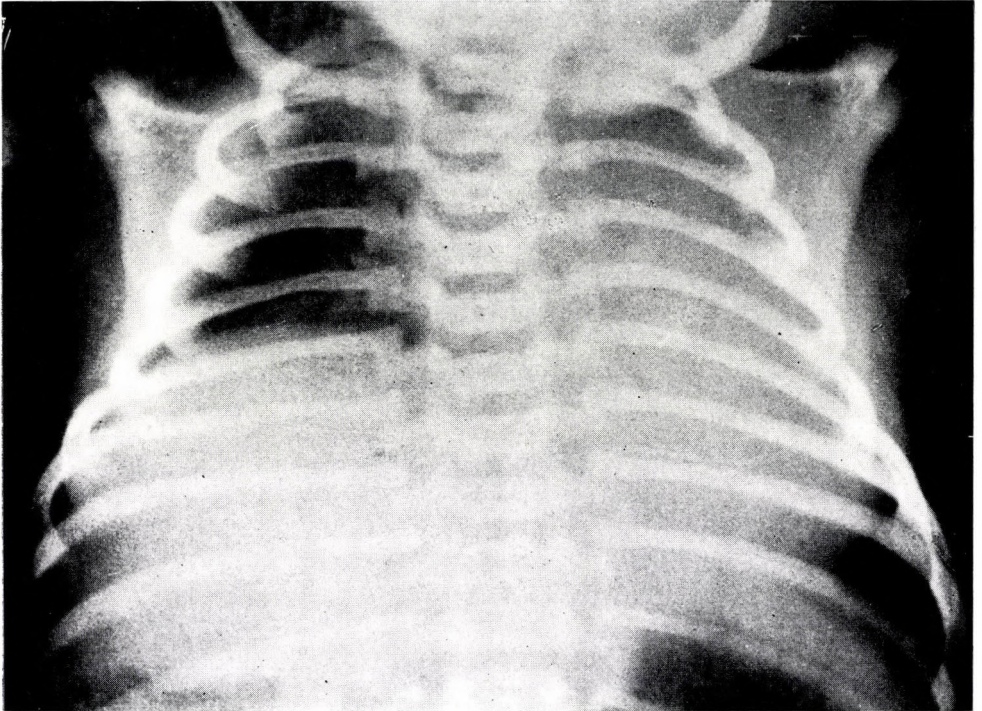


ABB. 11. Thoraxaufnahme 2. Lebenstag. Zwerchfellstand rechts 5. ICR, links 9. ICR. Mediastinum und Herz nach links verlagert.

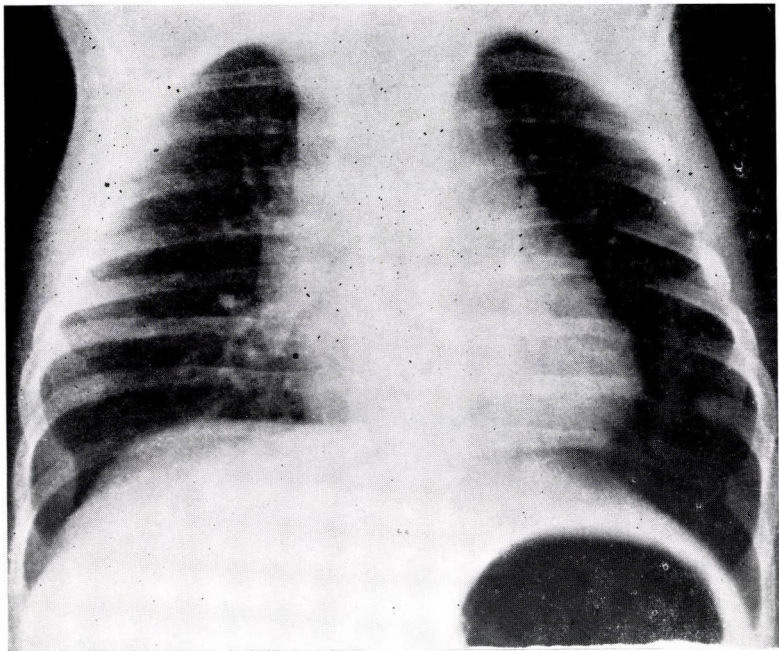


ABB. 12. Thoraxaufnahme 74. Lebenstag. Medialer Zwerchfellbuckel rechts. Seitengleicher Zwerchfellstand. Kein pathologischer Herz- und Lungenbefund.

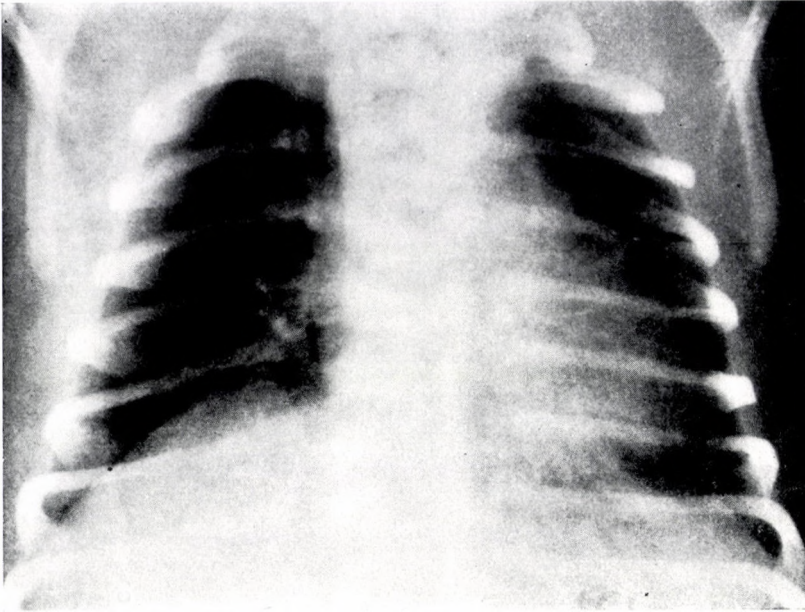


ABB. 13. Thoraxaufnahme 2. Lebenstag. Zwerchfell rechts 1. ICR höher stehend als links. Zwerchfellbuckel rechts. Kein pathologischer Herz- und Lungenbefund.

klinisch unauffällig. Zeichen einer respiratorischen Insuffizienz wurden nicht beobachtet. Bisher weitere ambulante Kontrollen zeigten bei unbeeinträchtigtem Allgemeinbefinden eine Rückbildungstendenz der Zwerchfellparese.

DISKUSSION

Trotz unterschiedlicher klinischer Initialsymptomatik der geburtstraumatischen Phrenicusparese [1, 11] dürfte die Diagnose dieser Erkrankung [10] heute kaum Schwierigkeiten bereiten. Die Leitsymptome sind Zeichen der cardiorespiratorischen Insuffizienz und röntgenologische Veränderungen (Elevation des

Zwerchfells, u. U. Lungenkompression und Mediastinalverlagerung).

Differentialdiagnostisch sind die kongenitale Zwerchfellmuskelhypoplasie und eine pleuro-peritoneale Hernie in Erwägung zu ziehen. Neben der Bevorzugung der rechten Zwerchfellseite weisen Angaben über einen erschwerten Geburtsverlauf und eine gleichzeitig bestehende Plexuslähmung auf die Zwerchfell-Lähmung hin.

Wie auch entsprechende Vergleiche [12] erkennen lassen, treten bei Phrenicuslähmungen die ersten Symptome in den ersten Lebenstagen auf, während Initialerscheinungen der kongenitalen Muskelhypoplasie nicht selten erst um den 4. Lebensmonat bemerkbar werden. Die durchgehende Kontinuität des Zwerchfells mit feh-

lendem intrathorakalen Prolaps von Baueingeweiden läßt in der Regel pleuro-peritoneale Hernien mühelos abgrenzen.

Die unterschiedliche Ausprägung der akuten klinischen Symptomatik dürfte durch die Art der Phrenicusläsion begründet sein. Je nach Ausprägung der Parese tritt das relaxierte Zwerchfell durch intraperitoneale Drucksteigerung und unter Wirkung des Irspirationssofes (paradoxe Atmung) nach oben, und es kommt zur Kompression der betroffenen Lunge, Verlagerung des Herzens und Mediastinums zur gesunden Seite und Beeinträchtigung der respiratorischen Funktion der kontralateralen Lunge sind sekundäre Folgen. So können die Kinder einer excessiven respiratorischen Insuffizienz schon bald erliegen [2]. In anderen Fällen führen chronische Hypoxie und rezidivierende pulmonale Infektionen bei konservativer Behandlung zwischen dem 2. und 6. Lebensmonat zum Tode [10]. Bei derartigen Verläufen stellt die Zwerchfellraffung einen lebensrettenden Eingriff dar [4, 5, 9, 11]. Die Indikation zur operativen Behandlung sollte u.E. von der Schwere des Krankheitsbildes, der Ausprägung der respiratorischen Insuffizienz, dem Grad der paradoxen Atmung, dem Auftreten der rezidivierenden Atelektase bzw. Bronchopneumonien sowie einer respiratorischen Azidose abhängig sein. Bei leichteren Verlaufsformen scheint uns unter der Bedingung exakter klinischer Kontrolle eine abwartende Haltung gerechtfertigt.

Wie unsere drei letztgeschilderten Fälle zeigen, ist bei fehlender Ateminsuffizienz eine spontane RepARATION ohne Gefährdung des Kindes durchaus möglich.

Damit widersprechen wir Bishop und Koop [2], die eine konservative Therapie generell als gefährlich ansehen. Sobald eine Progredienz des Krankheitsgeschehens unter Priorität der klinischen Befunde ablesbar wird, sollte man sich jedoch möglichst früh zur aktiven Therapie entschließen.

Die Operation besteht in der trans-thorakalen Raffung des Zwerchfells, die als geschlossene Faltung oder in der durch uns geübten Art der offenen Doppelung mit primärer Durchtrennung des relaxierten Zwerchfells vorgenommen werden kann.

Inwieweit Behandlungsversuche mittels CPAP Atmung eine Ergänzung des therapeutischen Spektrums darstellen, ist bei der Seltenheit der Phrenicusparese und bislang nur 2 publizierten Fällen [3] noch nicht endgültig zu beurteilen.

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Doz. Dr. sc. med. K. MENZEL
Kinderklinik der Medizinischen
Akademie
DDR — 50 Erfurt
Am Schwemmbach 32a

Energy/Protein Index: III. Correlation with a biochemical parameter which reflects protein nutritional imbalance

By

M. AMADOR, J. BACALLAO, MIRTA, HERMELO, R. FERNÁNDEZ, C. TOLON,
H. PÉREZ

Department of Paediatrics, Centre of Cybernetics and Institute of Biochemistry, Faculty of Medical Sciences, University of Havana, Cuba.

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To establish the usefulness of the Energy/Protein index, a study was made to assess its correlation with a biochemical parameter able to detect marginal forms of protein-energy malnutrition such as the non-essential/essential aminoacid ratio.

A simple linear regression model was proposed and tested in a sample of ninety-seven malnourished children, by means of analysis of variance. The model was satisfactory. A highly significant ($p < 0.001$) correlation coefficient of $r = 0.552$ was found.

Energy/Protein Index is a new anthropometric index described by us. It relates the logarithm transformation of the triceps skin-fold (S) and the logarithm of middle arm muscular circumference (MAMC) [1, 4.] The index shows little variability among well-nourished preschool children, and is not sex-dependent [1].

As this index relates a parameter such as the triceps skin-fold which reflects body energy reserves with another one depending on the status of protein nutrition [12, 13, 20, 27], it allows to assess the relative impairment of both factors which characterize protein-energy malnutrition (pem) thus making it possible to distinguish between the two kinds of pem, marasmus and kwashiorkor.

Thus, by means of the Wellcome Trust Classification [9], we could study the behaviour of the index in four groups of malnourished children and found it possible to discriminate between mild and severe forms of marasmic pem and between these and kwashiorkor [2]. This proved true for the clinically detectable forms of pem but it remained necessary to study the ability of the index to detect marginal or subclinical forms, when just biochemical changes are present.

Protein imbalance may be detected according to its severity, by several biochemical parameters. The non-essential/essential aminoacid ratio (neaa/eaaratio) is one of the first factors to show alterations even in

marginal cases. Although the issue is controversial, the ratio has been employed with success by many authors [5, 11, 17, 21, 23, 24, 29, 32]. Moreover, we found a significant correlation between neaa/eaaratio and MAMC [3]. Thus, a significant correlation was expected between the E/P index and some biochemical parameters such as the neaa/eaaratio.

MATERIALS AND METHODS

Ninety-seven preschool children admitted to the Nutrition Ward at the William Soler Paediatric Hospital, Havana, with the diagnosis of protein-energy malnutrition were studied.

The diagnosis of pem was established from the weight for height deficit in a child with pondostatural retardation [28]. Reference standards for weight and arm circumference (MAC) was measured in each patient in the middle third of the left upper arm, using a fibre-glass tape. Triceps skin-fold thickness was obtained at the same site using a Harpenden skin-fold caliper with a standard pressure of 9.3 g/mm². All anthropometric measurements were recorded in duplicate by the same previously trained observer, and with the help of an assistant who wrote out and verified the data. The methods of measurement were as described by Jelliffe [19]. Starting from MAC and S values, MAMC was obtained according to the formula [20]

$$\text{MAMC} = \text{MAC} - \pi \times S, \quad \text{where}$$

MAC = middle arm circumference in cm;

MAMC = middle arm muscular circumference in cm;

S = triceps skin-fold thickness in cm;

$\pi = 3.1416$

The transformation to a log scale of S according to the caliper employed is as follows [10]:

$Z = \log_{10} (\text{reading in } 0.1 \text{ mm} - 18)$.
The E/P index was calculated by the formula (3.5):

$$\text{E/P index} = \frac{\text{Transformed S}}{\log_{10} \text{MAMC}}$$

Simultaneously with anthropometric and clinical assessment, on admission a venous blood sample was drawn from each child. After clotting, serum was separated by centrifugation.

Paper chromatography of the serum was performed according to Whitehead [31], with some modification [6]. The ratio non essential/essential aminoacids was obtained as the quotient of the photocolometric reading after elution of the correspondent spots of the chromatogram. [31].

The Pearson correlation coefficient between E/P index and non-essential/essential aminoacid ratio was calculated, and a significance test for this correlation was performed. Then, a simple linear regression model was postulated, the regression parameters were calculated and the hypothesis of linearity was verified by means of an analysis of variance. The E/P index was taken as the dependent variable [8, 22, 33].

RESULTS

The correlation coefficient estimate was $r = 0.552$ and it turned out to be highly significant at a level of $\alpha < 0.01$. The significance test was based upon $t = r \sqrt{\frac{n-2}{1-r^2}}$

which follows a t - Student distribution with $n-2$ degrees of freedom.

The following ANOVA table summarizes the results of the calculations performed to test the hypothesis of linearity.

Source of variation	Sum of squares	D. F.	Means squares	Variance ratio
Within groups	3.460 768	73	0.047 408	
Regression	1.657 695	1	1.657 695	
about the regression	0.949 693	22	0.043 168	0.910 564
Total	2.607 388	23	0.113 365	

$F^{22} (0.05) = 1.70$

Thus, the F value was not significant and the hypothesis of a linear relationship between the two variables could not be rejected. Finally, the regression equation is

$Y = b X + a$, where

$Y = E/P$ index

$X = neaa/ea$ ratio

$a = 1.094 56$

$b = 0.206 63$

DISCUSSION

We found a close relationship between E/P index figures and neaa/ea ratio values. High values for the E/P index corresponded to high values of the aminoacid ratio, and the results obtained showed that both the anthropometric and the biochemical parameters have a similar capacity for the detection of relative changes between energy and protein status.

The selection of neaa/ea ratio as the biochemical parameter to be correlated was based upon the positive results obtained in a previous work, where a correlation coefficient $r = 0.486$ ($p < 0.001$) was found between this ratio and MAMC [3].

Considering the objections raised by several authors regarding the neaa/ea ratio and the influence on its value of diet composition instead of protein status [7, 25], we tried to prevent the eventual influence of the dietary factors by taking the blood samples at the moment of admission, before any treatment had been administered. In contrast with blood sampling, anthropometric measurements are a simple task, easily performed by non-medical personnel. Moreover, calculation of the E/P index is performed by a simple mathematical formula which can be programmed in a general-purpose minicomputer, and applied to field studies for the screening of malnutrition in the community.

Several authors have attempted to quantify the magnitude of the impairment of energy and protein status, considering the study of adiposity and muscle mass at the middle third of the upper arm [13, 14, 15, 16].

Gurney and Jelliffe [15] set up a hypothesis about the possibility of classifying malnourished children in different categories of nutritional deficiencies. They developed a nom-

ogram [16] which allows the calculation of fat and muscle areas at the middle upper arm level, and had proved useful in community nutrition surveys.

Our E/P index quantifies the relative impairment of energy and protein nutritional status and therefore offers more complementary data than a study of separate measurements. The ability of the index to discriminate among different forms of malnutrition (kwashiorkor and marasmic forms of pem) and the finding of a significant linear correlation with biochemical parameters of recognized value in the detection of marginal protein malnutrition, lend to the E/P index a diagnostic value in the early detection of energy or protein imbalance.

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Prof. M. AMADOR
 Servicio de Nutrición
 Hospital Pediátrico "William Soler"
 San Francisco 10 112,
 Habana 8, Cuba

Recensiones

Funktionsdiagnostik im Kindesalter. Herausgegeben von U. STEINIGER und H. THEILE. 757 Seiten mit 173 Abbildungen und 101 Tabellen. George Thieme Verlag, Leipzig 1974. M 49,—

Die Medizin unseres Zeitalters entwickelt sich in Richtung der zunehmenden Spezialisierung und der Differenzierung der Untersuchungsmethoden. Diese Entwicklung erschwert aber manchmal die Orientierung, die Ausbildung eines einheitlichen Bildes einer bestimmten Krankheit sowie die Beurteilung der Indikationen der erforderlichen Untersuchungen. Das vorliegende Buch bietet eine ernste Hilfe zur Lösung dieser Problematik, indem es eine Zusammenfassung der funktionsdiagnostischen Methoden im Kindesalter enthält. Den eigenartigen Ansprüchen der Pädiatrie entsprechend ist der Kreis der behandelten Untersuchungen beträchtlich weit. In den einzelnen Kapiteln findet man alles Wesentliche von der Entnahme des Untersuchungsmaterials an, durch die speziellen Untersuchungsverfahren (Isotopenuntersuchungen, Organ- und Organsystemuntersuchungen) bis zu den den Grenzgebieten (Orthopädie, Augenheilkunde, Otorhinolaryngologie). Den Autoren ist es gelungen, dieses umfangreiche Material kurz zusammenzufassen. Bei der Besprechung der einzelnen Methoden werden die Grundprinzipien sowie die Normalwerte und die Leistungsfähigkeit des Verfahrens erläutert.

Das ausführliche Inhaltsverzeichnis sowie die rationelle Aufteilung der Kapitel (Untersuchungsmethoden, Untersuchungen der Organsysteme und Organe) sind besondere Verdienste des Buches, das genaue Sachverzeichnis dient der leichteren Orientierung. Das Werk kann jedem Pädiater, Kreis-, Krankenhaus- bzw. Laboratoriumsarzt aufrichtig empfohlen werden, und auch wissenschaftlern spezieller Fachgebiete bietet das ausführliche Literaturverzeichnis eine Reihe nützlicher Informationen.

I. SZAMOSFALVI

Hygiene in Halle-Neustadt. Untersuchungen eines Hygiene-Komplex-Praktikums in Halle-Neustadt von 1969—1973. Herausgegeben von K. RENKER. 310 Seiten mit 46 Abbildungen und 55 Tabellen. Verlag Volk und Gesundheit, Berlin. M 22,—

Die Mitarbeiter des hygienischen Instituts der Martin-Luther-Universität durchführten in Zusammenarbeit mit Medizinstudenten zwischen 1969 und 1973 sich auf die hygienischen Zustände, Wohnungs- und Arbeitsverhältnisse von Halle-Neustadt beziehende Untersuchungen.

Halle-Neustadt ist eine junge Industriestadt mit 30 000 Einwohnern; 1969 betrug das durchschnittliche Lebensalter der Einwohner 23,5 Jahre, die Zahl der zur

älteren Generation gehörenden Personen ist niedrig (im Zeitpunkt der Untersuchungen gab es in der Stadt nur 343 Rentner), woraus folgt daß die Mehrzahl der untersuchten Fragen den Problemenkreis der jungen Generation berührt. Aus der weitläufigen Datensammlung sind von der Sicht des Pädiaters folgende Informationen hervorzuheben: Obwohl seit 1972 die jungen Frauen auch in der DDR das Entscheidungsrecht in bezug auf die Austragung bzw. Unterbrechung ihrer Schwangerschaft besitzen, liegt die Betonung auf der Verhütung der ungewünschten Schwangerschaft. Die regelmäßige Anwendung der oralen Antikonzeptiva ist bereits eine Gewohnheit der meisten jungen Frauen geworden.

Den Kindern und Kinderinstitutionen widmeten die Untersuchungen einen großen Raum; hierzu gehören die ausführliche Analyse der Tagesordnung der Kindergärten und Schulen, Beschäftigung der Kinder, Lärmbelastung, Eigentümlichkeiten der Beleuchtung sowie der Charakteristika der Ernährung und der Krankheiten. Es wurde auch der Tages- und Arbeitsablauf der Pädagogen studiert und damit im Zusammenhang die Wichtigkeit des engen Kontakts zwischen Lehrern und Eltern betont.

Auf die Gesamtbevölkerung übergehend befaßte sich das Team der Untersucher mit einer langen Reihe von Fragen, wie z. B. Freizeitverhalten, Sportmöglichkeiten, System der ärztlichen Versorgung, Häufigkeit und Betreuung der Hypertoniekrankheit, städtische Trinkwasserversorgung, Abwasserableitung, Hygiene in den Betrieben, Arbeitsschäden und noch viele andere zur Sozialhygiene gehörende Probleme. Anhand der ermittelten Daten werden Vorschläge unterbreitet zur Verfertigung von Zukunftsplänen, die die optimalen Umweltsbedingungen des Lebens gewährleisten könnten.

A. SZÉKELY

Clinical Pharmacology of Anti-Epileptic Drugs. Edited by SCHNEIDER, H., JANZ, D., GARDNER-THORPE, C., MEINARDI, N., SHERWIN, A. L. International Symposium held in Bethel, Bielefeld, Germany, May 1974. Springer-Verlag, Berlin—Heidelberg—New York 1975. X + 370 pages with 129 figures and 89 tables. DM 128.—

The therapy of epilepsy has been revolutionized by the application of azepine preparations as well as by the determination of the serum level of the antiepileptic drugs. The therapeutic application of dipropylacetate is emphasized, since the drug seems to influence the epileptic mechanism. Pharmacokinetics are discussed in detail as well as the chemistry of the individual drugs and their serum levels. The possibilities of therapy with drug combinations are pointed out and illustrated with tables and figures. The methods of serum level estimations are discussed. In contrast to the rather uncertain spectrophotometric method, the recently constructed EMIT apparatus can reliably determine the serum phenytoine, barbital, pyrimidine, succinimidine and carbamazepine levels by an immunochemical procedure in 50 μg blood, thus in less blood and more rapidly than do the gas-chromatographic methods.

The book ends with an up-to-date index of drug synonyms; it will be interesting even for those who are not engaged in the treatment of epilepsy.

O. KOHLHÉB

R. NATUSCH, G. DITSCHERLEIN: *Nierenbiopsie.* Technik, Morphologie und Klinik. 220 Seiten mit 102 Abbildungen in 148 Einzeldarstellungen und 14 Tabellen. Johann Ambrosius Barth, Leipzig 1976. M 61,—

Die Monographie umfaßt die wesentlichsten internationalen Ergebnisse auf dem Gebiet der Nierenbiopsie sowie eigene in zehnjähriger Forschung gesammelte

Erfahrungen der Autoren. In gesonderten Kapiteln werden die Probleme der Biopsie im Kindesalter und in der Schwangerschaft, außerdem die experimentelle Biopsie behandelt.

Der erste Teil des Buches befaßt sich mit der Technik: Indikationen, Kontraindikationen, Möglichkeiten und Komplikationen. Die häufigste Komplikation bei 8 221 Untersuchungen war die Mikrohämaturie (32,4%); seltene Komplikationen sind: Organmitpunktion, makroskopische Hämaturie, arteriovenöse Fistel und Aneurysma. Aufgrund der Literaturangaben ist eine Letalität von annähernd 0,1% wahrscheinlich.

Ausführend werden die von den Autoren bevorzugten Methoden (MENGHINI-Nadel und Spritze, ferner VIM-SILVERMAN-Spalt-nadel) und die Lokalisationsverfahren (Radiologie, Szintigraphie und Ultraschall) erörtert. Die Gefahren der Blindbiopsie werden betont. In besonderen Fällen eignet sich auch die offene (chirurgische) Biopsie.

Die Überwachung des Patienten nach erfolgter Punktion ist eine entscheidende Phase der Nierenbiopsie hinsichtlich der frühen und späten Komplikationen [1 1/2 Stunden strenge Bettruhe, 18 und 24 Stunden lange Beobachtung].

Die perkutane Nierenbiopsie findet auch in zunehmendem Maße Eingang in die kindernephrologische Diagnostik. Verfasser führten 241 Biopsien bei 174 Kindern durch. Das Alter der Kinder lag bei 20 Patienten unter 5 Jahren; das jüngste punktierte Kind war 3 Monate alt. Von den zur Auswertung analysierten Nierenbiopsien waren 87,6% erfolgreich, d. h. es wurde Nierengewebe gewonnen. Als Vorteil der perkutanen Biopsie ist zu erwähnen, daß sie mehrfach wiederholt werden kann.

Kapitel 8. enthält die histologische Bearbeitung des Biopsiezylinders: konventionelle Lichtmikroskopie, Semidünnschnitttechnik, Elektronenmikroskopie und Immunhistologie.

In einem gesonderten Teil ist die Bedeutung der experimentellen Nieren-

biopsie bei Kaninchen und Ratten vorzufinden.

Der zweite Teil der Monographie wird dem morphologischen und klinischen Bild einzelner Nierenerkrankungen gewidmet. Das von dem Autoren verwendete Schema zur Nomenklatur und Klassifikation der Glomerulonephritis versucht die strittigen Angelegenheiten klarzustellen. Im Kapitel 11 sind Morphologie und Klinik einzelner Glomerulonephritisformen in Tabellen mit histologischen Abbildungen dargestellt. Kapitel 12 analysiert die Klinik der interstitiellen Nephritis und Pyelonephritis und demonstriert ausführlich die zahlreichen histologischen Bilder. Danach werden Klinik und Histologie der seltener vorkommenden Nierenerkrankungen (Hämolyse, hämolitisch-urämisches Syndrom, diabetische Nierenveränderungen, Graviditätsnephropathie) erläutert. Kapitel 18 enthält die verschiedenen histologischen Veränderungen und die histologische Differentialdiagnose der akuten und chronischen Rejektion von allotransplantierten menschlichen Nieren.

Kapitel 21 bespricht den diagnostischen und differentialdiagnostischen Wert der perkutanen Biopsie bei unklaren Prozessen (unklare Proteinurie und unklare Hämaturie). Das letzte Kapitel betont die Bedeutung von perkutanen Wiederholungsbiopsien; die Verfasser konnten die Effektivität von durchschnittlich 86,2% durch Wiederholungsbiopsien auf 91,8% steigern.

Die ausgezeichnete Monographie, das Ergebnis enger jahrelanger Zusammenarbeit zwischen der II. Medizinischen Klinik und dem Pathologischen Institut der Berliner Charité, vermittelt durch enge Verknüpfung klinischer und morphologischer Aspekte neuartige Erkenntnisse der Nephrologie. Interessenten sind Nephrologen, Internisten, Urologen, Pädiater und Pathologen.

L. TURAI

H. SPIESS: *Impfkompendium*. 2. überarbeitete Auflage, 222 Seiten mit 22 Abbildungen, 25 Tabellen und 4 Farbtafeln. Georg Thieme Verlag, Stuttgart 1975. DM 18,80

Dieses in Taschenbuchformat erschienene Werk beginnt mit einem Überblick der immunologischen Grundlagen, der Möglichkeiten des spezifischen Schutzes und der modernen Impfmethoden. Hiernach folgt die ausführliche Erläuterung der allgemein angewandten Schutzimpfungen, wie BCG, Di-Per-Te, Poliomyelitis, Pocken und Masernimpfungen, und der seltener gebräuchlichen Immunisierungsmöglichkeiten gegen Röteln, Mumps und Influenza. Es wird auch auf die Besprechung der heute größtenteils noch im experimentellen Stadium befindlichen Impfungen (RS, Parainfluenza und Adenovirusfektion) eingegangen. Nebst dem Problem der Schutzimpfung gegen Hepatitis befaßt sich das Buch auch mit den Impfmöglichkeiten gegen Varizella und Herpes simplex sowie mit den sich unter besonderen Verhältnissen als erforderlich erweisenden Impfungen, d. h. mit den spezifischen Schutzmöglichkeiten gegen Tollwut, Salmonella, Gelbfieber, Cholera und Pest. Die Einteilung sämtlicher Kapitel ist identisch, wodurch die Gleichmäßigkeit und die eindeutige Stellungnahme des Verfassers zur Geltung kommt. Indikationen und Kontraindikationen, epidemiologische und klinische Daten, Impfstoff sowie technische Ausführung und Effektivität der betreffenden Impfung werden in jedem Kapitel der modernen Anschauung gemäß ausführlich behandelt.

Dieses leicht handhabbare Büchlein bietet sowohl dem praktizierenden Arzt, als auch dem Medizinstudenten kurzgefaßte aber wesentliche Kenntnisse in bezug auf die neuesten Ergebnisse und Daten der Schutzimpfungen.

Á. SZÉKELY

C. RAPARORT, J. MARCUS, M. GLIKSON, W. JEDLICKI, S. LACHE: *Early Child Care in Israel*. International Monograph Series in Early Child Care. Vol. 7. Gordon and Breach, London 1976. 199 pages. Price: £ 4.80

In the introduction a detailed historical survey is given of early child care in Israel, explaining the almost antagonistical contradictions in cultural level, cultural aspirations and notions concerning education of the different people who had settled there at various times. The wish for assimilation "to become an Israeli", ensures the cooperation of the parents; the child is the agent of socialisation for the parent, too. All this, however, means little help in the attempts at providing an identical educational level of the children of the European cultural sphere and of those of the culturally lower layers of Eastern Jews and Arabs. It is in the light of this basic problem that systematic planning, the religious-ethnic traditions and the explanatory work of the specialists is studied. Most important is the personal influence of welfare nurses who often act as a mother substitute, e.g. when a new child is born or the mother is ill. In the nurseries little paedagogic work is done, but in the kindergartens, in addition to the traditional Montessori system activity, intense and directive programmes are elaborated for the development of those in disadvantageous position. In the schools, "activity-orientated" 1st and 2nd forms serve the same purpose. Here activity is centred on linguistic culture and arithmetical knowledge. These are supplemented by instructions for the family, according to the observations of Smilansky they are most efficient if their personal discussion occurs in the home of the child. Among the systemic forms of education the nurseries and kindergartens of the kibbutzes are important. Beside intellectual education which is similar as that described above, they lay stress on the emotional effect of strong group-

cohesion. According to longitudinal examinations, the attachment to the parents is not weaker than of the traditionally educated children, but fraternal jealousy is less frequent, the feeling to belong to an adult community is strong, the children know well the life of their parents and the environmental adult world. It is characteristic of the educational principle of kibbutzes that independence is ensured, aggressive behaviour is not limited and sometimes even promoted, and no physical punishment is applied.

The description of educational methods is followed by a discussion of the training of specialists. According to the new paedagogical principles, experiments are performed for common training of kindergarten nurses and teachers in the 1st and 2nd forms. Specific courses are organized for the teachers of children in culturally disadvantageous position and of those who have some kind of deficiency.

It is a merit of the book that its authors always emphasize the failures in outlook as well as in organization by the government and the institutions; their elimination would greatly enhance integration of the different populations.

Z. GERŐ

Handbuch der medizinischen Radiologie
Band V, Teil I. *Röntgendiagnostik der Skeletterkrankungen Teil I.* Von J. FRANZEN, F. HEUCK, J. KOLÁŘ, V. ŠVAB, R. VRABEC, G. ZUBIANI. Redigiert von L. DIETHELM. X + 841 Seiten mit 430 Abbildungen in 886 Einzeldarstellungen. Springer-Verlag, Berlin - Heidelberg - New York 1976. DM 640,-

In den letzten Jahren haben die Forschungen unsere Kenntnisse über das Organ Knochen beträchtlich erweitert. Auch die radiologischen Untersuchungen haben dabei eine wichtige Rolle gespielt. Diese Errungenschaften sind in diesem Buch zusammengefaßt.

Das Buch gliedert sich in einen allgemeinen und einen speziellen Teil. Der ganze etwa 330 Seiten umfassende allgemeine Teil wurde von einem einzigen Autor, F. Heuck geschrieben, der selber mit mehreren wichtigen Feststellungen zu den erreichten Fortschritten beigetragen hat. Seine Arbeit, in 12 Kapitel geteilt beginnt mit dem physiologischen bzw. pathologischen Wachstum und der Reifung. Dann folgen Veränderungen der Knochenstruktur, periostale Reaktionen, Knochenschaden, heterotope Knochenbildung, Radiologie der Gelenkerkrankungen, Densitometrie auch mit Isotopen, quantitative Bildanalyse und Isotopen-Dosimetrie. Ein Kapitel behandelt die Szintigraphie und das letzte die radiologische Diagnostik der Skeletterkrankungen, mit praktischen Hinweisen zur Ausführung der Untersuchung und der Diagnosestellung.

Der zweite Teil des Bandes besteht aus fünf Kapiteln. Im ersten werden die durch Hitze und Kälte hervorgerufenen Veränderungen behandelt. Dann folgen Knochenschäden verursacht durch Stromeinwirkung, und das dritte Kapitel befaßt sich mit den Auswirkungen von Strahleneinwirkung. Dadurch, daß alle drei einander verwandten pathologischen Prozesse von Mitglieder des radiologischen Instituts der Universität zu Prag verfaßt wurden, wurde eine angenehme Harmonie und Zusammenklang in der Auffassung erreicht, was auch zu erwarten war von Autoren, die sich seit Jahrzehnten mit diesem Thema beschäftigen. Im vierten Kapitel findet man die Knochenmarkerkrankungen, Myelofibrose und Myelosklerose. Das fünfte Kapitel ist den mannigfaltigen zirkulatorischen Knochenveränderungen gewidmet, geteilt in zwei Gruppen: Knochenatrophie und Knocheninfarkt.

Nach dem Studium des Werkes bekommt man den Eindruck, daß es den Verfassern hervorragend gelungen ist, dieses heikle Thema, das lange ein noli me tangere war, den Lesern vorzustellen.

Sie haben altbewährte Feststellungen und neue Errungenschaften berücksichtigt und nicht selten kritisch gewertet. Es muß noch erwähnt werden, daß man nicht nur mit der Radiologie des Knochens, sondern auch mit den neuesten biochemischen Forschungen bekannt gemacht wird, so daß man nach Durchlesen des Werkes ein komplexes Bild über das Organ Knochen bekommt. Die einheitliche Betrachtung, die durch das ganze Buch spürbar ist, lobt Verfasser und Redakteur. Die mit großer Sorgfalt zusammengestellten Literaturangaben heben den Wert des Buches noch weiter. Illustrationen, Ausstattung sind, wie auch bei den bereits erschienen Bänden, musterhaft.

K. GEFFERTH

Handbuch der medizinischen Radiologie Band VI, Teil 3. *Röntgendiagnostik der Wirbelsäule* Teil 1. *Krankhafte Haltungsänderungen. Skoliosen und Kyphosen*. Von K. REINHARDT, redigiert von L. DIETHELM. XIX + 880 Seiten mit 444 Abbildungen in 730 Einzeldarstellungen und 83 Tabellen. Springer-Verlag, Berlin—Heidelberg—New York 1976. DM 585,—

Da das ganze Werk von einem Verfasser geschrieben wurde, wird eine einheitliche Auffassung und Behandlung erreicht und den einzelnen krankhaften Veränderungen der ihnen gebührende Raum gewidmet. Man fühlt eine angenehme Harmonie zwischen den Kapiteln und Ausführungen. Dem Titel nach würde man die Röntgendiagnostik der krankhaften Veränderungen der Wirbelsäule erwarten, man findet jedoch auch die Operations-, bzw. Behandlungsmethoden, sowie ihre Folgen und Komplikationen.

Das Thema wird in 19 Kapitel geteilt. In den ersten 7 Kapiteln findet man die Einleitung und Definitionen von Begriffen wie Skoliose, Kyphose, statistische Angaben, verschiedene Meßmethoden, technische Hinweise, die in Frage

kommenden Aufnahmeverfahren. Dann werden die Leser mit Normal- und Variationsformen, mit der Funktion der Wirbelsäule und mit Vererbungsfragen bekannt gemacht. Ein ausführliches und umfangreiches Kapitel wird den bei den verschiedensten Krankheiten vorkommenden Verkrümmungen in sagittaler Richtung gewidmet. Die Abhandlung der Scheuermannschen Erkrankung nimmt allein 22 Seiten ein. Man findet aber auch weniger häufige Krankheitsbilder wie Thalidomidysmelien, Homocystinurie, Folgezustände nach Shuntoperationen bei Hydrocephalus auch in detaillierter Vorführung mit guten Aufnahmen illustriert, sowie die erst in den letzten Jahren abgegrenzten Dysostosen nach den neuesten Einteilungen präsentiert. Um den Leser vor Übertreibungen in der Diagnosestellung und Überschätzungen der Röntgenveränderungen zu bewahren, wird in einem Kapitel die Normalform und die physiologische Skoliose beschrieben. Sehr ausgiebig werden die Verkrümmungen in seitlicher Richtung besprochen. Auch hier wird von den milden, harmlosen Formen wie Haltungsskoliosen und Fehlhaltungen ausgegangen. Dann werden der Reihe nach die bei sämtlichen Krankheitszuständen vorkommenden Verkrümmungen berücksichtigt, wobei auch die Schädel-skoliose nicht vergessen wird. Den Folgeerscheinungen der Skoliose und deren röntgenologischen Symptomatik wird das folgende Kapitel gewidmet, mit Auswirkungen auf die Atembewegungen, Lungenzirkulation, Magenerkrankungen usw. ja auch sogar über Behandlung wird gesprochen. Über Prognose und Verlauf, dann über Theorien der Entstehung erfährt der Leser in den nächsten Kapiteln. Zwei Kapitel werden den bei Tieren auftretenden Verkrümmungen und den Tierexperimenten gewidmet. Vererbungsfragen werden leider nur kurz berührt; darüber hätte man gerne Ausführlicheres erfahren. Ein Kapitel enthält die konservative und operative Behandlung der Skoliosen und Kyphosen, sowie deren Komplikationen.

Wie wichtig die seitlichen Verkrümmungen der Halswirbelsäule sind, spiegelt sich auch darin, daß ihnen zwei Kapitel eingeräumt werden. Auch hier werden die bei Kindern vorkommenden Formen nicht vergessen.

Die Behandlung der einzelnen Krankheitsformen ist übersichtlich. Der Verfasser schickt eine kurze Erklärung voraus. Handelt es sich aber um weniger geläufige Krankheiten, bekommt man eine ausführlichere Darlegung wie z. B. bei Homocystinurie. Nicht selten werden auch wichtige kasuistische Mitteilungen auszugsweise referiert. Bei manchen Krankheitsbildern wäre jedoch eine definitivere Stellungnahme wünschenswert, wie z. B. bei der Legg-Calvéseher Erkrankung. Für den pädiatrisch interessierten Radiologen ist es von besonderem Wert, daß auch Kinderkrankheiten, so die erst in den letzten Jahren beschriebenen Dysostosen sachgemäß vorgeführt werden. Das alle wichtigen Quellen aufzählende Literaturverzeichnis erstreckt sich auf 120 Seiten, das Namen- und Sachverzeichnis auf je 60 Seiten, was als ein guter Beweis wissenschaftlichen Wertes des Werkes gelten kann. Die Ausstattung, die Abbildungen und Skizzen sind von höchster Qualität. Das Buch kann jedem, auch dem pädiatrisch interessierten Radiologen warm empfohlen werden.

K. GEFFERTH

SCHRÖTER, W., PRINDULL, G. und KAEHLER, U.: *Blutkrankheiten im Kindesalter*. 144 Seiten mit 22 Abbildungen und 4 farbigen Tafeln. Urban und Schwarzenberg, München—Berlin—Wien 1976. DM 38.—

Diese Monographie, die auch in der »Klinik der Gegenwart« Band X. veröffentlicht wurde, umfaßt ein großes Thema. Nach einem kurzen Überblick der Erythro-, Leuko- und Thrombozytose sowie der Blutgerinnung des gesunden Kindes beschäftigt sich der erste Teil mit den Erkrankungen des erythropoetischen Systems. Außer den Anämien in der Neugeborenenperiode erörtert dieses Kapitel vor allem die hämolytischen und aplastischen Anämien. Auch die anderen Entitäten dieser Krankheitsgruppe werden kurz überblickt. Die folgenden Abschnitte befassen sich mit den Polyzythämien, Methämoglobinämien und mit den Erkrankungen der Stammzellen sowie der Granulozyten. Ein langes Kapitel ist den Erkrankungen der Lymphozyten gewidmet. Der moderne Überblick der Immunmangelsyndrome leistet eine große Hilfe in der Diagnostik und Therapie dieser Krankheiten. Ohne Anspruch auf Vollständigkeit gibt der folgende Teil ein Bild über die neoplastischen Blutkrankheiten (Leukämien, neoplastische Lymphome) und die Erkrankungen des retikuloendothelialen Systems. Die thrombozytären Blutungsübel, die vaskulären Hämostasestörungen und die Koagulopathien bilden die Themen der letzten Abschnitte der Monographie.

Das ausgezeichnete Buch bietet den Pädiatern wertvolle Hilfe, da »der Alltag in Praxis und Klinik immer wieder zeigt, daß die Methoden der hämatologischen Diagnostik und die im letzten Jahrzehnt definierten Krankheitsbilder nur ungenügend bekannt sind«, wie darauf die Autoren im Vorwort hinweisen.

R. SZIGETI

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Kerpel-Fronius, E., Gács, G.: Serum insulin values. Acta paediat. Acad. Sci. hung. **16**, 197 (1975).

Crosse, V. M.: The Preterm Baby. 7th ed. Churchill Livingstone. Edinburgh and London 1971, P. 165.

Detter, J. C.: Biochemical Variation. In: Textbook of Human Genetics, ed. G. Fraser, O. Mayo. Blackwell Scientific Publications, Oxford 1975, P. 115.

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ACTA PAEDIATRICA

ТОМ XVIII—ВЫП. 1

РЕЗЮМЕ

МИФЫ О ГРУППАХ КРОВИ

А. С. ВИНЕР

В медицине все еще существуют многочисленные мифы, неправильные верования и автор рассматривает некоторые из них которые еще очень распространены в области групп крови. Он детально рассматривает какие неправильные положения, как например что форма сгустка крови меняется в зависимости от групповой принадлежности крови в системе АВО; или то, что все больное с контрактурой Дюруйтrena принадлежит к типу Rh₁ и Rh₂; или то предположение, что существует связь между группами крови и многочисленными болезнями и даже между темпераментом людей; или предположение существования ант—М-лектина или d и таким образом анти-d сыворотки, точно также фактора LW (Ландштейнера—Винера). Наконец автор осуждает способ обозначения по Ресу-Сенгеру и подчеркивает преимущества его собственной номенклатуры.

ОПЫТ, ПРИОБРЕТЕННЫЙ КОЛИЧЕСТВЕННОЙ РЕНОГРАФИЕЙ ПРИ ПИЕЛОНЕФРИТЕ В ДЕТСКОМ ВОЗРАСТЕ

Ш. КЕВЕШ, К. ПУМП

В работе рассматриваются данные 36 детей, страдающих пиелонефритом. Авторы дают количественную оценку радиоренографии и делают из нее выводы относительно почечной функции. Авторы констатируют, что количественная оценка радиоренографии выгодная, она чувствительно и избирательно осведомляет о наличии пиелонефрита и оказывает помощь в деле его лечения.

РАСПРЕДЕЛЕНИЕ ИЗОФЕРМЕНТОВ АМИЛАЗЫ В СЫВОРОТКЕ У СТРАДАЮЩИХ МУКОВИСЦИДОЗОМ ГОМО- И ГЕТЕРОЗИГотов

Э. ТАКАЧ, К. ШОХАР, А. ЛАСЛО, П. ПЕНЗЕШ, К. ДЮРКОВИЧ

Авторы разработали простой метод количественного определения и дифференцирования изоферментов амилазы в сыворотке (электрофорез полиакриламидным гелем и денситометрия), пригодные и для проведения генетического исследования популяции. Для определения распределения вышеуказанных изоферментов, авторы использовали соотношение активности (изофермента панкреатической и слюнной амилазы (рату P/S). У здоровых взрослых и у детей соотношение P/S в 85% случаях было выше 1 (среднее: 1,87 S.E. ± 0,23), в то время как носители гетерозиготных генов в 90% случаев давали результаты ниже 1,0 (среднее: 0,67 . S. E. ± 0,13). У полных муковисцидозных гомозиготов величина соотношения P/S была меньше 0,1. Последнее объясняется компенсаторным повышением активности амилазы слюны.

Описанный метод пригодный для исследования экзокринной функции поджелудочной железы и изоферментов амилазы в сыворотке. На основании соотношения P/S муковисцидозные гетерозиготы могут быть дифференцированы от муковисцидозных гомозиготов и от здоровых лиц.

ЧАСТОТА АНТИГЕНЕ Н—А ПРИ МУКОВИСЦИДОЗЕ

Г. КАЙЗЕР, А. ЛАСЛО, К. ДЮРКОВИЧ

Авторы провели типизация Н. А 12 гомозиготных, заболевших муковисцидозом детей и 32 гетерозиготных геноносителей, всего в отношении 29 антигенов из серии HLA—А и 2В. Основой диагноза у

гомозиготов было определение концентрации электролитов в поте, и, наряду с определением содержания липазы и амилазы в дуоденальном соке и в кале, бромидный тест Щепанского; идентификация гетерозиготов проводилась на основании бромидного теста. Сравнивая полученные результаты с таковыми типизации 130 здоровых доноров, авторы наблюдали среди больных и среди гетерозиготных геноносителей большую встречаемость HLA-B18: 50 и 31% по сравнению со средними величинами среди здоровой европейской популяции в 14%. Связь в группегомозиготов более тесная ($P < 0,005$), чем у геноносителей ($P < 0,02$).

ПАРАНЕОБЛАСТИЧЕСКИЙ СИНДРОМ

Д. ШУЛЕР, Р. КООШ, И. КРАУЗЕ, А. ПЕТЕР

Авторы описывают у ныне 5-летнего ребенка, котором в 1 1/2 годичном возрасте была успешно удалена медиастинальная нейробластома, возникшую после удаления нейробластомы мозжечковую энцефалопатию, в связи с которой авторы излагают встречающиеся в детском возрасте паранеобластические синдромы. В данном случае поскоклонус не наблюдался. Симптомы энцефалопатии под влиянием интратекального введения метотрексата (MTX), затем BCN. и CCN. быстро улучшались и через шесть месяцев за исключением некоторого умственного отставания (1,0 : 88) у ребенка не было симптомов. Авторы подробно излагают цитологическое исследование ликвора, проведенное в течении мозжечковой энцефалопатии. Состояние ребенка и в настоящее время, через 41 месяц после операции, безупречное.

СИНДРОМ НИКОЛАУ: ОСЛОЖНЕНИЕ ЛЕЧЕНИЯ ПЕНИЦИЛЛИНОМ ЗАТЯЖНОГО ДЕЙСТВИЯ

Г. ВЕЙНМАНН, Л. ШЕФЕР

Авторы наблюдали у двух детей, возникший после случайной интраартериальной инъекции пенициллина затяжного действия, возникновение синдрома Николау. Это опасная болезнь, проявляющаяся шоковым состоянием, lividной окраской кожи, образованием пузырей и далее вторичными параличами, требует немедленное тромболитическое лечение. Это лечение нужно срочно начать противошоковой терапией и гепаринизацией. Для профилактики синдрома Николау инъекции сле-

дует давать, особенно грудным и малым детям, с должной предосторожностью, с насасыванием ширица и т. д. в боковую широкую мышцу.

ЗНАЧЕНИЕ ОПРЕДЕЛЕНИЯ СОДЕРЖАНИЯ ЛИЗОЗИМА В СЫВОРОТКЕ

Л. КАРМАЖИН, А. МАКАИ, Ф. РОЗГНИ,
М. СЕВЕТЕШ, М. БАЛОГ

Авторы исследовали изменение активности лизозима в сыворотке у детей в возрасте от 1 года до 14 лет при различных болезнях и сравнивали эти данные с таковыми здоровых контролей. Лейкемические больные не фигурировали в рассмотренном больничном материале. По данным исследования, определение фермента пригодно для выявления или для исключения бактериальной этиологии процессов с невыясненной этиологией: для оценки эффективности иммуносупрессивной терапии и для раннего распознавания бактериальных инфекций, возникающих во время иммуносупрессивного лечения.

КИСЛОРОДНАЯ ТЕРАПИЯ И МАССИВНЫЕ ЛЕГОЧНЫЕ КРОВОТЕЧЕНИЯ В НОВОРОЖДЕННОМ ВОЗРАСТЕ

М. ФЕКЕТЕ, М. ХОРВАТ, Л. БАРДОШИ,
И. МЕШТЯН

Авторы наблюдали вследза проведением интенсивной кислородной терапии значительное учащение легочных кровотечений в новорожденном возрасте. Свой больничный материал они анализировали с точки зрения клинических и терапевтических параметров, играющих роль в этиопатогенезе легочных кровотечений. Они предполагают, что между интенсивной кислородной терапией и учащением легочных кровотечений существует связь, но они сомневаются в том, чтобы кислород при этом сыграл первостепенную роль.

ПРОСТОЙ МЕТОД ВЫБОРОЧНЫХ-ИССЛЕДОВАНИЙ ДЛЯ РАСПОЗНАВАНИЯ ВРОЖДЕННЫХ АНОМАЛИЙ РАЗВИТИЯ

К. МЕХЕШ

Автор разработал простой метод выборочного медицинского обследования для выявления скрытых врожденных аномалий развития, у кажущихся здоровыми ново-

рожденных. Составные элементы системы оценки: аномалии развития, смерть грудного ребенка по невыясненной причине в семейном анамнезе, мертворождения, внутриутробная атрофия плода (по 2 балла) и 6 меньших аномалий развития: антимонолоидная глазная щель, гипертелоризм, преаурикулярный свищ, четырехпальцевая складка, аномалии сосков и больших пальцев ног (по 1 баллу).

Из обследованных таким методом 1000 новорожденных у 28 число баллов было 3 или больше, среди них у 6 были обнаружены врожденные аномалии развития в ходе отдельного обследования. Одновременно с этим у всех остальных новорожденных и у новорожденных с числом баллов меньше 2 только в двух случаях была обнаружена скрытая аномалия развития. Хотя отдаленное обследование грудных детей не было полным, результаты указывают на то, что метод полезный для выбора подозрительных случаев для проведения сложных и дорогостоящих клинических и генетических исследований.

ПАРЕЗ ДИАФРАГМАЛЬНОГО НЕРВА В РЕЗУЛЬТАТЕ РОДОВОЙ ТРАВМЫ

К. МЕНЦЕЛ, В. ГЕНСЛЕР, Э. ГОТТШАЛК,
М. ЛИНКЕ, Б. ТЁПКЕ

Родовая травма обычно после осложненных родов вызывает паралич диафрагмального нерва. Большинство таких случаев

комбинируется с параличом верхнего или полного сплетения. В противоположность к европеритонеальным грыжам и врожденных гипоплазиям диафрагмы, обычно затронут правый диафрагмальный нерв. В тяжелых случаях следует немедленно провести трансторакальную пликацию диафрагмы. Авторы приводят 5 наблюдавшихся ими случаев.

ПОКАЗАТЕЛЬ ЭНЕРГИЯ/БЕЛОК. III СРАВНЕНИЕ ПОКАЗАТЕЛЯ С ПАРАМЕТРОМ, ХАРАКТЕРНЫМ ДЛЯ НАРУШЕНИЯ РАВНОВЕСИЯ БЕЛКОВОГО ПИТАНИЯ

М. АМАДОР, Й. БАКАЛЛАО, М. ХЕРМЕЛО,
Р. ФЕРНАНДЕС, К. ТОЛОН, Х. ПЕРЕС

Для определения пригодности показателя энергия/белок авторы сравнили в составшей из 97 неправильно питающихся лиц группе этот показатель с биохимическим параметром, течно выявляющим также и краевые формы расстройств питания. Сравнение проводилось с коэффициентом незэссенциальных/эссенциальных аминокислот. Авторы исследовали линейную регрессию двух коэффициентов. Модель оказалась подходящей и статистически достоверной, $r = 0,552/p 0,001$.

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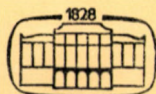
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Az *Acta paediatrica Academiae Scientiarum hungaricae* angol, francia, német, és orosz nyelven közöl értekezéseket a gyermekgyógyászat és határterületei köréből. Megjelenik negyedévenként; 4 füzet képez egy kötetet.

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Peridural lipomatosis

By

J. VESPER, E. MOESER, K. J. NEUMÄRKER

Clinic of Neurology and Clinic of Surgery, Department of Medicine (Charité), Humboldt University, Berlin, GDR

(Received 11th November, 1976)

Fifteen cases of peridural lipomatosis are presented. All patients were treated surgically in the years 1965 to 1974 and reexamined in 1975. In 5 cases the condition improved, in 4 cases it was unchanged and in 6 patients it deteriorated. It is emphasized that the question of surgical therapy must be decided individually.

Since the description of its typical neurological and radiological symptoms [5, 10] peridural lipomatosis has been an entity well-known to neurologists and neurosurgeons. The clinical picture comprises gait disturbances, paresis of the lower limbs, bladder dysfunction and other neurological and orthopaedic signs. The diagnosis is based upon electromyographic and X-ray studies including air myelography. By the latter method the peridural space is determined indirectly on the basis of the distance between the subarachnoidal space and the spine. The distance is normally 3–4 mm (Fig. 1). If the widening of the peridural space and narrowing of the subarachnoidal space is associated with radiological or other signs of pressure and progressive neurological symptoms, surgery is indicated.

In the years 1965 to 1974, we observed 15 children. Their age ranged from 2 to 7 years. Their symptoms

are shown in Table I; characteristic were the gait disturbances, spastic paresis and hypotonic paresis of the lower limbs, long tract signs, foot deformities, sensory disturbances and primary bowel or bladder disturbances. EMG and X-ray studies including air myelography were carried out in all patients. Particularly in spastic cases the EMG

TABLE I

Presenting signs and symptoms in 15 patients with peridural lipomatosis

Main symptoms	Number
Gait disturbance	8
Spastic paresis of lower limbs	4
Atonic or hypotonic paresis of lower limbs	5
Long tract signs	5
Foot deformity	4
Growth asymmetry of leg	3
Primary bowel or bladder dysfunction	2
Sensory disturbance	1

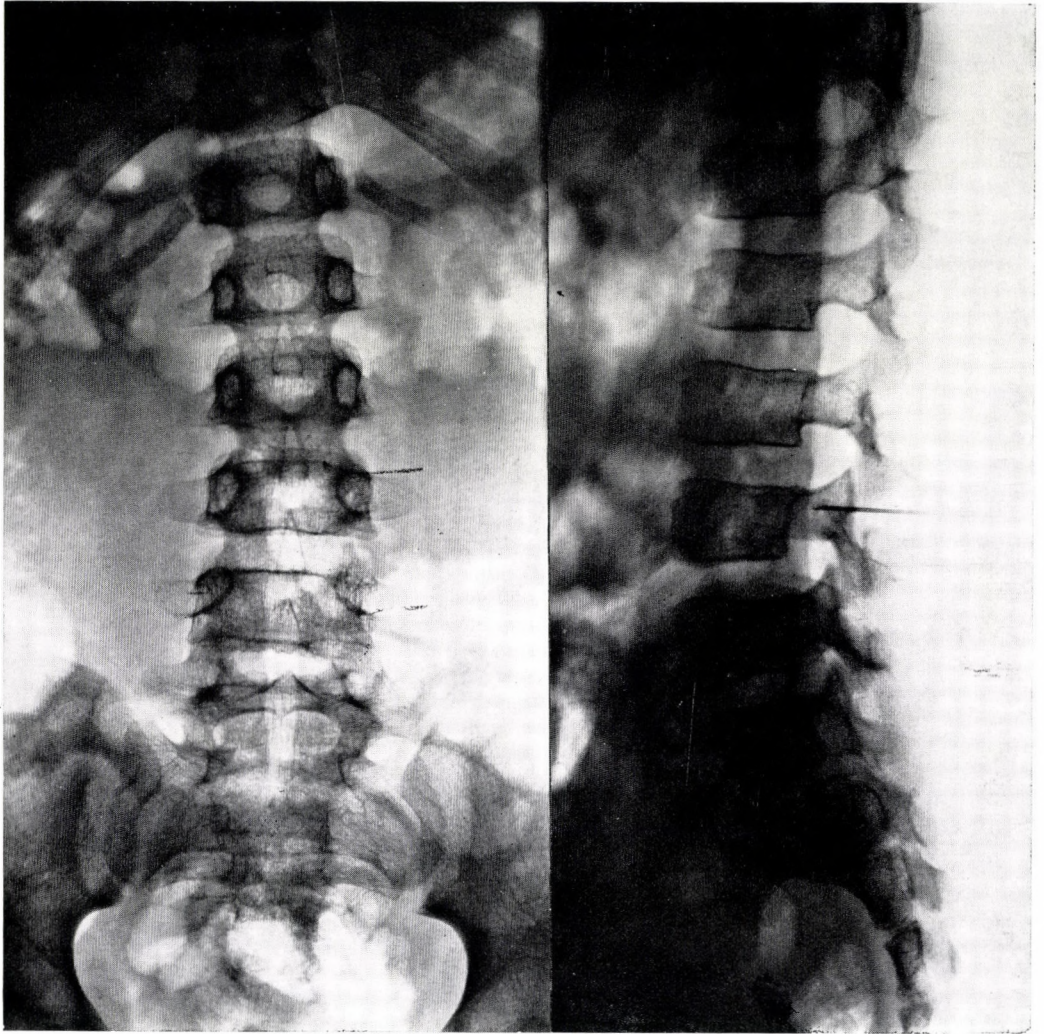


FIG. 8-year-old boy with peridural lipomatosis L4/L5. The distance between spine and subarachnoidal space is 8 mm.

revealed a proximal damage of the peripheral neurone in addition to supraspinal disturbances. Typical X-ray signs were observed in every case, including a narrowing of the spinal canal, excavation of the dorsal part of the spine, widening of the interpedicular space, deformation of

the pedicle, anomalies of the spines and laminar arches, etc. These signs were often combined with dysraphic malformations: spina bifida in 7 cases, hydrospina in 4 cases, scoliosis connected with postural anomalies in different regions of the vertebral column in 8 cases, etc.

TABLE II

Level of peridural lipomatosis in the lumbosacral region in 15 cases

Case No.	D12	L1	L2	L3	L4	L5	S1	S2	S3	S4	S5
1			—	—	—	—	—				
2				—	—	—	—				
3			—	—	—	—	—	—	—		
4				—	—	—	—	—	—		
5					—	—	—				
6					—	—	—				
7					—	—	—				
8					—	—	—				
9			—	—	—	—	—				
10			—	—	—	—	—				
11				—	—	—	—				
12					—	—	—	—	—		
13				—	—	—	—	—	—		
14			—	—	—	—	—	—	—		
15			—	—	—	—	—	—	—		

The localization of peridural lipomatosis in these patients is shown in Table II; it is seen that the favoured site was the lumbosacral region.

Treatment was surgical in all the 15 cases. The operation consisted in decompressive laminectomy with biopsy and total or subtotal removal of fatty tissue, particularly in the dorsal and lateral parts of the peridural space. In the ventral part the surgical procedure was often limited, because the nerve roots were enlarged and connected with the fatty tissue.

The characteristic histological finding was mature fatty tissue partly mixed with fibrous elements. Signs of malignancy were absent.

When examining the patients in 1975, the results were as follows.

In 5 cases an improvement was found with complete or incomplete regression, particularly of the gait disturbance.

In 4 cases the neurological condition persisted in an unchanged form, showing no improvement.

TABLE III

Peridural lipomatosis associated with neuromuscular systemic diseases

Disease	Number
Spinal muscle atrophy	
Werdnig-Hoffmann type	2
Kugelberg-Welander type	1
Congenital muscle dystrophy	1
Neurogenic muscle atrophy, unclassified	1
Neurofibromatosis Recklinghausen	1

In 6 patients a deterioration of the neurological symptoms occurred. In these cases the condition was connected with systemic diseases, as shown in Table III. Muscle atrophy in the upper limbs developed after the operation in 2 cases.

COMMENT

In accordance with a number of authors [1, 4, 6, 7, 9, 11, 12] it may be said that the exact pathogenesis of spinal lipomas and of peridural lipomatosis is unclear. The high incidence of associated congenital anomalies, the age at onset and the preferentially lumbosacral location suggest a developmental origin from embryonic mesenchymal cells or residues of embryonic ectodermal cells involved in the formation of the spinal cord [2, 3]. The cause of the dysraphic syndromes in the lower back could be a metabolic error before the fifth somite stage [3].

The clinical features in our 15 cases were not specific. The same symptoms may occur in various other diseases, for instance different forms of restriction of cranial migration of the spinal cord [9], tumours in the lumbosacral region [1, 8, 11, 12], systemic diseases beginning with neurological symptoms in the legs [13], etc. In most cases the combination of clinical neurological and radiological findings will allow to decide for a surgical approach. It is nevertheless important that the widening of the peridural space revealed by air myelography is not always a sign of mechanical pressure, as shown by those of our cases in which the lipomatosis was associated with some systemic disease.

In accordance with Matthias and Lausberg [9] it should be emphasized that the question whether or

not an operation is indicated in childhood, must be considered individually in each case.

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Dr. med. J. VESPER,
Nervenklinik der Charité
Schumannstr. 20/21
DDR-104 Berlin

Effect of NH_4Cl -induced metabolic acidosis on urinary calcium excretion in young infants

By

E. SÜLYÖK

Department of Paediatrics, University Medical School, Pécs

(Received 11th November, 1976)

Urinary calcium and net acid excretion as well as the acid-base parameters of the blood were determined before and after a NH_4Cl load applied in a single dose of 2.8 mEq/kg body weight.

In order to assess the effect of maturity and postnatal development, a study was made on (a) 47 newborn infants with a birth weight of 1000–4380 g on the 7th day; and (b) 11 prematures with a birth weight of 1000–1970 g, weekly for 6 consecutive weeks. The results were compared to those for infants of 3–11 months of age.

(i) At one week of age, NH_4Cl ingestion resulted in a significantly greater increase of metabolic acidosis in infants with a birth weight under 2000 g than in the larger ones. With increasing postnatal age the metabolic acidosis of premature infants increased to about the same extent in response to NH_4Cl load irrespective of the pre-loading level of acidosis or postnatal age.

(ii) Both the urinary NAE and UCae of one week-old infants increased markedly with increasing birth weight and they were invariably augmented by the acid load.

NH_4Cl -induced NAE and UCae were significantly higher in infants with a birth weight over 2500 g than in their smaller matches ($p < 0.025$).

(iii) In prematures, in spite of the postnatal development of renal capacity to excrete hydrogen ions, the NH_4Cl -induced UCae remained unchanged, or expressed in per cents of the pre-loading level even a slight, statistically not significant decrease could be observed during the first six weeks of life.

(iv) It is suggested that the skeletal buffering measured as NH_4Cl -induced urinary calcium loss, may be an important defence mechanism against acidosis already in the early period of life. Low-birth-weight prematures are, however, compromised in face of an acid load by the limited buffer function of the bones.

Skeletal buffering has been shown to be an important defence mechanism against acidosis in the different forms of chronic renal diseases and in subjects given exogenous acid load. The chronic metabolic acidosis results in demineralization of the bones, increased urinary calcium loss

and in a negative calcium balance [3, 17, 18, 19, 26].

This well-known relationship between the skeletal system and metabolic acidosis is somewhat complicated during the early weeks of life. The imbalance between metabolic acid production and the limit-

ed renal capacity to excrete hydrogen ions, particularly in low-birth-weight neonates, leads to late metabolic acidosis [13, 14]. Skeletal growth and calcium deposition in the bones liberates hydrogen ions, producing a further acid load on the already disturbed acid-base homeostasis [15]. The higher the retention rate of calcium the more pronounced the acidosis in small premature infants [6].

In the present study an attempt was made to investigate the role of the skeletal system in the control of acidosis, by measuring urinary calcium excretion (UCaE) in NH_4Cl -induced acidosis. The influence of birth weight and postnatal age on the NH_4Cl -induced changes in UCaE was also studied.

MATERIAL AND METHODS

Three groups of male infants were selected for the study.

Group I comprised 47 one-week-old newborn infants who were assigned according to their birth weight into the three categories, (a) 1000–1500 g (n: 13, mean: 1312 g); (b) 1500–2000 g (n: 22, mean: 1754 g); and (c) more than 2500 g (n: 12, mean: 2935 g). The corresponding mean gestational age was 30.6 (range: 28–33), 34.1 (range: 30–41) and 37.9 (range: 36–41) weeks, respectively.

Group II consisted of 11 premature infants with a mean birth weight of 1644 g (range: 1000–1970 g) and a mean gestational age of 32 (range: 29–35) weeks.

In all cases the pregnancy, the delivery and the perinatal course were uneventful. The birth weight of all infants, except for a small for dates pair of twins in group I/b

(birth weight: 1850 and 1890 g, gestational age: 41 weeks), fell within the 10th and 90th percentiles according to the local chart [8].

The infants were fed appropriate cow's milk formulas by a round the clock feeding pattern at 2-hourly intervals until they weighed about 1500 g, and 3-hourly thereafter. Food intake was gradually increased in all infants to attain a calorie and fluid intake of 120–140 cal/kg and 180–200 ml/kg, respectively, by the end of the second week of life. 3000 IU vitamin D_3 was given on alternate days after 14 days of age.

Group III included 22 healthy male infants of 6817 g mean body weight (range: 4500–11750 g) and 6.9 months mean postnatal age (range: 3–11 months). Vitamin D_3 was given in a dose of either 3000 IU on every second day or 50 000 IU weekly after 2–4 weeks of age. No clinical, biochemical or radiological features of rickets were observed prior to the study. The babies were fed cow's milk formulas providing about 2.5 g protein and 100–120 cal/kg/day, respectively.

PROCEDURES

Urinary calcium and net acid excretion as well as the acid-base parameters of the blood were determined before and after an NH_4Cl load applied in a single dose of 2.8 mEq/kg body weight. Urine was fractionally collected under toluene for a period of 12 hours. The specimens were refrigerated, pooled and analysed immediately for pH, titratable acidity, ammonia and within a few hours for calcium. The collection started at 10 p.m. for a control period of 12 hours. At 10 a.m. 2.8 mEq/kg NH_4Cl was given by mouth or stomach tube and urine collection continued for another 12 hours.

Arterial blood samples were obtained at the end of the control period and about 4 hours after NH_4Cl ingestion. The NH_4Cl loading test was performed on the 7th day

of life in group I, on the 7th day and later weekly for 6 consecutive weeks in group II and on one occasion in group III.

ANALYTICAL METHODS, CALCULATIONS

Arterial blood acid-base status was determined by the method of Astrup [1]. Urinary pH was measured at 38°C with a Radiometer pH meter, titratable acidity according to Folin (end point of titration, pH 7.4), urinary ammonia according to McCullough [21] and urinary bicarbonate was calculated from the Gamble nomogram, using the corresponding pH value [9]. Urinary calcium was measured complexometrically [23].

Net acid excretion consisted of the sum of urinary titratable acid plus ammonium ion minus bicarbonate. Statistical analysis

was performed by calculating the means and the standard errors. The p values presented were determined by Student's *t* test.

RESULTS

Metabolic acidosis

To characterize the changes in metabolic acidosis, the negative base excess before and after NH_4Cl ingestion is shown in Fig. 1. In one-week-old newborns the base excess initially was similar irrespective of birth weight. All infants responded to the NH_4Cl loading by increasing the negative base excess (Fig. 1/a).

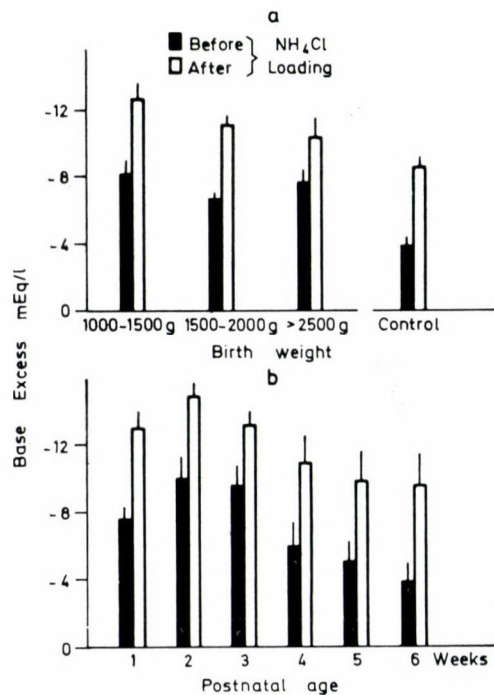


FIG. 1. Base excess in one-week-old newborn infants with different birth weights (a) and a group of preterm infants during the first six weeks of life (b), before and after 2.8 mEq/kg NH_4Cl administration. Vertical bars represent the standard errors of the means.

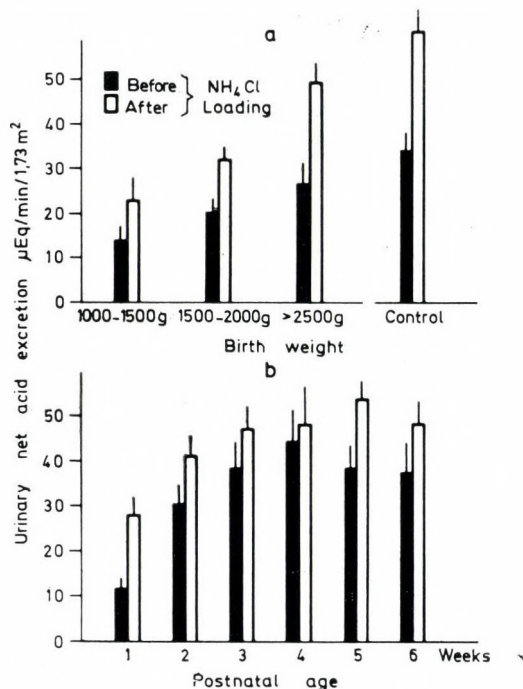


FIG. 2. Urinary NAE of one-week-old newborn infants with different birth weights (a) and a group of prematures during the first six weeks of life (b), before and after 2.8 mEq/kg NH_4Cl administration.

This increase was significantly higher in infants with a birth weight under 2000 g than in the larger ones ($p < 0.05$)

The postnatal development of metabolic acidosis in premature infants (group II) is seen in Fig. 1/b. The metabolic acidosis was the most pronounced in the second and third weeks of life and it fell to about 4 mEq/l by the end of the study. This value agreed well with that found for older infants. The NH_4Cl load resulted in an increase of acidosis of about the same degree irrespective of either the pre-loading base excess, or the postnatal age of the infants.

Urinary net acid excretion (NAE)

Urinary NAE of one-week-old infants markedly increased with increasing body weight and it was invariably augmented by the acid load. The NH_4Cl -induced H^+ excretion (Δ NAE) was significantly higher in infants with a birth weight over 2500 g than in their smaller matches (Fig. 2/a).

With increasing postnatal age the NAE of premature infants was steadily increasing and reached its maximum of about 45 $\mu\text{Eq}/\text{min}/1.73 \text{ m}^2$ at the end of the fourth week. Subsequently it was maintained at that level or even a slight, statistically

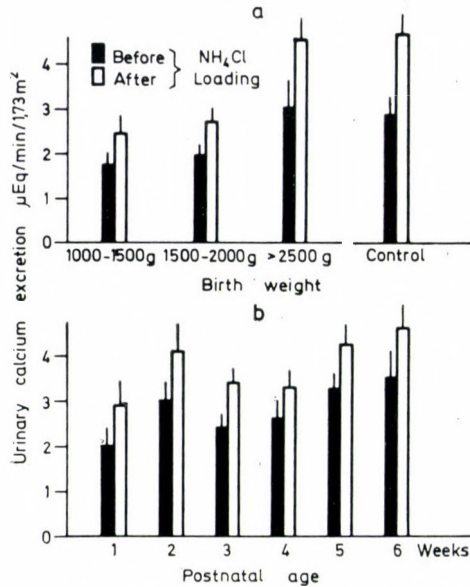


FIG. 3. UCaE of one-week-old newborn infants with different birth weights (a) and a group of prematures during the first six weeks of life (b), before and after 2.8 mEq/kg NH_4Cl administration.

insignificant, decrease could be observed. In response to NH_4Cl administration the NAE significantly rose, but the magnitude of this rise considerably changed with postnatal age. During the first four weeks of life Δ NAE gradually decreased to a value of 4 $\mu\text{Eq}/\text{min}/1.73 \text{ m}^2$ followed by an increase in the 5–6th weeks which was comparable to that found in the first week, but significantly lower than that observed in older infants (Fig. 2/b).

Urinary calcium excretion (UCaE)

As shown in Fig. 3/a, UCaE of the newborn infants markedly increased with increasing birth weight both before and after NH_4Cl loading,

while the NH_4Cl administration resulted in a significantly higher rate of UCaE in infants with birth weight over 2500 g ($p < 0.025$).

UCaE of premature infants showed a clear tendency to rise during the study period of six weeks, although this trend did not reach significance and it was interrupted by a higher value found in the second week (Fig. 3/b). NH_4Cl ingestion enhanced the rate of UCaE in each postnatal age and paired *t*-testing showed the differences to be significant ($p < 0.025$).

Relationship between UCaE and NAE

Figure 4 compares the NH_4Cl -induced increase of urinary NAE and UCaE. It can be seen that in

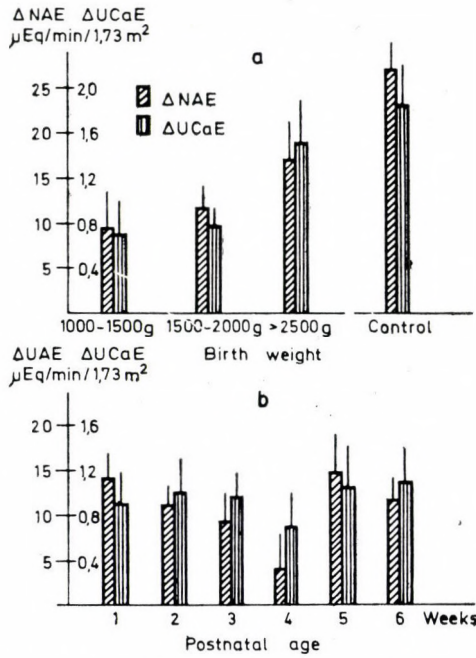


FIG. 4. NH_4Cl -induced urinary NAE and UCae of one-week-old newborn infants with different birth weights (a) and a group of prematures during the first six weeks of life (b).

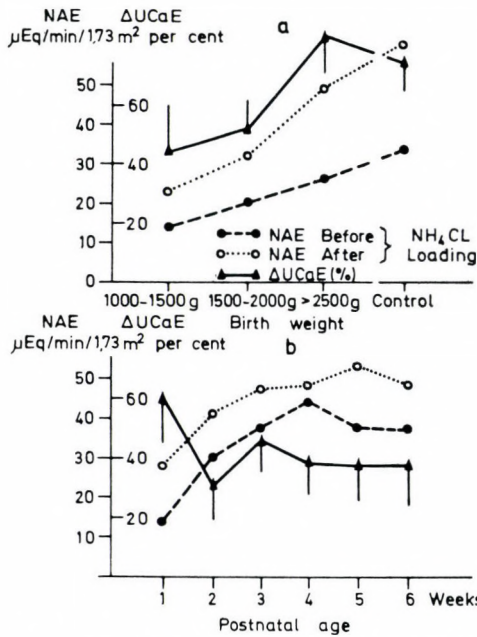


FIG. 5. Urinary NAE before and after NH_4Cl administration and the NH_4Cl -induced UCae expressed in percentage of the basal value of one-week-old newborn infants (a) and a group of prematures during the first six weeks of life (b).

the first week of life both increased at a similar rate with increasing body weight (Fig. 4/a). The pre-matures of group II responded to NH_4Cl loading with about the same increase of UCaE irrespective of postnatal age, and their NAE gradually fell until the fourth week, followed by an increase in the further periods of study (Fig. 4/b).

In older infants both responses were parallel and significantly higher than that found for the premature infants ($p < 0.01$).

Urinary NAE both before and after NH_4Cl ingestion and the NH_4Cl induced increase of UCaE expressed as a percentage of pre-loading value are shown in Figure 5. It can be seen that the newborn infants with birth weights above 2500 g were able not only to excrete more hydrogen ions but also to increase the UCaE similar as the older infants (Fig. 5/a). In pre-matures, the percentage increase of UCaE in response to NH_4Cl load was most pronounced in the first week (60.8%), and with the increasing renal capacity to excrete hydrogen ions it decreased to 36% by the 5–6th postnatal week. This general declining trend was interrupted by a deep fall in the second week of life (Fig. 5/b).

DISCUSSION

A complex relationship has been demonstrated between metabolic acidosis and calcium metabolism. Acute metabolic acidosis raises serum cal-

cium concentration by directly releasing calcium from the bones and also by enhancing the PTH effect to mobilize calcium from the bones. In the kidney, acidosis directly inhibits tubular calcium reabsorption, but at the same time enhances the effect of PTH to increase it. These two opposite effects of acidosis on renal calcium handling result in an increased urinary calcium loss [4].

In addition to metabolic acidosis, the UCaE influenced by other factors, even in healthy subjects, such as dietary calcium intake [16], calcium-phosphorus intake ratio [20, 32], fat composition of the diet [2, 11], skeletal size [16], hormones [25], vitamin D supply [24] and the maturity of the kidney [30].

In order to assess the effect of metabolic acidosis on UCaE, it was necessary to standardize the experimental conditions (similar nursing conditions, standard feeding pattern and vitamin D supply) and to keep constant the factors other than acidosis. This latter criterion was fulfilled by applying an NH_4Cl load at the end of the control period of 12 hours, followed by a test period of the same duration. In this way each subject served as his own control and the changes in UCaE were thought to be due solely to the NH_4Cl -induced metabolic acidosis.

On the basis of the well-established relationship between metabolic acidosis and UCaE [3, 17, 18, 19, 26], the acidosis-induced urinary calcium loss may be regarded as a reliable measurement of skeletal buffering.

It must, however, be taken into account that in response to acidosis calcium is released not only from the bones, but from the exchangeable calcium pool as a whole [27]. On the other hand, the bone also contains a very large quantity of sodium and in metabolic acidosis sodium is also released into the extracellular fluid in exchange for hydrogen ions [5].

The present results seem to suggest that in newborn infants the buffering function of the skeleton is increasing with increasing birth weight. This finding is consistent with earlier observations demonstrating that in the human fetus calcium accumulates at an increasing rate as pregnancy advances, particularly after the 28th week [28, 29].

In prematures, the postnatal calcium retention rate was found to be lower than that *in utero*, resulting in a cumulative calcium deficit which manifests with a marked bone demineralization at the age of 6–7 weeks [6, 7, 10, 22, 29]. This cumulative calcium deficit may be responsible for our findings showing that the acidosis induced UCae in premature infants remains unchanged or, expressed in percents of the preloading level, even a slight, statistically not significant decline may be seen as the infants grow older.

The higher rate of UCae in response to NH_4Cl ingestion in infants of higher birth weight might be due to the more advanced maturation of renal handling of calcium. The results obtained in prematures, where

the acidosis induced-UCae remains unchanged in spite of the postnatal development of renal capacity to excrete calcium, provide, however, suggestive evidence that in NH_4Cl acidosis the increase of urinary calcium loss does not depend on renal maturity and it is mainly influenced by skeletal size and mineralization.

Most of the present data on the acid-base parameters of the blood and urinary NAE have been published previously [12, 31]. In this study the UCae was related to them in an attempt to assess the relative importance of skeletal buffering in the control of acidosis.

Assuming a bone buffer equivalent quoted by Kildeberg of 20 mEq H^+/OH^- for each 1000 mg Ca^{++} laid down or reabsorbed from the skeleton [14], the observed changes in calcium excretion may be regarded to reflect an unimportant skeletal buffering relative to the urinary NAE.

In chronic NH_4Cl -induced acidosis, however, the quantity of retained acids was matched on an equivalent [17], or—as a result of carbonate-phosphate interchange within the apatite crystal—even less than equivalent basis, by negative calcium balance [18]. These data seem to suggest a higher bone buffer equivalent, consequently a more efficient skeletal buffering.

The present study does not provide sufficient quantitative information as to the role of the skeleton in the control of acidosis, therefore simultaneous hydrogen ion and calcium balance studies are needed to

describe quantitatively the relationship between metabolic acidosis and the skeletal system. Still, our findings can be interpreted as indicating that skeletal buffering may be an important defence mechanisms, against acidosis even in the early period of life, when the growth and mineralization of the skeleton has mainly been regarded as an additional factor to increase the endogenous acid production [6, 14, 15].

It is also suggested that low-birth-weight neonates are handicapped in maintaining the normal acid-base status not only by the limited renal capacity to excrete H^+ , but also by the limited buffer function of the bones.

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E. SULYOK, M. D.,
 József A. u. 11
 H-7623 Pécs, Hungary

Psychischer Zustand im Schulalter von wegen Hydrozephalus operierten Kindern

Von

L. VÉKÁSSY und E. PARAICZ

Institut für Neurochirurgie, Budapest

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I. Die wegen Hydrozephalus operierten Kinder eignen sich zur Erziehung und können unterrichtet werden. Sie verfügen über einen ausreichenden Intellekt und über die Möglichkeit zur selbständigen Lebensführung. Unter unseren 30 schulpflichtigen Patienten besuchen 17 die Grundschule, 8 eine heilpädagogische Schule, 2 eine Klasse mit geringerer Schülerzahl (Übergang zwischen Grundschule und Heilpädagogie), während 2 Kinder schulbefreit sind.

II. Sie verfügen über einen guten Kontakt, ihre Gruppenposition und ihre interpersonalen Beziehungen sind gut, sie weisen jedoch affektive Schwankungen auf.

III. Als Folge geistig-physischer Belastungen melden sich bei ihnen emotionale Schwankungen, in der Familie sind ihre Beziehungen dependent und sie haben einen intensiven Anspruch auf Empathie.

IV. Neue, unerwartete Reize lösen bei diesen Kindern Schwierigkeiten aus, ihre vegetativen und motorischen Eigenschaften sind akzentuiert, ihre Aufmerksamkeit zeigt Schwankungen, sie werden rasch müde, und präferieren das Thema „Krankheit“.

V. Für die Schule und für die Eltern muß eine genau umgrenzte Behandlungsweise ausgearbeitet werden, die sich zur Förderung des Resozialisationsprozesses der mit Hydrozephalus operierten Kindern eignet.

Die bei der Behandlung der hypertensiven, progressiven Form des Hydrozephalus des Säuglingsalters angewandte ventrikuläre Shuntoperation brachte sowohl in der Klinik der Krankheit als auch in den späteren somatopsychischen Ergebnissen grundlegende Änderungen mit sich. Die Zahl der neurologisch und psychosomatisch kompensierte Fälle hat sich wesentlich erhöht. Da seit Einführung des erwähnten Eingriffs bereits Jahre vergangen sind, bot sich eine Möglichkeit zur Überprüfung der Entwicklung dieser Kinder. In diesem Sinne trachteten wir in vor-

liegender Arbeit die Frage zu beantworten, wie sich unsere, das Schulalter erreichten und bereits die Schule besuchenden, mit Hydrozephalus operierten Patienten in der Familie bzw. in der Schule verhalten.

ÜBERBLICK DER LITERATUR

NULSEN [6] fand bei einem summierten Krankenmaterial (95 eigene Fälle, 544 Fälle von SPITZ sowie 655 Fälle von FOLTZ) in 55–70 % der Fälle einen IQ zwischen 0,75 und 0,85. 15 der 34 Kindern, bei denen MEALEY und Mitarb. [5] eine

atriale Shuntoperation durchführten, waren nach 7 Jahren noch am Leben, 5 von ihnen verfügten über eine normale Intelligenz, und weitere 5 waren unterrichtbar. In einer Gruppe, in der der Prozeß spontan stagnierte, fand LAURENCE [3] in 41 % der Fälle einen IQ-Wert zwischen 100 und 85, während nach den Angaben von HAGBERG und SJÖGREN [1] eine normale Intelligenzleitung in der Hälfte der Fälle zu registrieren war. HEMMER und DILL [2] führten ihre Untersuchungen 5–10 Jahre nach dem Eingriff durch: der IQ war zwischen 90 und 110 in 42 % der Fälle, zwischen 70 und 90 in 55 % der Fälle; über das Schicksal von 34 der 174 operierten Fälle berichteten die erwähnten Verfasser nicht. LORBER [4] beobachtete in 22 von 28 Hydrozephalusfällen; der IQ im Alter von 7–11 Jahren in 3 Fällen 120–129, in 11 Fällen durchschnittlich, in 4 Fällen niedrig und in 5 Fällen retardiert. So vertrat er die Ansicht, daß der chirurgische Eingriff bei keinem kongenitalen Hydrozephalus versäumt werden darf. UNGER und Mitarb. [8] berichteten über 42 Kinder, bei denen eine Shuntoperation vorgenommen wurde; die Werte des IQ waren bei 17 normal, bei 10 Patienten war eine schwere geistige Retardation zu finden.

Im Laufe unserer vorangehenden Untersuchungen gelangten wir zur Feststellung, daß die geistige Entwicklung der shuntoperierten Patienten das dem Alter entsprechende Niveau meistens erreicht oder annähert [7]. Wir untersuchten 23 Kin-

der im Alter zwischen 2 und 5 Jahren; ihre Entwicklung war durch verspätete Maturation und eine empfindliche, instabile Affektneigung charakterisiert. Der mentale Zustand war in 14 Fällen intakt, in 9 retardiert (die Retardation belief sich in 3 Fällen auf 1 Jahr und in 6 Fällen auf 2 bzw. mehr Jahre). In einer darauffolgenden Untersuchungsserie überprüften wir die sich auf die Entwicklung und auf den mentalen Zustand beziehenden Daten von 100 Hydrozephalus-operierten Kindern. Die Entwicklung war oft verzögert: sie saßen mit 11 Monaten, standen mit 14, liefen mit 24, redeten mit 31 und wurden stubenrein im Alter von 29 Monaten. 37 Kinder waren linkshändig, sie zeigten eine affektiv-emotionelle Instabilität, ihre Aufmerksamkeit war fluktuierend und ermüdete rasch, ihre Beziehungen wiesen einen dependenten Charakter auf. In der Familie und der Schule bildeten sie soz. einen Fremdkörper und wurden somit betont affektiv behandelt. Weder die Umgebung noch das Kind wußten es, wie sie überhaupt mit dem Shunt leben sollen: Die mentalen Leistungen entsprachen in 80 % dem Alter und den Anforderungen der Schule, in 9 % der Fälle belief sich die Retardation auf 1 Jahr, in 7 % auf 2 Jahre, während 4 % der Fälle waren imbezil.

Ein Vergleich der mentalen Leistungen der in der Literatur publizierten verschiedenen Gruppen ist schwierig, da keine einheitliche und mitunter sogar unbekannte Untersuchungs-

verfahren und Intelligenzkategorien verwendet worden sind. Außerdem handelt es sich offensichtlich um zwei verschiedene Gruppen. Zur Zahl der spontan stagnierenden Fälle zählt man heute auch jene Fälle, die früher ohne Shunt tödlichen Ausgangs waren, dank der Operation aber mit guten Fähigkeiten am Leben gehalten werden konnten. Das ist eine neue, sich gerade jetzt ausbildende Gruppe der Kinder, deren Charakteristika noch unbekannt sind.

Die kontinuierliche Spätkontrolle der mentalen Funktionen muß in die Behandlung unbedingt eingebaut werden, da ja die sich aus den früheren Schädigungen der Assoziationsysteme ergebenden Symptome sich verhältnismäßig rasch normalisieren, weshalb die zentrale Funktion einen brauchbaren Parameter der Gehirnentwicklung darstellt. Unter den Patienten, die an schwerer Hypertension litten und früher ohne Shunt verstorben wären, erreicht heute bereits eine stets ansteigende Zahl das Schulalter und so bietet sich die Möglichkeit ihre mentale Leistung, ihre Anpassungsfähigkeit bzw. ihre Persönlichkeitseigenschaften kennenzulernen, d. h. unsere diesbezüglichen Kenntnisse zu erweitern.

MATERIAL UND METHODIK

Unser Material besteht aus 30, an unserer Abteilung operierten (atriale Shuntoperation, mit dem Pudenz-Heyerschen Katheter; die Eingriffe fanden im Alter zwischen 5 und 14 Monaten statt) Kindern, die heute bereits das Schulalter

(zwischen 6 und 11 Jahren) erreicht haben; 3—9 Jahre nach der Operation sandten wir den Eltern und der Schule dieser Kinder einen Fragebogen, welcher in 5 wichtigen Themenkreisen gehörende 60 Fragen enthielt; die erwähnten Themenkreise waren:

- I. mentale Leistung,
- II. Kontakt,
- III. Schwierigkeiten, charakteristischen Eigenschaften,
- IV. Gefühle-Emotionen
- V. Vorschläge.

Da wir die vielseitige Beantwortung der gestellten Fragen bestrebten, werden in vorliegender Arbeit nur die auf 48 Fragen erhaltenen Antworten ausführlich erläutert (einige Fragen überdeckten oder ergänzten einander).

1. *Geschlecht*: 16 Mädchen, 14 Knaben.

2. *Alter*: Alle Kinder haben das 6. Jahr vollendet und sind demzufolge schulpflichtig.

3. *Wo wohnen sie* (in der Familie, in einem Institut, in einer Wochenschule (von wo sie nur am Wochenende nach Hause gehen, oder bei Pflegeeltern): 28 Kinder leben in der Familie, 2 im Institut.

4. *Wohin wurde das Kind eingeschult*

17 Kinder in die Grundschule,

8 Kinder in eine heilpädagogische Schule

3 Kinder sind schulbefreit (1 Jahr Verschiebung)

2 Kinder besuchen eine Klasse mit geringerer Schülerzahl (Übergangsstufe zwischen Grundschule und Heilpädagogie)

5. *Spezielle Schulabteilung*: 2 der 17 Grundschüler besuchen eine Schulabteilung für Mathematik.

6. *Durchfall bei der Prüfung oder nicht versetzt*: Alle 17 Grundschüler haben die Prüfung bestanden und wurden versetzt, 3 der 8 Schüler der Heilpädagogie fielen im ersten Semester der ersten Klasse durch.

7. *Welche Schule bzw. welche Klasse besucht das Kind?*

17 Kinder besuchen die Grundschule (von der I. bis zur IV. Klasse),

8 Kinder eine heilpädagogische Schule (1 Kind einen vorbereitenden Kurs für Blinde, 4 Kinder eine Klasse für debile und 3 eine für imbecile Fälle),

2 Kinder eine Klasse mit geringerer Schülerzahl,

3 Kinder erhielten 1 Jahr Verschiebung (ihnen haben wir auch weiterhin den Besuch des Kindergartens empfohlen).

8. *Studienergebnisse*: Die Ergebnisse der 17 Grundschüler zeigten folgendes: ausgezeichnet 3 Kinder, Sehr gut 4 Kinder, Gut 6 Kinder, Zweizudrei 3 Kinder und Genügend 1 Kind, während sich die Zensuren der 8 Schülern der Heilpädagogie folgenderweise gestalteten: Gut 2, Zweizudrei 3, und durchgefallen 3 Kinder.

9. *Welches Unterrichtsfach verursacht die größten Schwierigkeiten?* Bei den Grundschulern steht das Turnen an erster Stelle; dies widerspiegelt sich nicht immer in den Zensuren, weil die Mehrzahl unserer Kinder vom Turnen befreit wurde. An zweiter Stelle steht Schreiben und Lesen, was eng zur vorangehenden Erscheinung gehört, d.h. eigentlich eine feinere Projektion desselben ist. Das drittschwerste Lehrfach ist das Rechnen. Bei den Schülern der heilpädagogischen Schule steht als schwerstes Lehrfach das Rechnen an erster Stelle, danach folgt Lesen und Schreiben und an dritter Stelle das Turnen. Der Unterschied läßt sich vielleicht mit einer anderen pädagogischen Auffassung und Anschauung erklären.

10. *Ist das Kind beim Lernen auf eine Hilfe angewiesen?* Bei 14 Grundschulern wurde die Frage bejaht, 3 Kinder lernen selbständig, alle Schüler der Heilpädagogie benötigen eine Hilfe beim Lernen.

11. *Besucht das Kind ein Tagesheim?* Keiner der Grundschüler besucht ein Tagesheim und nur 2 der Schüler der heilpädagogischen Schule sind Tagesheimbesucher.

12. *Unter wessen Obhut ist das Kind?* In 19 Fällen ist es die Mutter, in 5 die Großeltern und in 6 Fällen ein Familienmitglied (»jemand«).

13. *Wessen pädagogischer Einfluß kommt*

am stärksten zur Geltung? In 24 Fällen der der Mutter, in 4 hat die Großmutter und in 2 der Vater ein Wort zu reden.

14. *Wie gestaltet sich die Aufmerksamkeit des Kindes?* All die 27 Schulkinder neigen zur Ermüdung, ihre Aufmerksamkeit ist schwach und ungleichmäßig, sie können langfristig weder belastet, noch in Anspruch genommen werden.

15. *Hat das Kind zuhause irgendwelche körperliche Arbeit zu verrichten?* Ihre körperliche Leistungsfähigkeit ist schwach, die Eltern bemerken aber einstimmig, daß sie sich fürchten, ihre Kinder zu irgendeiner physikalischen Arbeit zu bewegen; 28 Kinder arbeiten somit im Haushalt nicht, während 2 gelegentlich, wenn sie Lust haben, den Eltern behilflich sind.

16. *Interessen?* Bei 11 Schülern der Grundschule hat das Interesse keinen kinetischen Charakter, 6 Kinder sind dagegen an solchen Spielen (Ballspiel, Turnen, Radfahren, Schwimmen) interessiert. Unter den Schülern der Heilpädagogie gehören 5 in die letzterwähnte Gruppe, während in 3 Fällen eine Passivität mit mentalem Hintergrund vorliegt.

17. *Links- oder rechtshändig?* 14 Kinder sind rechtshändig, 9 linkshändig und 7 bilateral.

18. *Fanden Versuche zur Umgewöhnung statt?* In 11 Fällen; bei 3 der 9 Linkshändigen und 2 der Bilateralen waren sie erfolgreich.

19. *Sprachfehler?* Bei 7 Kindern Dyslalie, bei 2 Tachyphrasie, 1 Kind mit Nasenstimme; 2 der 7 Kinder mit Dyslalie sind Schüler eines heilpädagogischen Instituts.

20. *Störungen beim Schreiben und Lesen?* In 9 Fällen (4 besuchen die Grundschule und 5 die heilpädagogische Schule).

21. *Was ist die Ansicht der Eltern bezüglich der Fähigkeiten bzw. der Rückständigkeit ihrer Kinder?* Sämtliche Eltern betonten, daß sie sich freuen, daß das Kind am Leben blieb und sie mit ihren Fähigkeiten zufrieden sind. Was die Verhaltensweise der Kinder anbelangt, werden Intoleranz, Ermüdbarkeit und durch kleine Reize ausgelöste große Reaktionen beklagt;

außerdem wird immer wieder die Frage gestellt, wie denn das Kind leben soll, ohne seinen Kopf (das Ventil) zu gefährden.

22. *Handfertigkeit?* Die Kinder gelten im Vergleich zu den Altersgenossen bzw. Geschwistern im allgemeinen als ungeschickt. Nach Meinung der Schule verfügen 6 der 17 Grundschüler und 4 der 8 Schüler der Heilpädagogie über keine befriedigende Handfertigkeit.

23. *Körperliche Geschicklichkeit?* Ein Grundschüler und alle Schüler der Heilpädagogie werden in dieser Beziehung schlecht qualifiziert. Die Daten sind aber ungenau, weil die meisten Kinder vom Turnen teilweise oder ganz befreit sind.

24. *Hat das Kind Angst von irgendetwas?* In 14 Fällen sprach die Antwort für eine transzendente Angst, 9 Kinder fürchten sich von Krankheiten die irgendwie mit ihrem Kopf zusammenhängen; hier sei noch erwähnt, daß jedes Kind viele Fragen im Zusammenhang mit seinem Kopf betreffenden Krankheiten stellt.

25. *Welche Fragen beschäftigen das Kind?* 21 Kinder befragen ihre Eltern regelmäßig, weshalb sie dies oder jenes nicht tun dürfen, weshalb sie so besonders gehütet werden, weshalb sie nicht wie ihre Kameraden spielen, laufen oder sich beschäftigen dürfen, weshalb sie als Kleinkinder operiert wurden, wann das Rohr entfernt wird und ob sie etwa sterben müssen, wenn das Rohr irgendwie einen Schaden erleidet?

26. *Freundschaft, Beziehungen zu den Kameraden?* 6 Kinder spielen gerne allein, nach Ansicht der Schule unterscheiden sich diese Kinder von ihren Altersgenossen nicht. Der seelische Zustand, der ihre Aktivität determiniert, ist die Müdigkeit. Stimmungen, Witterungsänderungen (»Fronteinbruch«) sind bei diesen Kindern beeinflussende Faktoren. Ihre Gruppenposition ist nicht peripher, dagegen bilden sie aber auch keinen Mittelpunkt der Gemeinschaft.

27. *Ruhige oder unruhige Kinder?* 19 Kinder neigen zur Unruhe, Reizbarkeit, Affektivität und Eruption. 6 sind ruhig,

passive; 3 torpid (imbezil), 2 launisch und unberechenbar paradox.

28. *Verhalten in der Schule:* Ihr Verhalten wird durch frühere Dispositionen bestimmt, dementsprechend können sie in der Schule »brav« oder »schlimm« sein. Irgendwelche Einwände gegen ihr Verhalten seitens des Klassenlehrers bestehen nur in 5 Fällen, dagegen sitzen 22 der 27 Schulkinder in der ersten Bank.

29. *Hat das Kind eine Vorliebe zum Auftreten?* Die Eltern von 3 Grundschulern sowie die von 5 Schülern der heilpädagogischen Schule bejahten die Frage; die letzterwähnten Kinder gehören unter die mental schwächer regulierten Fälle.

30. *Ihre Rolle in der Gemeinschaft?* Jedes Kind kann aktiviert werden und sie beteiligen sich an der Arbeit der Klasse, sie sind zuverlässig und nehmen Aufgaben innerhalb ihres eigenen Belastungsniveaus auch freiwillig auf sich. Die früher bereits erwähnten Ermüdungsfaktoren werden auch im Zusammenhang mit dieser Frage betont.

31. *Tapfer, tollkühn, unüberlegt?* Diese Eigenschaften lagen bei keinem unserer Kinder vor, was indessen für einen regulierten Charakter spricht.

32. *Besitzt das Kind die Fähigkeit das Erlernte in fremder Umgebung zu realisieren?* Die Schule äußerte über 3 Kinder die Meinung, daß ihre Leistungen geringer sind, wie das zu erwarten wäre, diese Kinder zeigten aber dieselbe Selbstverwirklichung wie ihre nicht operierten Klassenkameraden. Die operierten Kinder sind nicht durch niedrigere Leistungen charakterisiert.

33. *Schlaf?* 11 Kinder reden im Schlaf, sie wälzen sich herum und knirschen die Zähne. 9 Kinder schlafen nur langsam ein, sie wachen aber spät auf, 3 schlafen viel (long sleep), in 7 Fällen steht bei dieser Frage keine Bemerkung.

34. *Körpergewicht, Körperhöhe?* Ihr Appetit ist unterschiedlich, sie sind größtenteils wählerisch. Körpergewicht und Körperhöhe entsprechen sowohl bei den Mädchen, als auch bei den Knaben dem ungarischen Durchschnitt.

35. *Wer erteilt die Ratschläge im Zusammenhang mit der Krankheit?* In 24 Fälle die Mutter, in den übrigen Fällen die Schule oder ein Familienmitglied. Auch hier stehen die Mütter im Vordergrund, während sich das Krankenhaus (obwohl Kinder und Eltern auch nach der Operation eine lange Zeit hindurch unsere Ambulanz besuchten) an dieser Arbeit nicht beteiligt. Die Eltern geben oft Ratschläge und Erklärungen die aller Wahrscheinlichkeit nach von guter Absicht herrühren, dagegen aber ungenau sind.

36. *Turnt das Kind in der Schule?* 23 Kinder sind vom Turnen vollkommen und 4 teilweise befreit, die 3 Kinder, die den Kindergarten besuchen, dürfen ebenfalls nur bestimmte Turnübungen durchführen. Das ist eine sehr beachtenswerte Angabe, sie zeigt nämlich, daß allen unseren Schulkindern viel Freude an der Bewegung entzogen wird, welche Umstände sie im Lernen und auch in ihrer Selbstsicherheit nachteilig beeinflussen.

37. *Was wird dem Kind wegen seiner Krankheit verboten?* Selbständiger Verkehr mit Fahrzeugen, Radfahren, Klettern auf eine Leiter, einen Baum und überhaupt die Höhe selbst, Fußballspielen, Schaukeln, Raufereien sind 19 Kindern verboten. Das Kind ist also von einer ausgesprochenen Lokomotionsbarriere umgeben. Die Stichthaltigkeit dieser Bewegungsbeschränkung sollte von ärztlicher Seite unbedingt überprüft werden.

38. *Verhältnis zu den Geschwistern?* In 9 Fällen deuteten die Eltern auf die sich aus der Krankheit ergebenden Begünstigungen zu Lasten der Geschwister soz. als Kompensation hin. Diese Erscheinung ist ein Faktor der betont emotionalen Erziehung.

39. *Vorschläge oder Bitten an das Krankenhaus?* Aus allen Antworten klang die Sorge heraus, wie denn das operierte Kleinkind mit einem Rohr im Kopf erzogen werden soll und wo die Grenze liegt, die ohne Gefährdung des Kindes nicht überschritten werden darf.

40. *Charakteristische Eigenschaften?* Abhängigkeit, Liebkosen, Enteignung der

Eltern, schwache Konstitution, Anfälligkeit zu Krankheiten (Erkältung, Entzündung, Infektionskrankheiten, »Leichtfertigkeit«, Angst von Krankheiten, Reizbarkeit, zyklische Stimmungen.

41. *Krankheitsveranlagung?* In 14 Fällen besteht eine ausgesprochene Prädisposition zu Krankheiten, 12 Kinder stehen wegen Exhaustionsbeschwerden unter neurologischer Behandlung.

42. *Selbständigkeit?* Im Einklang mit der Meinung der Schule berichteten 24 Eltern über mangelnde Selbständigkeit und eine Hemmung der Aktivierung bzw. der Erreichung von Leistungen.

43. *Neigung zum Weinen, zur Empfindlichkeit und zum Stimmungsumschwung?* Diese Eigenschaften melden sich bei allen operierten Kindern von Zeit zu Zeit.

44. *Gesichtspunkte bei der Erziehung?* In der Erziehung dominiert das Gefühl und eine größere Zulässigkeit; viele Eltern klagen über Selbstversorgungsschwierigkeiten.

45. *Schwierigkeiten der Erziehung?* In den Antworten widerspiegelt sich die Unsicherheit der Eltern: Sie wissen nicht wie sie sich ihrem Kind gegenüber verhalten sollen. Sie wissen nicht, ob ihre Zulässigkeit richtig ist, sie möchten ihre Erziehung auf reelle Grundlagen legen. Auch die zukünftige Berufswahl macht ihnen Sorgen, es ist schwierig, einen Beruf zu finden, welcher das Kind nicht gefährdet und mit seiner körperlich-geistigen Toleranz in Einklang gebracht werden kann.

46. *Lernen (leicht oder schwer), Vergesslichkeit?* 8 der die Grundschule besuchenden Kinder lernen leicht, 4 sind nicht genügend fleißig, 5 lernen schwer. Alle Schüler der heilpädagogischen Schule haben große Schwierigkeiten beim Lernen, sie können ihre Ergebnisse nur um den Preis von harter Arbeit erreichen. 1 der 2 Kinder die die Klasse mit geringerer Schülerzahl besuchen, hat große Schwierigkeiten beim Lernen, 2 Kinder werden nächstes Jahr wahrscheinlich in eine heilpädagogische Schule verlegt, und 2 sind auf intensive Hilfe angewiesen.

47. *Enuresis?* Über das Bestehen von *Enuresis nocturna* klagten die Eltern von 9 Kindern (6 besuchen die Grundschule, 3 die heilpädagogische Schule).

48. *Neigung zur Erregtheit?* Vegetative Zeichen in schwächerer oder stärkerer Form liegen in 21 Fällen vor, affektive Labilität in 8 und Kollapsneigung in 1 Fall.

BESPRECHUNG

Unser Material besteht aus Schulkindern, die sich zur Erziehung und Unterrichtung eignen und somit über sämtliche Möglichkeiten der Sozialisation verfügen. Ihre Schulergebnisse sind gut, ihre Leistungen entsprechen dem Niveau der Durchschnittspopulation. Diese Angaben sprechen dafür, daß bei den wegen Hydrozephalus operierten Kindern — mit dem Vorbehalt, daß eine entsprechende Selektion nötig ist — ein langfristiger, realer Erziehungs- und Unterrichtsplan aufgestellt werden kann.

Unter den Lehrfächern verursacht das Turnen die meisten Schwierigkeiten. Eine Erklärung dafür liefert einerseits die operationsbedingte Bewegungsbeschränkung, andererseits die ängstliche Sorge, die das Kind in der Schule und im Elternhaus umgibt. Diese letzterwähnte Erscheinung manifestiert sich sogar in mehreren Formen (Spiel, Berufswahl, Schwimmen, Belastung usw.).

Unsere 14 dyslektischen Kinder stellen eine feinmotorische Projektion der kinetischen Störung dar (5 Grundschüler, 9 Schüler der Heilpädagogie).

Zur selbständigen Arbeit benötigen die meisten Kinder eine Hilfe. Die Frage, ob dies ausschließlich eine

Folge des Hydrozephalus wäre, kann jedoch nicht mit Sicherheit entschieden werden. Mit dem Schuleintritt hat das Kind nämlich eine neue, Zeit und Anpassung beanspruchende Lebensweise zu erlernen. Der Umstand dagegen, daß 21 Kinder zu Hause erzogen werden und nur 9 Kinder ein Tagesheim besuchen, spricht für einen Anspruch auf Unterstützung (27 Kinder werden regelmäßig von der Mutter betreut, so daß die Mütter deshalb nicht werktätig sind).

Schule (Klassenlehrer) und auch Eltern betonen übereinstimmend die von Zeit zu Zeit nachlassende Aufmerksamkeit, die schwache Belastbarkeit und die daraus stammenden unterschiedlichen Leistungen der Kinder. Im Einklang mit unseren früheren Untersuchungsergebnissen betrachten wir diese Erscheinung und die damit verbundene, sich rasch erschöpfende physikalische Leistungsfähigkeit mit schwacher Intensität für einen charakteristischen Zug des Hydrozephalus.

Wahrscheinlich infolge der angsthaften elterlichen Sorge zeigen 11 der 17 Grundschüler kein kinetisches Interesse, welche Tatsache unter Berücksichtigung der dem Lebensalter entsprechenden Kennzeichen für einen Regressionseffekt der Umgebung zu bewerten ist.

Sowohl in unserem früheren Material als auch im Laufe vorliegender Untersuchungen fanden wir unter dem operierten Kindern eine große Zahl der linkshändigen bzw. der eine Bilateralität aufweisenden Fälle. Diese Tatsache können wir nicht erklären.

In unserem Material lag auch die Zahl der Fälle mit einem Sprachfehler, Dyslexie bzw. Dysphragie ziemlich hoch. Diese feinen motorischen Funktionen können die Folgen der im Säuglingsalter bestandenen anhaltenden Hypertension sein: Im Laufe des Entwicklungsganges sind die sich später ausgebildeten Anlagen verletzbarer.

Die Eltern sind mit dem körperlich-seelischem Zustand ihrer wegen Hydrocephalus operierten Kinder zufrieden, sie halten sie für klug, für geeignet zur Ausführung von Aufgaben und sind überzeugt, daß sie über die Möglichkeit der selbständigen Lebensführung verfügen. Diese elterliche Attitüde ist ein positiver Zug der Erziehung.

Der Umstand, daß die operierten Kinder über eine weniger ausgeprägte körperliche bzw. Handgeschicklichkeit verfügen, als ihre Altersgenossen, kann vielleicht mit dem bereits erwähnten Verhalten oder mit einer Nervensystemverletzung erklärt werden. Von dieser Sicht aus wäre eine Änderung der Regression, angsthaften, betont emotionellen Erziehungsweise unbedingt nötig, damit diese Kinder in einem breiteren Bewegungsraum eine größere Bewegungsfreiheit genießen. Dies spielt auch in der Persönlichkeitsentwicklung eine wichtige Rolle und ermöglicht die Vermeidung einer frustrierenden Erziehung.

Einige unserer Kinder fürchten sich von Krankheiten. In Anbetracht der schmerzhaften, langhaltenden stationären Behandlung, die diese Kinder im frühen Säuglingsalter erlebt haben,

betrachten wir diese Erscheinung als ein wiederkehrendes »imprinting«.

Ihre Position in der Gemeinschaft ist gut, sie sind kontaktstabil und werden in Gruppenpositionen nicht auf die Peripherie gedrängt; eventuelle, sich in den Daten widerspiegelnde Ungleichmäßigkeiten ergeben sich in erster Linie aus der Superiorität, die diese Kinder in der Familie genießen.

Auch muß betont werden, daß die sich mit der Problematik des Hydrocephalus beschäftigenden Spezialisten den Eltern, der Familie und der Schule bewußt und aktiv beistehen müssen, um die weitere Verbreitung der gegenwärtig beobachtbaren Übertreibungen zu verhindern.

Beachtenswert sind die den Schlafstörenden Begleitepisoden. Die registrierten Erscheinungen — Pavor nocturnus, Somnambulaz und Somnoloquismus — sprechen dafür, daß es sich in diesen Fällen um Entspannungsschwierigkeiten handelt, die besonders dann auftreten, wenn sich in der Psyche der Kinder etwa wegen eines neuen Ereignisses irgendwelche Änderungen abspielen. Die Erscheinungen sind nicht dauerhaft, sie melden sich als kurzfristige Reaktionen.

Körpergewicht, Höhe und Proportionen der operierten Kinder entsprechen den physiologischen Standards.

Die Zahl der vom Turnen dispensierten Fälle ist hoch; dies beeinflußt das Kind ungünstig, da sich die Entwicklung der kinetischen Elaboration und der motorischen Sicherheit verzögern.

Bei allen Kindern konnte irgendeine Nuance des Krankheitsvorteils fest-

gestellt werden. Dies stammt aus dem emotionalen Verhalten der Eltern und der Umgebung und muß durch Anwendung des Realitätsprinzips ausgeglichen werden.

Ein sehr wichtiges, von sämtlichen Eltern hervorgehobenes Resozialisationsproblem ist die Unsicherheit in Erziehungsfragen: Wie sollen sie das Kind erziehen, wie sollen sie sich mit ihm beschäftigen, was ist dem mit Shunt lebenden Kind erlaubt oder verboten? Soll es einen Kindergarten besuchen, darf es in die Schule gehen, kann es ohne seine Gesundheit zu gefährden den dortigen Anforderungen nachkommen? Obwohl diese Fragen unbedingt angezeigt sind, müssen wir mit der Antwort schuldig bleiben, weil sich diesbezüglich noch keine einheitliche Anschauung ausgebildet hat. Die sich mit dem Hydrocephalus befassenden Erziehungsanstalten leben gegenwärtig noch in der Periode der Datensammlung.

Dr. L. VÉKÁSSY
Amerikai út 57
H-1145 Budapest, Hungary

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The effect of birth asphyxia on plasma free amino acids in preterm newborn infants

By

K. SCHULTZ, J. MESTYÁN and Gy. SOLTÉSZ

Department of Paediatrics, University Medical School, Pécs

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The postnatal plasma amino acid pattern was compared in 16 asphyxiated and 13 non-asphyxiated preterm newborn infants. The lactic acidosis induced by asphyxia was associated with a marked rise in the total amino acid content of the plasma. Among the 17 individual amino acids determined the concentrations of alanine, proline, taurine, glutamate, valine, methionine and lysine were significantly elevated. The accumulation of alanine was particularly marked and its concentration showed a significant linear correlation with that of lactate ($p < 0.001$). A similar relationship was observed between other potentially glucogenic amino acids and lactate. It is suggested that an impaired gluconeogenesis may be responsible for the accumulation of glucogenic amino acids. The response of the plasma aminogram to asphyxia resembles that associated with hypoglycaemia in the small-for-gestational-age infant, where a delay in the maturation of key gluconeogenic enzymes seems to account for the reduced hepatic disposal of glucose precursors.

The postnatal accumulation of gluconeogenic amino acids [7, 12], lactate and pyruvate [7] in the plasma of hypoglycaemic SGA newborn infants strongly suggests a decreased capacity of hepatic glucose synthesis, leading to a reduced uptake of the glucose precursors by the liver. In addition to reduced disposal, an increased production or release of amino acids can also contribute to the hyperaminoacidaemia associated with hypoglycaemia. This particularly applies to alanine, the most prominent glucose precursor among the amino acids.

It is well-known that besides conversion to lactate, transamination of pyruvate to alanine is the alternate

pathway of pyruvate disposal and is the key metabolic process of the glucose-alanine cycle [5]. It seems therefore reasonable to suppose that under conditions associated with pyruvate accumulation in the muscles, e.g. hypoxia, an increased production of alanine can be a major mechanism in the development of hyperaminoacidaemia. In view of this possibility and the frequent occurrence of birth asphyxia in severe intrauterine malnutrition, the plasma amino acid pattern has been studied in neonates suffering from moderate or severe birth asphyxia. It appeared interesting to establish whether or not a correlation existed between the asphyxia-induced

lactic acidosis and the postnatal changes of plasma amino acids. To exclude the effect of intrauterine undernutrition on the plasma aminogram, only appropriate for gestational age preterm infants have been included in the study.

MATERIAL AND METHODS

Two groups of preterm newborn infants appropriate for gestational age (AGA) were studied: 13 non-asphyxiated and 16 asphyxiated infants. Mean birth weight, gestational age, postnatal age and ranges are shown in Table I. All infants had a birth weight between the tenth and ninetieth percentile on our local intrauterine growth chart. All of the non-asphyxiated infants were delivered vaginally after uncomplicated pregnancy and had an Apgar score higher than 7 at one minute.

Two of the asphyxiated infants were delivered by Caesarean section and five after difficult breech presentation. Infants included in this group had an Apgar score lower than 7 at birth, and were, after being resuscitated in the delivery room,

admitted to the neonatal referral centre for further observation and treatment. Pertinent data regarding pregnancies, deliveries and infants in the asphyxiated group are shown in Table II. Eleven severely asphyxiated infants died between 1 to 3 days of age; necropsy revealed massive intracranial haemorrhage in all of them.

Blood was drawn by puncture of the antecubital or cephalic vein at the time of admission, 1–12 hours after birth, before the first feeding. Glucose and lactate concentrations were determined by the orthotoluidine method of Price [15] and by the method reported by Huckabee [9]. Specimens of heparinized venous blood were promptly centrifuged and the plasma was deproteinized by addition of four volumes of 5% sulphosalicylic acid. The protein-free supernatant was immediately frozen and stored at -20°C until assayed.

Amino acid analysis was performed by an automatic Beckman Multichrom Liquid Column Chromatograph using norleucine as an internal reference standard. The levels of 17 amino acids were quantitated.

Regression equations were calculated by the method of least squares. Differences between group averages were compared by the standard *t* test.

TABLE I
Mean gestational age, postnatal age and birth weight in the two groups of infants*

	Non-asphyxiated preterm infants	Asphyxiated preterm infants
Gestational age (wk)	32.7 (29–35)	31.1 (28–34)
Birth weight (g)	1772 (1250–2450)	1501 (800–1970)
Postnatal age (hr)	8.3 (3–12)	3.6 (1–7)
Number of infants	13	16

* Ranges for age and weight are in parentheses.

TABLE II
Clinical data of 16 preterm infants with birth asphyxia

Infant		Pregnancy, labor and delivery	Apgar score		pH (on ad- mis- sion)	Gesta- tional age (wk)	Birth weight (g)	Outcome	Necropsy
No	Sex		at 1 min	at 5 min					
1	M	Cholestasis during pregnancy, breech delivery	1	3	6.97	30	1680	Died	Meningeal haemorrhage. HMD
2	M	Toxemic pregnancy, meconium stained amn. fluid	4	8	7.27	32	1880	Died	Ventricular haemorrhage
3	M	Uneventful pregnancy, spontaneous delivery	6	10	7.27	33	1970	Survived	—
4	F	Twin pregnancy, spontaneous delivery	1	3	7.14	30	1250	Died	Periventricular haemor- rhage. HMD
5	F	Twin pregnancy, spontaneous delivery	5	3	7.12	30	1350	Died	Meningeal haemorrhage. HMD
6	F	Transverse presentation, difficult breech delivery	6	10	7.36	32	1840	Survived	—
7	M	Uneventful pregnancy, spontaneous delivery	5	9	7.37	29	1240	Died	Meningeal haemorrhage.
8	M	Twin pregnancy, breech delivery, traction	2	9	7.12	30	1280	Died	Meningeal haemorrhage. HMD
9	M	Uneventful pregnancy, spontaneous delivery	4	6	7.09	31	1320	Died	Ventricular haemorrhage. Pulmonary haemor- rhage. Epidural haem- orrhage. HMD
10	F	Uneventful pregnancy, spontaneous delivery	6	8	7.20	31	1630	Died	Ventricular haemorrhage. HMD
11	M	Uneventful pregnancy, breech delivery	6	8	7.04	28	1080	Died	Meningeal haemorrhage.
12	F	Uneventful pregnancy, breech delivery	5	8	7.34	31	1500	Died	Pulmonary atelectasis. HMD
13	M	Breech presentation, cesarean section	2	4	7.25	—	1550	Survived	—
14	M	Early separation of the placenta, cesarean section	1	7	7.33	34	1850	Survived	—
15	F	Uneventful pregnancy, spontaneous delivery	6	10	7.30	34	1800	Survived	—
16	M	Uneventful pregnancy, spontaneous delivery	5	7	7.18	—	800	Died	Meningeal haemorrhage

RESULTS

As Table III shows, the mean blood lactate concentration and the combined concentration of 17 amino acids were significantly higher in the asphyxiated AGA preterm newborn infants (3.38 ± 0.28 vs. 1.92 ± 0.09 mmol/l and 2713 ± 82 vs. 2081 ± 91 μ moles/l; $p < 0.001$). Mean blood glucose concentration was higher in the asphyxiated than in the non-asphyxiated group, but the difference was not significant statistically. It should be noted that 9 of the asphyxiated infants received 10 %

glucose and bicarbonate infusion before admission to the neonatal unit.

The plasma concentrations of 17 individual amino acids in the two groups of infants are shown in Table IV. In newborns suffering from birth asphyxia the plasma concentrations of alanine, proline, taurine, glutamate, valine, lysine and methionine were significantly elevated. If the concentrations of the glucogenic proline, valine, lysine obtained in both groups, were related to alanine (Fig. 1), their elevation in the plasma turned out to be closely related.

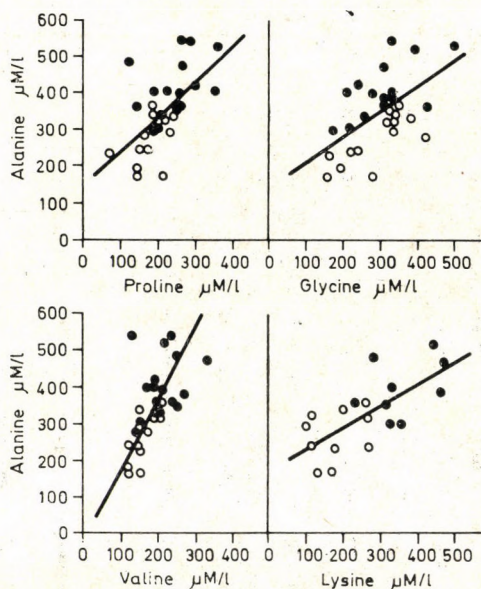


FIG. 1. Plasma glycine, proline, valine and lysine* concentrations in 16 asphyxiated (closed circles) and 13 non-asphyxiated (open circles) preterm newborn infants, related to plasma alanine concentrations.

$$\text{Alanine vs. glycine, } y = 140.1 + 0.69x, r = 0.564 \text{ } p < 0.01$$

$$\text{Alanine vs. proline, } y = 150.4 + 0.93x, r = 0.594 \text{ } p < 0.001$$

$$\text{Alanine vs. valine, } y = 14.3 + 1.94x, r = 0.949 \text{ } p < 0.001$$

$$\text{Alanine vs. lysine, } y = 177.6 + 0.57x, r = 0.687 \text{ } p < 0.01$$

*10 measurements neglected in statistical analysis because of poor resolution of peaks.

TABLE III

Mean total plasma amino acid, blood glucose and blood lactate concentration

	Mean (\pm SE) total plasma amino acid concentration μ M	Mean (\pm SE) blood lactate concentration mM	Mean (\pm SE) blood glucose concentration* (mg/100 ml)
Non-asphyxiated preterm infants (n = 13)	2081 \pm 91	1.95 \pm 0.09	52.8 \pm 5.7
Asphyxiated preterm infants (n = 16)	2713 \pm 82	3.38 \pm 0.29	72.4 \pm 12.6
p value	p < 0.001	p < 0.001	—

* Nine infants received glucose infusion prior to admission.

TABLE IV

Plasma concentration (μ M \pm SE) of 17 amino acids in the two groups of newborn infants

Amino acid	Non-asphyxiated preterm infants	Asphyxiated preterm infants
Taurine	252 \pm 13	315 \pm 18 ⁺⁺
Aspartate	46 \pm 5	40 \pm 3
Glutamate	48 \pm 3	68 \pm 7 ⁺
Citrulline	25 \pm 2	26 \pm 2
Proline	175 \pm 14	237 \pm 17 ⁺⁺
Glycine	285 \pm 24	308 \pm 21
Alanine	267 \pm 19	409 \pm 20 ⁺⁺⁺
Cystine	122 \pm 24	140 \pm 13
Valine	156 \pm 8	210 \pm 13 ⁺⁺
Methionine	22 \pm 3	31 \pm 3 ⁺
Isoleucine	47 \pm 4	56 \pm 6
Leucine	98 \pm 8	122 \pm 12
Tyrosine	141 \pm 17	117 \pm 8
Phenylalanine	107 \pm 9	128 \pm 10
Lysine	179 \pm 21	358 \pm 27 ⁺⁺
Histidine	52 \pm 10	74 \pm 8
Arginine	57 \pm 8	76 \pm 6

+ p < 0.05

++ p < 0.01

+++ p < 0.001

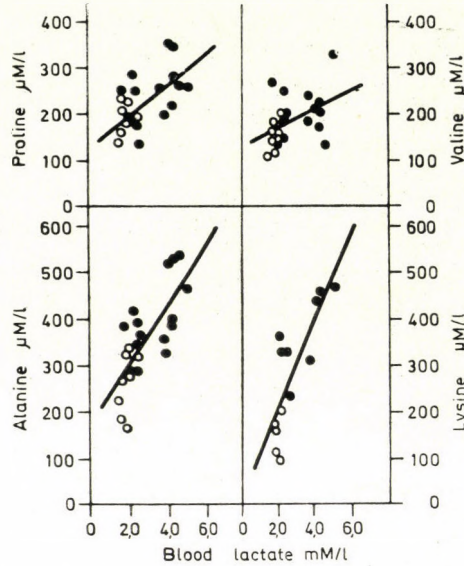


FIG. 2. Regression analysis of alanine vs. lactate, proline vs. lactate, valine vs. lactate and lysine* vs. lactate concentrations in the first twelve hours of life in 15 asphyxiated (closed circles) and 8 non-asphyxiated (open circles) preterm newborn infants.

Alanine vs. lactate, $y = 167.4 + 65.29x$, $r = 0.752$ $p < 0.001$

Proline vs. lactate, $y = 122.6 + 34.25x$, $r = 0.593$ $p < 0.01$

Valine vs. lactate, $y = 131.6 + 19.59x$, $r = 0.437$ $p < 0.05$

Lysine vs. lactate, $y = 20.3 + 94.32x$, $r = 0.798$ $p < 0.01$

*10 measurements neglected in statistical analysis because of poor resolution of peaks.

In Fig. 2, plasma alanine, proline, valine and lysine values are plotted against blood lactate concentrations. A significant positive linear correlation was observed between blood lactate and the four glucogenic amino acids (alanine vs. lactate, $r = 0.752$, $p < 0.001$; proline vs. lactate, $r = 0.593$, $p < 0.01$; valine vs. lactate, $r = 0.437$, $p < 0.05$; lysine vs. lac-

tate, $r = 0.798$, $p < 0.01$). Even individual observations point towards a close relationship between alanine and lactate levels. The relevant data of a pair of twins, with different degrees of birth asphyxia are shown in Table V. As it can be seen, plasma alanine and blood lactate concentrations were much higher in the severely asphyxiated twin A.

TABLE V

Blood lactate and plasma alanine levels in asphyxiated twins

	Birth weight (g)	Gestational age (wk)	Postnatal age (hr)	Apgar score at 1 min	Lactate mM	Alanine μ M
Twin A	1250	30	3	1	4.37	392
Twin B	1350	30	3	5	2.08	296

DISCUSSION

The results allowed to conclude that lactic acidosis due to birth asphyxia was associated with hyperaminoacidaemia. This is in agreement with the observation made in human adults suffering from circulatory failure or idiopathic lactic acidosis without evidence of poor tissue oxygenation [11]. The changes in plasma amino acid pattern were also similar as those obtained in adults. Among the 17 amino acids determined, the increase of alanine concentration was particularly marked and accounted for a portion of the total increment in the plasma amino acid content.

It appears reasonable to assume that an increasing amount of alanine is produced in lactic acidosis caused by asphyxia, which leads to an imbalance between release from the muscle and uptake by the liver. The close correlation between pyruvate and alanine concentration found under different conditions [6, 11] on the one hand, and the significant correlation between lactate and alanine level observed in the present study, on the other hand, support the contention that an increased availability of pyruvate may result not only in increased lactate production but also in increased conversion of pyruvate to alanine catalyzed by alanine aminotransferase.

Since the plasma concentrations of other amino acids were also found to be elevated, and the elevation of certain glucogenic amino acids were closely related to that of alanine,

mechanisms other than increased production and release must also be considered in the mechanism of hyperaminoacidaemia associated with birth asphyxia. On the basis of some experimental studies [2, 3, 10, 11, 13, 17, 18] it may be assumed that a failure of amino acid removal, due to the impaired hepatic gluconeogenesis can be an additional mechanism which contributes to amino acid accumulation in the plasma. This assumption is supported by studies in adult rats, according to which hypoxia causes a marked inhibition of gluconeogenesis [1]. Observations in newborn rats [1, 8, 14] also point toward the importance of oxygenation in the establishment of hepatic glucose synthesis after birth. Even the increased lactate and pyruvate concentration can be partly responsible for the reduced hepatic utilization of glucogenic amino acids. In the isolated perfused rat liver Marliss et al. [11] have shown that when lactate and pyruvate concentrations were increased in the perfusate, uptake of alanine and its conversion to glucose decreased.

Another aspect of the possible impairment of gluconeogenesis associated with hyperlactataemia, induced by asphyxia, is the inhibitory effect of the low cellular pH. According to rat liver perfusion studies [3, 4, 10], lactate consumption decreases when intracellular H^+ concentration increases. This might also apply to the hepatic utilization of amino acids. Furthermore, examinations in vitro have shown that the activity of pyruvate carboxylase, an important enzyme in

hepatic glucose synthesis, is highly pH dependent [16, 17].

Finally, the quantitative and qualitative plasma amino acid profile observed in birth asphyxia resembles that associated with hypoglycaemia in the small-for-gestational-age newborn infant [7, 12]. In such babies a delay in the maturation of key enzymes appears to be an important factor in the reduced removal rate of glucose precursors. In view of the similar responses in the circulating free amino acid pool in hypoxia and hypoglycaemia and the frequent occurrence of perinatal asphyxia in severely malnourished newborn infants, it is conceivable that a transient or lasting tissue hypoxia might aggravate the metabolic consequences of hypoglycaemia.

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K. SCHULTZ, M.D.

József A. u. 11

H-7623 Pécs, Hungary

The effect of gestational age and intrauterine nutrition on plasma free amino acids in the human newborn

By

K. SCHULTZ, Gy. SOLTÉSZ and J. MESTYÁN

Department of Paediatrics, University Medical School, Pécs

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The postnatal changes in plasma amino acids and blood glucose of preterm appropriate for gestational age (PAGA) and small for gestational age (PSGA) infants were compared. The mean blood glucose concentration was significantly depressed ($p < 0.001$) in the PSGA infant group. Neither the total concentration of the determined 17 plasma amino acids nor the plasma level of the three important glucogenic amino acids (alanine, glycine, proline) were significantly higher in the premature small for gestational age infants than in those, whose birth-weight was appropriate for gestational age. The mean concentrations of leucine, phenylalanine and aspartate were significantly lower ($p < 0.05$) and of glutamate significantly higher ($p < 0.05$) in the PSGA group. No correlation was found between blood glucose and the main glucogenic amino acids. Combining the present results for preterm infants with those full term well-nourished and small-for-gestational-age infants, among the 17 amino acids only alanine turned out to be significantly related to gestational age in the combined group of SGA infants.

The results show that hypoglycaemia in preterm SGA infants is not associated with hyperaminoacidaemia as it has been observed in full term SGA neonates. To explain this difference, it is suggested that the duration of intrauterine malnutrition is a decisive factor in the maturation of hepatic gluconeogenesis. This would mean that birth before term, i.e. a short exposure to unfavourable nutritional conditions, does not severely affect the postnatal activation of gluconeogenesis.

In recent studies, the role of impaired gluconeogenesis in the aetiology of hypoglycaemia in SGA infants has been shown [2, 3, 7, 8]. The postnatal accumulation of the gluconeogenic amino acids lactate and pyruvate in the plasma of SGA infants suggested a reduced hepatic uptake of these precursors and a decreased glucose synthesis. The extent of amino acid accumulation in the plasma was directly related to the degree of gluco-

se deficiency and the severity of intrauterine undernutrition [8]. Direct assays of hepatic gluconeogenic enzyme activities in animals [1, 6, 11] and recently in human studies [5] suggest that the defect in gluconeogenesis would probably be due to a delay in induction of the key rate-limiting gluconeogenic enzymes.

Neonatal hypoglycaemia in the full term SGA infant is associated with increased plasma concentrations of

gluconeogenic substrates [3, 8]. No information is, however, available on the quantitative and qualitative amino acid pattern of preterm newborn babies. In the present study we have compared the postnatal changes in plasma amino acids of well nourished and undernourished preterm infants to establish whether gestational age, in addition to the intrauterine nutritional status, had any influence on their plasma aminogram.

MATERIAL AND METHODS

20 newborn infants born before 37 weeks of gestation were studied. Nine infants had birthweights below the tenth percentile according to our local intrauterine growth chart, and showed clinical signs of undernutrition. These infants formed the group of preterm small-for-gestational-age infants (PSGA). The remaining 11 preterm babies were all well nourished with a birth weight appropriate for ges-

tation (PAGA). Mean gestational ages, birth weights and postnatal ages in the two groups of infants are shown in Table I. All the normally grown premature infants were born after uneventful pregnancy. In 5 of the PSGA infants studied, pregnancy was complicated with toxæmia.

A blood glucose level of less than 20 mg/100 ml was accepted as a criterion of hypoglycaemia, and such low levels were observed in 6 PSGA infants between 1–12 hours postnatally. One infant developed convulsions during hypoglycaemia, which did not respond to intravenous injection of glucose.

Peripheral venous blood was taken from all the infants at the time of admission (1–12 hours after birth) before the first feeding. Blood glucose was measured in duplicate by the orthotoluidine method of Price [9]. Amino acid analysis was performed by an automatic Beckman Multichrom Liquid Column Chromatograph and norleucine was used as an internal reference standard. The levels of 17 individual amino acids were quantitated. The standard *t* test was used for statistical analysis. Regression equations were calculated by the method of least squares.

TABLE I
Gestational age, birth weight and postnatal age of
the two groups of infants*

	Preterm AGA infants	Preterm SGA infants
Gestational age (wk)	32.7 (29–35)	33.2 (31–36)
Birth weight (g)	1792 (1250–2450)	1409 (1070–1770)
Postnatal age (hr)	9.7 (3–12)	6.1 (3–12)
No of infants	11	9

* Ranges for age, weight and postnatal age are in parentheses

RESULTS

Table II compares the total and individual plasma amino acids in PAGA and PSGA infant. The latter was not only characterized by a significant weight deficit, but blood glucose concentration was also significantly depressed (54.5 ± 6.3 mg/100 ml versus 24.6 ± 2.6 mg/100 ml). From Table II it is obvious, that neither the sum of concentrations of the 17 amino acids determined, nor the plasma content of the three important

gluconeogenic amino acids (alanine, proline, glycine) were significantly higher in the PSGA infants than in those whose birthweight was appropriate for gestational age. The plasma levels of the branched chain amino acids (leucine, isoleucine, valine) tended to be lower in the malnourished group, but except leucine ($p < 0.02$) the differences were not significant statistically. Among the other amino acids, phenylalanine and aspartate were significantly lower ($p < 0.05$) and glutamate significantly higher

TABLE II
Mean plasma concentrations ($\mu\text{M} \pm \text{SE}$) of 17 amino acids in the two groups of preterm infants

Amino acid	Preterm AGA infants	Preterm SGA infants
Taurine	257 ± 15	261 ± 27
Aspartate	54 ± 5	$40 \pm 4^*$
Glutamate	47 ± 5	$68 \pm 8^*$
Citrulline	25 ± 6	23 ± 4
Proline	195 ± 23	187 ± 20
Glycine	285 ± 24	244 ± 12
Alanine	280 ± 23	319 ± 22
Cystine	76 ± 14	93 ± 14
Valine	160 ± 10	138 ± 11
Methionine	24 ± 3	21 ± 3
Isoleucine	51 ± 3	39 ± 6
Leucine	100 ± 9	$69 \pm 8^{**}$
Tyrosine	146 ± 18	103 ± 17
Phenylalanine	114 ± 11	$82 \pm 8^*$
Lysine	186 ± 20	217 ± 21
Histidine	61 ± 12	85 ± 13
Arginine	61 ± 10	44 ± 8
Total	211 ± 126	2033 ± 201

* $p < 0.05$

** $p < 0.02$

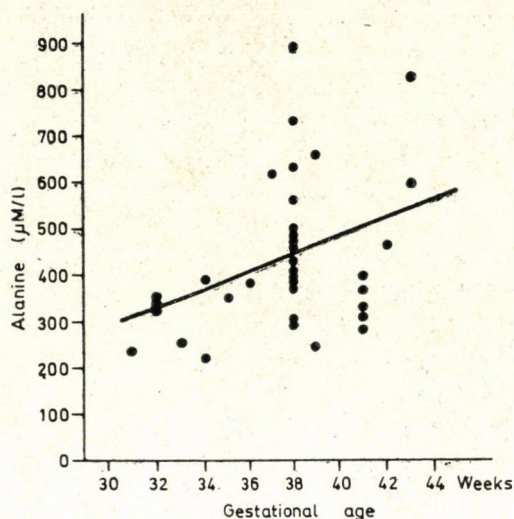


FIG. 1. Relationship between plasma alanine and gestational age in the combined group of SGA (9 preterm and 26 full term) infants: $y = 19.769x - 306.746$; $r = 0.378$; $p < 0.05$.

($p < 0.05$) in the PSGA infants. Thus in the hypoglycaemic preterm SGA infants neither the total plasma amino acid content, nor the individual amino acid concentrations were strikingly different from that of non-hypoglycaemic babies. The significant inverse correlation between blood glucose and the four main glucogenic amino acids observed in full term SGA infants [8] was not demonstrable in preterm SGA infants. It appears that maturity plays an important role in the postnatal changes of the plasma amino acids in relation to blood glucose changes in intrauterine malnourished infants.

Since the accumulation of glucogenic amino acids seemed to characterize the hypoglycaemia only in full term SGA infants, it may be a reflexion of gestational age rather than of a lack of glucose. To test this possibility,

individual amino acid levels were related to gestational age which has been extended up to 43 weeks by combining the results of the present two study groups of preterm infants with full term, well-nourished and small-for-gestational-age infants. Among the 17 amino acids only alanine turned out to be significantly related to gestational age ($r = 0.378$ $p < 0.05$) in the combined group of SGA (9 preterm + 26 full term) infants (Fig. 1). In contrast, no significant correlation was obtained in the normally grown (11 preterm + 15 full term) neonates.

DISCUSSION

Our previous results not only showed that hypoglycaemia was associated with hyperaminoacidaemia

mainly due to the increased levels of the glucogenic amino acids, but also revealed a close inverse correlation between blood glucose and the most important amino acid precursors e. g. alanine, proline and glycine. Such a relationship between hypoglycaemia and total plasma amino acid content on the one hand, and between blood glucose and glucogenic amino acid concentration on the other hand, could not be demonstrated in SGA infants born before term. This difference between the two groups of hypoglycaemic underweight infants points towards the importance of gestational age or maturity in relation to the postnatal changes of glucose and amino acid metabolism. It should, however, be emphasized, that the difference in the metabolic behaviour applies only to intrauterine malnourished infants; in the normally grown babies the postnatal changes of plasma amino acids are quite similar and appear to be independent of gestational age.

There are several possibilities to explain the lack of an increase in the plasma glucogenic amino acid levels in hypoglycaemic preterm SGA infants. Since hyperaminoacidaemia in hypoglycaemic full term SGA infants is considered to result from an impaired or delayed activation of hepatic gluconeogenesis, it appears reasonable to assume that the postnatal initiation of endogenous glucose synthesis in preterm SGA babies is as efficient as in well-nourished full term infants. Otherwise the increased flow of amino acids to the liver elicited by

fasting and their decreased hepatic uptake should lead to elevated plasma levels as it occurs in mature SGA infants. Since this is not the case, either a rapid activation of gluconeogenesis occurs together with an increased disposal of glucogenic amino acids like in normal full term infants, or the reduced capacity for endogenous glucose synthesis due to immaturity does not induce an increased mobilization of amino acid precursors and therefore the plasma levels do not increase after birth. But like in the normal full term infants, the postnatal fall in the concentration of alanine, the most important glucogenic amino acid, suggest that hepatic glucose synthesis becomes active soon after birth in well-nourished and undernourished premature neonates. If this explanation reflects the real situation, than why does not intrauterine malnutrition affect the postnatal activation of gluconeogenesis in babies born before term?

It appears that the duration of intrauterine malnutrition is a decisive factor in the impairment or delay of the biochemical maturation of the liver and hence in the less efficient metabolic transition from the intrauterine to the extrauterine environment. A long exposure to unfavourable nutritional conditions may not only result in a more severe undernutrition of the fetus, but can also lead to perinatal complications, which may threaten survival of the fetus, or cause various disturbances in neonatal adaptation.

Perinatal asphyxia is a common

occurrence in the second half of the third trimester of pregnancies complicated by placental insufficiency, which is often superimposed on the somatic consequences of intrauterine malnutrition, and may contribute to the biochemical and physiological abnormalities interfering with various processes induced by birth and extrauterine conditions. In view of the possible role of asphyxia in the transitory impairment of neonatal gluconeogenesis in full-term underweight infants, the anaerobic metabolism leads to similar quantitative and qualitative alterations in the plasma aminogram as the alterations associated with hypoglycaemia [10]. It is conceivable that in these infants in contrast to those born prematurely, hyperaminoacidaemia and hyperalaninaemia are partly due to manifest or subclinical hypoxia, which has been shown to reduce the hepatic uptake of alanine and to increase its synthesis and release in the muscle by enhanced conversion of lactate to alanine [4]. These metabolic consequences of asphyxia superimposed on the impaired glucose homeostasis caused by malnutrition deserve careful consideration in explaining the difference of the plasma amino acid profile associated with hypoglycaemia in term and preterm undernourished neonates.

Dr. K. SCHULTZ
József A. u. 11
H-7623 Pécs, Hungary

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Spätprognose des postoperativen permanenten atrioventrikulären Blocks III. Grades beim Kind

von

A. KISS und J. KAMARÁS

Landesinstitut für Kardiologie, Budapest

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Im Material von 1965 bis 1975 kamen 15 Fälle mit einem permanenten postoperativen kompletten atrioventrikulären Block vor. 2–11 Jahre nach der Operation sind 12 dieser Patienten am Leben. In 5 Fällen kam es zu einer Pacemakerimplantation, 3 dieser Patienten starben. In 1 Fall konnte die Wiederherstellung des Sinusrhythmus erreicht werden, in weiteren 5 Fällen vollzog sich eine Besserung der Reizleitung, die in 2 Fällen jedoch nur provisorisch war. Die mit dem Krankheitsbild verbundenen therapeutischen und prognostischen Beobachtungen werden erläutert.

Nach Herzoperationen entwickeln sich in einem Teil der Fälle kürzere oder längere Zeit lang bestehende Herzrhythmusstörungen. Ein dauerhaft bestehender Av.-Block kommt am häufigsten nach den Korrektur-eingriffen der Großgefäßtransposition, nach der Rekonstruktion einer Fallotschen Tetralogie und nach dem Verschuß von Vorhof- und Kammer-Septumdefekten vor [4, 20].

Zu Beginn der 60er Jahre gehörte der komplette Av.-Block (P. p. c. b.) noch unter die häufig vorkommenden Krankheiten [9], im Laufe von etwa 10 Jahren hat sich aber, dank der Besserung der technischen Bedingungen, der Vermehrung der chirurgischen Erfahrungen und den Ergebnissen der ausführlichen histologischen Untersuchungen des Reizleitungssystems, die Zahl dieser Fälle in bedeu-

tendem Maße – unter 2% (5) – verringert [4, 10, 15, 20, 21, 22].

Die Verfasser der geringzahligen, sich mit der Spätprognose des P. p. c. b. befassenden Mitteilungen vertreten in Bezug dieser Frage unterschiedliche Meinungen [4, 9, 18, 20], deshalb wollen wir über die späten Kontrolluntersuchungen unserer Patienten berichten. Als permanent betrachteten wir den postoperativen kompletten Av.-Block in Fällen, in denen das Krankheitsbild 1 Monat nach dem Eingriff noch unverändert bestand.

KRANKENMATERIAL UND ERGEBNISSE

An unserer Abteilung standen zwischen 1965 und 1975 15 Patienten mit P. p. c. b. unter Behandlung. Die charakteristischen Angaben unseres Materials veranschaulicht Tabelle I

TABELLE I
Kranken-

Nr.	Name	Lebensalter (Jahre) und Operationsjahr	Diagnose und Eingriff	Therapie	Beobach- tungszeit (Jahre)
1.	F. J.	13 - 1965	VSD + inf. Pulmonalstenose - e. c. c.	∅	11
2.	I. I.	9 - 1965	VSD + ASD II. - e. c. c.	∅	11
3.	J. H.*	7 - 1965	ASD I. + Mitralinsuffizienz	PM	3
4.	K. P.	7 - 1966	ASD II. - Hypothermie	Isoprenalin	10
5.	É. G.	14 - 1967	Fallot IV. - Rekonstruktion - e. c. c.	∅	9
6.	M. B.	14 - 1967	Fallot IV. Rekonstruktion - e. c. c.	PM	9
7.	K. V.	11 - 1967	Aortenstenose + Insuffizienz - e. c. c.	PM	9
8.	A. P.*	6 - 1967	Fallot IV. -Rekonstruktion - e. c. c.	PM	8
9.	L. B.*	14 - 1974	VSD + inf. Pulmonalstenose + Aorteninsuffizienz (Kunst- klappe) - e. c. c.	PM	½
10.	V. S.	9 - 1967	VARIANTEN VSD - e. c. c.	externer Schrittma- cher (1 Mo- nat)	8
11.	F. F.	5 - 1968	Fallot IV. -Rekonstruktion - - e. c. c.	Proterenol	8
12.	T. P.	7 - 1968	ASD I. - e. c. c.	externer Schritt- macher (2 Wochen)	8
13.	M. F.	9 - 1969	ASD II. - Hypothermie	∅	7
14.	A. B.	5 - 1971	ASD II. + V. pulmonalis-Trans- position. Hyperthermie	∅	5
15.	E. O.	4 - 1974	ASD II Hypothermie	Isoprenalin	2

e.c.c. = Operation bei extrakorporaler Kreislauf
Hypothermie = Operation in Hypothermie

material

Av.Block (Grad)	Schrittmacherkomplikationen	Bemerkungen
III. unverändert	∅	Beschwerdefrei
III. unverändert	∅	Beschwerdefrei
III. unverändert	Im 4. postoperativen Monat Schrittmacherimplantati- on. Zweimal Generator- wechsel	Staphylokokken-Sepsis, Tod
III. unverändert	∅	Beschwerdefrei
III. unverändert	∅	Spontangeburt im 7. postope- rativen Jahr, beschwer- defrei
III. unverändert	Im 1. postoperativen Monat Schrittmacherimplantation. Dreimal Generatorwechsel	Beschwerdefrei
III. unverändert	Im 1. postoperativen Monat Schrittmacherimplantation. Dreimal Generatorwechsel	Beschwerdefrei
III. unverändert	Im postoperativen 4. Jahr Schrittmacherimplantation. Zweimal Generatorwechsel	Plötzlicher Tod
III. unverändert	Im 1. postoperativen Monat Schrittmacherimplantation	Plötzlicher Tod infolge elektrischer Störung des Schrittmachers
In der 5. postoperativen Woche Sinusrhythmus, nach 7 Jahren vorüberge- hender III. Später erneut Sinusrhythmus	∅	Im 7. postoperativen Jahr Av. — Block III. Grades. Unter Wirkung von Ste- roid + Isoprenalin nach 1 Monat Sinusrhythmus
Im 3. postoperativen Jahr I., nachher erneut III.	∅	Beschwerdefrei, Frequenzer- höhung auf Belastung
1 Jahr nach der Operation alternierend II. und Sinus- rhythmus. Nach 2 Jahren vorübergehend III. Zur Zeit Sinus-Bradykardie	∅	Beschwerdefrei
Seit dem postoperativen 6. Monat I	∅	Beschwerdefrei
Seit dem postoperativen 2. Monat II	∅	Beschwerdefrei
Bis zum 4. Monat alternie- rend II. und III. Vom 4. Monat ab dauernd III.	∅	Beschwerdefrei

PM = Schrittmacher
ASD = Vorhof-Septumdefekt

VSD = Kammer-Septumdefekt

In der Mehrzahl unserer Fälle wurden die Eingriffe mit extrakorporalem Kreislauf vorgenommen, in 4 Fällen entwickelte sich aber die Reizleitungstörung im Laufe von in Hypothermie durchgeführten Operationen.

In Bezug auf die Geschlechtsverteilung dominierte das weibliche Geschlecht indem 6 Knaben 9 Mädchen gegenüberstanden.

Die postoperative Beobachtungszeit belief sich auf 1/2–11 Jahre (im Durchschnitt 7,3 Jahre).

In 9 Fällen blieb der totale Block im Laufe der Jahre unverändert; in 3 dieser Fälle erweist sich nicht einmal eine Medikation als erforderlich. 1 Patient führt nebst Jahre hindurch angewandter Isoprenalin-Therapie ein normales Leben und hat keine Herzbeschwerden. Sie (E. G., Fall 5) brachte im Alter von 20 Jahren unter externem Pacemakerschutz — zum Einschalten des Apparats kam es nicht — einen 3650 g wiegenden gesunden Knaben auf die Welt.

Zur Pacemakerimplantation kam es in 5 Fällen, trotzdem verloren wir 3 dieser Patienten: 2 starben unerwartet, in bestem Allgemeinzustand, A. P. (Fall 8) beim Schwimmen, L. B. (Fall 9) in einem Dodgem des Luna-Parks, wegen der elektrischen Störung des Schrittmachers; der dritte Patient (J. H., Fall 3) fiel einer sich nach Pacemakerwechsel entwickelten Staphylokokken-Sepsis zum Opfer.

In 6 unserer Fälle konnte eine mehrfache Änderung der atrioventrikulären Reizleitung beobachtet werden. In einem Fall (V. S., Fall 10) löste den P. p. c. p. eine normale Überleitung ab, anlässlich eines sich nach 7 Jahren abgespielten Morgagni–Adams–Stokes-Anfalls wurde jedoch totaler Av.-Block registriert; Isoprenalin und Steroidverabreichung erwiesen sich als erfolgreich, innerhalb eines Monats konnte der Av.-Block behoben und der Sinusrhythmus wiederhergestellt werden. Durch Belastung ließ sich eine supra-

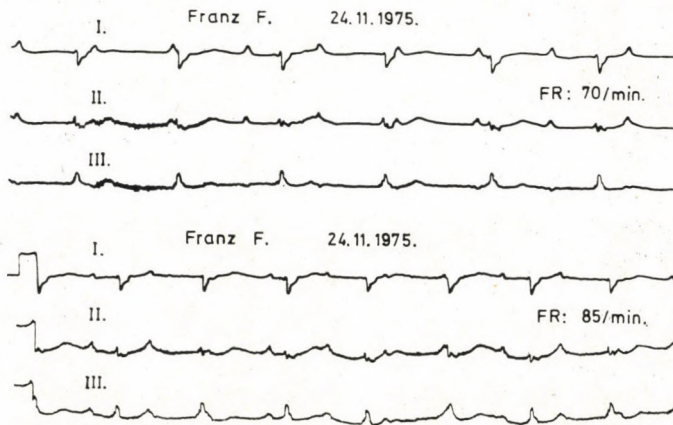


ABB. 1. F. F. 12jähriger Patient; nach der Belastung beschleunigt sich die Frequenz des untergeordneten Pacemakerzentrums.

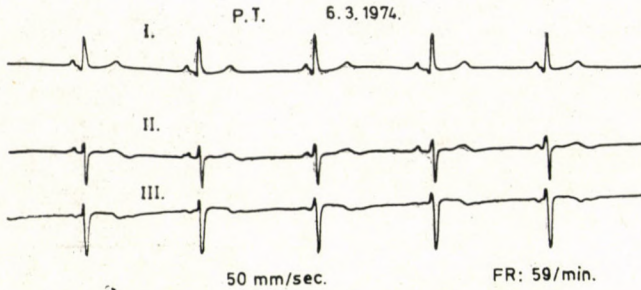


ABB. 2. P. T. im 6. postoperativen Jahr vor der Belastung: Interferenz-Dissoziation, Frequenz 59/min, Av. junctioneller Rhythmus.

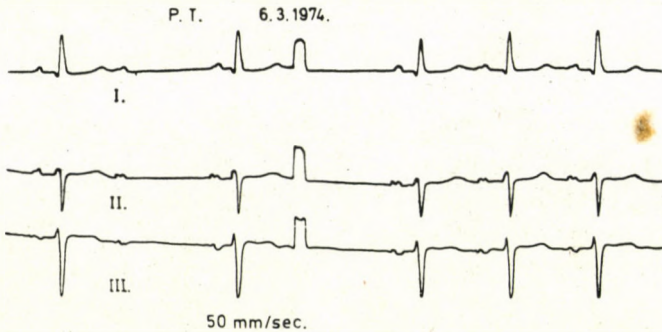


ABB. 3. Unter Wirkung der Belastung entwickelt sich ein Av.-Block 2:1, Frequenz 47/min, sodann Sinusrhythmus mit einer Frequenz von 95/min.

ventrikuläre Tachykardie mit 180/min Frequenz provozieren. In weiteren 3 Fällen war eine Besserung der Reizleitung zu verzeichnen (T. P., M. F. und A. B., Fälle 12, 13, 14), in den restlichen 2 Fällen (F. F. und E. O., Fälle 11 und 15) war diese Besserung nur vorübergehend.

Unsere Beobachtungen sprechen dafür, daß ein untergeordnetes Pacemakerzentrum zur Steigerung seiner Frequenz fähig ist (F. F., Fall 11) (Abb. 1).

In einem unserer Fälle (A. B., Fall 14) befand sich das Reizleitungssystem wahrscheinlich in der unmittelbaren Nähe des Septumdefekts, weil sich der Block bereits vor dem meri-

torischen Teil der Operation, d.h. bei der intraatrialen Palpation entwickelt hat.

Aus der Anamnese von T. P., (Fall 12) ist die mehrfache Änderung der Reizleitung zu entnehmen. Beachtenswert war folgendes: Im zweiten postoperativen Jahr meldete sich nach spontaner Besserung der komplette Av.-Block anlässlich eines Katarrhs der oberen Luftwege wieder. Ein Teil der im Laufe der Operation implantierten provisorischen Pacemaker-Elektrode verursachte 6 Jahre später eine traumatische Perikarditis und wurde chirurgisch in mehreren Stücken entfernt. Zeitweise traten Interferenz-Dissoziation und atrioven-

trikulärer junctioneller Rhythmus auf, mittels Belastung konnte ein Av.-Block II. Grades ausgelöst werden (Abb. 2 und 3).

Gegenwärtig (1976) sind 12 unserer Patienten am Leben, und zwar 10 von ihnen bereits seit 6–11 Jahren.

BESPRECHUNG

Mit der Pacemakertherapie des P. p. c. b. befaßt sich eine Vielzahl der Mitteilungen [z. B. 2, 3, 6, 8, 13, 14, 15, 16], die erste Pacemakerimplantation wurde ebenfalls wegen eines chirurgischen Blocks durchgeführt [23]. Liu und Mitarb. [16] vertreten die Ansicht, daß die Pacemakerimplantation in der postoperativen Phase unbedingt indiziert ist [16]. Wir schließen uns anhand unserer Erfahrungen eher der Meinung jener Verfasser an, die die Pacemakertherapie im Kindesalter nur nach gründlicher Erwägung empfehlen [2, 3, 18, 20], zumal unsere Fälle tödlichen Ausgangs zur Pacemaker-Gruppe gehörten (J. H., A. P., L. B.). Die Einpflanzung des Geräts indizierten wir nur in Fällen in denen sich ein Morgagni-Adams-Stokesscher-Anfall abspielte; wegen durch Bradykardie bedingten verminderten Minutenvolumen griffen wir nicht zur Pacemakerimplantation.

Averill [1], Murphy [18] und Rautenburg [20] berichteten über die Änderungen der Reizleitung: Laut ihrer Beobachtungen kann sich eine Besserung zwar nach Monaten oder eventuell auch nach Jahren einstellen,

in der Mehrzahl der Fälle ist diese nur vorübergehend. Über ähnliche Beobachtungen schrieben Poster und Mitarb. [19]: In dem erläuterten Fall handelte es sich um ein im Alter von 12 Jahren, wegen Fallotscher Tetralogie operiertes Kind, nach einigen Monaten konnten die Besserung des P. p. c. b. und die Wiederherstellung des Sinusrhythmus registriert werden. 2 Jahre nach dem Eingriff entwickelte sich aber im Zusammenhang mit einer Influenza wieder ein kompletter Av.-Block; nach 1jähriger Beobachtung wurde die Pacemakerimplantation indiziert.

Anhand der Analyse unserer Fälle gelangten wir zu folgenden Feststellungen:

1. 12 der 15 Patienten sind 2–11 Jahre nach der Operation am Leben; 2 von ihnen leben mit und die übrigen ohne eingepflanzten Schrittmacher;

2. der P. p. c. b. kann nach mehreren Monaten oder auch einem Jahr regredieren, mitunter kommt sogar eine normale Überleitungszeit zustande;

3. die atrioventrikuläre Überleitung bleibt auch in regredierenden bzw. eine normale Überleitung zeigenden Fällen lädiert, welcher Umstand im Laufe von Infektionskrankheiten bzw. unter Wirkung einer physikalischen Belastung zur vorübergehenden Verschlechterung der Überleitung führen kann.

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Dr. A KISS

Nagyvárad tér 1

H-1096 Budapest, Hungary

A teratological evaluation of anticonvulsant drugs

By

P. LAKOS and E. CZEIZEL

National Institute of Hygiene, Budapest

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Reviewing the important teratological data on anticonvulsants, the Hungarian experiences are reported. In the Hungarian Congenital Malformation Register use of the anticonvulsants diazepam and phenobarbiturates during pregnancy was determined in infants delivered with cleft lip with or without cleft palate, posterior cleft palate and, as a control, anencephaly and spina bifida. The teratogenic effect of diphenylhydantoin was confirmed, while that of diazepam and phenobarbital was not supported.

The incidence of epilepsy is usually estimated at 1%, but reliable epidemiological data show an incidence from 0.3 to 0.7% and a prevalence from 2 to 7%. According to Kurtzke [20], the incidence from birth to the age of 5 years is 0.5 to 1.5%, from 5 to 15 years, 0.25%, and beyond 15 years, 0.05 to 0.25%. Thus, it is not unusual for epileptics to seek advice regarding planned or already existing pregnancies.

The problems of family planning are the heredity of epilepsy and the possible teratogenic effects that might occur in epileptic pregnancies.

It was Meadow [24] who noticed that among the mothers of cleft lip and/or cleft palate babies, a higher than normal number had taken anticonvulsants during pregnancy. In the wake of this observation, many investigations were undertaken, the results

of which are summarized in Table I. In infants born to epileptic mothers the incidence of congenital malformations was 6.4 to 6.7%, significantly ($p < 0.001$) higher than the 2.9% for infants born to non-epileptic women.

Among the epileptic pregnant women some had and some had not been treated during pregnancy. In the infants born to those receiving anticonvulsants during pregnancy the occurrence of congenital malformations was 7.4 to 7.8%, 2.5 times higher than the control figure ($p \ll 0.001$). On the other hand, in infants born to mothers who did not receive treatment during pregnancy, the occurrence of congenital malformations, 3.2%, did not significantly exceed the normal rate. Thus, the teratogenic effect of anticonvulsants would seem to be certain. However, those requiring treatment were in all probability suffering from

TABLE I

Teratogenic effects of anticonvulsants

Authors	Country	Control				
		N	CA		oral cleft	
			n	%	n	%
Janz and Fuchs [16]	GFR	—	—	—	—	—
Maroni and Markoff [23]	GFR	—	—	—	—	—
German et al [13]	USA	—	—	—	—	—
Elshove and van Eck [11]	Netherlands	11 986	221	1.8	32	0.27
Watson and Spellacy [30]	USA	50	0	0.0	0	0.00
South [36]	England	7 865	190	2.4	14	0.18
Speidel and Meadow [37]	England	483	7	1.4	1	0.21
Starreveld-Zimmerman et al [38]	Netherlands	—	—	—	—	—
Koppe et al [18]	Netherlands	12 300	426	3.5	21	0.17
Lowe [22]	Wales	31 877	877	2.8	50	0.16
Meyer [25]	GFR	—	—	—	—	—
Bjerkedal and Bahna [6]	Norway	112 328	2 471	2.2	1 797	1.60
Manson et al [29]	USA	50 591	1 240	2.5	76	0.15
Kuensberg and Knox [19]	Scotland	14 620	447	3.1	30	0.21
Niswander and Wertelecki [31]	USA	347 097	9 372	2.7	520	0.15
Millar and Nevin [26]	N.Ireland	32 227	1 235	3.8	70	0.22
Fedrick [12]	England	649	21 ^c (36 ^d)	3.2 (5.5)	0	0.00
Barry and Danks [14]	Australia	—	—	—	—	—
Annegers et al [2]	USA	84	0	0.0	0	0.00
Biale and Rhind [5]	Israel	—	—	—	—	—
Knight and Rhind [17]	Israel	—	—	—	—	—
Shapiro et al [35]	USA	49 977	3 216	6.4	—	—
Total		672 134	19 723 ^e (19 738 ^d)	2.9 (2.9)	2 611	0.39

Abbreviations:

* = treated and non-treated epileptics

N = total

CA = Congenital anomaly

n = number

administered during pregnancy

Treated epileptics					Non-treated epileptics					Epileptics*				
N	CA		oral cleft		N	CA		oral cleft		N	CA		oral cleft	
	n	%	n	%		n	%	n	%		n	%	n	%
225	5 ¹	2.2	3	1.33	120	0	0.0	0	0.00	345	5 ¹	1.4	3	0.87
21	1 ⁰	4.8	0	0.00	14	0	0.0	0	0.00	35	1 ⁰	2.9	0	0.00
243 ^a	13 ²	5.3	1	0.41	—	—	—	—	—	—	—	—	—	—
65	10 ²	15.4	5	7.69	—	—	—	—	—	—	—	—	—	—
51	3 ¹	5.9	0	0.00	—	—	—	—	—	—	—	—	—	—
22	2 ⁰	9.1	2	9.09	9	0	0.0	0	0.00	31	2 ⁰	6.5	2	6.45
365	17 ⁶	4.7	3	0.82	62	0	0.0	0	0.00	427	17 ⁶	4.0	3	0.70
281	22 ⁷	7.8	9	3.20	16	0	0.0	0	0.00	297	22 ⁷	7.4	9	3.03
125	11 ⁴	8.8	1	0.79	67	2	3.0	0	0.00	192	13 ⁴	6.8	1	0.52
134	9 ¹	6.7	1	0.74	111	3	2.7	0	0.00	245	12 ¹	4.9	1	0.41
199	37 ⁵	18.6	5	2.51	124	4	3.2	0	0.00	323	41 ⁵	12.7	5	1.55
378	17 ⁰	4.5	4	1.06	—	—	—	—	—	—	—	—	—	—
205	11 ¹	5.4	3	1.46	101	3	3.0	0	0.00	306	14 ¹	4.6	3	0.98
48	5 ^b	10.4	0	0.00	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	413	17 ⁵	4.1	3	0.73
110	7 ⁰	6.4	2	1.82	—	—	—	—	—	—	—	—	—	—
198	15 ⁰ (28 ² _d)	7.6 (14.1)	1	0.51	19	2	10.5	0	0.00	217	17 ² (30 ² _d)	7.8 (13.8)	1	0.46
73	13 ⁰	17.8	0	0.00	20	0	0.0	0	0.00	93	13 ⁰	15.7	0	0.00
141	10 ⁶	7.1	3	2.13	56	1	1.8	0	0.00	197	11 ⁶	5.6	3	1.52
—	—	—	—	—	—	—	—	—	—	56	9 ²	16.2	2	3.57
—	—	—	—	—	—	—	—	—	—	140	4 ³	2.9	2	1.43
208	21	10.1	—	—	97	11	11.3	—	—	305	32	10.5	3	0.98
3092	223 ⁷ (242 ² _d)	7.4 (7.8)	43	1.42	816	26	3.2	0	0.00	3622	230 ⁴ (243 ⁴ _d)	6.4 (6.7)	41	1.13

- a = treatment unknown
- c = diagnosed at birth
- b = of 5 anomalies, 1 major, 2 minor and 2 questionable
- d = diagnosed in later life

Index numbers above the figures indicate the number of congenital heart defects

more severe epilepsy, with frequent seizures and in worse somatic and mental condition. On the other hand, one could accept the argument that a treated woman who gave birth to a malformed infant might later have a healthy infant if left untreated during pregnancy [14]. In contrast, Shapiro et al [35], found no appreciable difference in the occurrence of defective infants born to treated vs. non-treated epileptic mothers.

When investigating the eventual teratogenic effect of anticonvulsants, two questions have to be elucidated, viz. (i) which are the malformations which will most frequently increase in number; and (ii) the difference in teratogenic effect between the different anticonvulsants.

(i) When treating an epileptic pregnant women the main malformation to be reckoned with is cleft lip and cleft palate [24]. As it is seen in Table I, the occurrence in the control groups was 3.39% (which is higher than the usual 0.2%), whereas in the infants born to epileptic mothers it was 1.13%.

On the other hand, among the offspring of women who during pregnancy had been treated with anticonvulsants, the point-prevalence at birth of cleft lip and cleft palate was 1.42% which represents a close to four-fold risk. Taking into consideration the normal prevalence at birth of these malformations, the rate of increase was at least 7-fold.

Congenital heart defects were also more frequent following anticonvulsant treatment during pregnancy; their frequency was nearly double

the normal occurrence. Moreover, an increase in the frequency of multiple malformations may also be regarded as characteristic, with malformations of the bone structure, especially the digits, predominating. Most frequently afflicted are the fingers and the ulnar side [1, 3, 4, 10, 15, 21]. The frequent occurrence of mental backwardness and of its cause (genetic, teratogenic, social influence?) is a debatable point [12, 29].

Some authors found a higher perinatal mortality of infants born to epileptic women who had received treatment during pregnancy [20, 12, 6, 2, 37]; this, in addition to congenital malformations, may be related to an increased frequency of haemorrhage [30, 12] and intrauterine mortality.

The aim of the present work was to study the teratogenic effects of anticonvulsants as well as the differences between them.

MATERIAL AND METHOD

In Hungary, nation-wide statistical data for congenital malformations have been kept since January 1, 1970, and by December 31, 1975, a total of 29,057 such infants, were on record in the Hungarian Congenital Malformation Register. The malformations were grouped in accordance with the 8th Revision of ICD. To study the possibility of a correlation between diazepam treatment during pregnancy and cleft lip and cleft palate [33, 34] we sent to the parents of every infant born with cleft lip and/or cleft palate and posterior cleft palate a questionnaire, in which we enumerated three groups of drugs. These were (1) the 10 most common sedatives, among them diazepam; (2) 6 anticonvulsants;

and (3) progestogen preparations for the protection of pregnancy. The mothers were asked to underline the drugs used during pregnancy and to indicate the weeks during pregnancy when these drugs were taken. The anticonvulsants were studied as having a supposedly positive teratogenic effect, while the progestogens for the protection of pregnancy were studied as having a negative effect.

As a control group, we selected babies with anencephaly and/or spina bifida. The reason we chose this group was that these malformations lend themselves to standard description, their reporting — similarly as that of cleft lip and cleft palate — may be considered 100% and the role played by the drugs under investigation has not yet come up in their aetiology.

RESULTS

Results are shown in Table II. About 50% of the cases could be evaluated.

Table III shows the correlation between diazepam treatment during pregnancy and the 3 groups of malformations under investigation. In the cleft and/or cleft palate and the anencephaly-spina bifida groups the occurrence of diazepam treatment was practically the same, whereas in the posterior cleft palate group, insignificantly lower. Even when considering the critical period of the malformations no significant difference was found.

TABLE II
Cases in the Hungarian Congenital Malformation Register, 1970—1975, and evaluated cases

Type	Registered cases		Evaluated cases	
	No	%	No	%
Cleft lip and/or cleft palate	995	100.0	413	41.51
Posterior cleft palate	228	100.0	121	53.07
Anencephalospina bifida	1476	100.0	843	57.11

TABLE III
Diazepam treatment during pregnancy in the 3 groups of congenital malformations

Congenital disorder	Time of drug administration								
	No	month of pregnancy					through-out pregnancy	unknown	total
		1	2	3	4-6	7-9			
Cleft lip and/or cleft palate	413	11 (2.66)	5 (1.21)	4 (0.97)	10 (2.42)	6 (1.45)	1 (0.24)	27 (6.54)	64 (15.50)
Posterior cleft palate	121	2 (1.65)	—	—	2 (1.65)	—	—	8 (6.61)	12 (9.92)
Anencephaly-spina bifida	843	7 (0.83)	15 (1.78)	15 (1.78)	27 (3.20)	13 (1.58)	8 (0.95)	43 (5.10)	128 (15.18)

Percentages in parentheses

TABLE IV
Anticonvulsant treatment during pregnancy in three congenital malformation groups (figures for barbiturates in parentheses)

Congenital disorders	No	Month of pregnancy					Whole pregnancy	Total	
		1	2	3	4-6	7-9		No	per cent
Cleft lip and/or cleft palate	413	1 (1)	1 (1)	— (2)	— (1)	—	9 (1)	11 (6)	(2.66)* (1.45)**
Posterior cleft palate	121	—	—	—	—	(1)	1 (1)	1 (2)	(0.82) (1.65)
Anencephaly-spina bifida	843	— (1)	— (3)	— (2)	— (6)	— (1)	2 —	2 (13)	(0.23) (1.54)

* $x^2 = 15.9$; $p < 0.001$. ** $x^2 = 0.014$; $p < 0.10$

Data for anticonvulsant treatment during pregnancy are seen in Table IV. We evaluated separately the effects of diphenylhydantoin (DPH) derivatives, of phenobarbital and of other anti-epileptic drugs. In the case of phenobarbital no specific teratogenic effect could be proved, i. e. the frequency and the period of time when the drug had been administered, showed no deviation in the 3 types of malformations studied. In the case of the other anticonvulsants including the DPH derivatives, there were significant differences, as shown in Table V. Such treatment was significantly

more common in the cleft lip and/or cleft palate group. The majority of the mothers had received treatment throughout pregnancy. Of the 121 and 843 pregnant women who gave birth to infants with posterior cleft palate and anencephaly-spina bifida, only one and two, respectively, had had anticonvulsant treatment during pregnancy. Thus, anticonvulsants seem to have a role in the aetiology of cleft lip and/or cleft palate.

Progestogen treatment showed an identical frequency in the 3 types of malformation.

DISCUSSION

The results seem to have proven the teratogenic effect of DPH. At the same time we have failed to find a teratogenic effect in the case of progestogen, in agreement with the data in the literature. Nor was there any evidence of a teratogenic effect of diazepam and of phenobarbital in the 3 types of malformations studied [9] including the earlier suspected cleft lip and cleft palate.

TABLE V
Anticonvulsant treatment

Drug	Cleft lip and/or cleft palate	Posterior cleft palate	Anencephaly-spina bifida
Phenytoin	4	—	2
Phenacemide	1	—	—
Morfolep	1	—	—
Trimethadione	2	1	—
Mephenytoin	1	—	—
Primidone	2	—	—

For the correct evaluation of the teratogenic effect it is necessary to separate the malformations of different aetiologies. Thus, isolated cleft lip and/or cleft palate have a multifactorial aetiology. One sign of genetic predisposition may be a cleft lip and/or cleft palate occurring in the first or second degree relatives. The aetiology of posterior cleft palate is not quite clear but the role played by teratogenic effects seems significant. On the other hand, cleft lip and cleft palate occurring with multiple malformations are different in aetiology; they may be associated with monogenic, chromosomal and teratogenic syndromes.

Of the thus far registered 43 babies with cleft lip and cleft palate delivered by epileptic women, it was possible to ascertain the type in 33 instances; there were 24 isolated and 9 multiple cases. We must therefore expect a more frequent occurrence of both the isolated and the multiple type. The question needs, however, further studies.

Of the anticonvulsants we may attribute a mild teratogenic effect to DPH-derivatives. DPH penetrates well across the placenta, therefore its concentration is the same in the blood of the mother and the fetus [27, 28]. There are reports on the teratogenic effect of primidone, carbamazepine, trimethadione and paramethadione [4, 9, 13, 14, 21], but these observations are not yet sufficient to formulate a final opinion. The phenobarbiturates are unlikely to have a teratogenic effect, but their combination with DPH has been claimed to

exert an increased teratogenicity [12, 22]. The majority of authors blames the absence of folic acid for the teratogenic effect of DPH. DPH has namely been shown to cause an acute folic acid deficiency which soon disappears on withdrawal of the drug. The correlation between folic acid deficiency and certain congenital disorders has been suggested by several studies [7, 39]. The reverse is also true: prolonged folic acid administration will neutralize the effect of DPH, and may thus cause a recurrence of seizures. In this way folic acid is a potential convulsant and its level in the epileptic focus is higher than in the rest of the brain [32].

There are several ways to interpret the increased frequency of congenital anomalies in the babies of treated epileptic mothers:

- (i) the effect of anticonvulsants taken during pregnancy;
- (ii) the effect of the epileptic condition;
- (iii) some effects associated with epilepsy. The social standing of epileptics is usually below average and infections are therefore more frequent in them. Besides, their choice of sexual partners is limited and often disadvantageous, etc.

The first and second questions can be answered on the basis of the frequency of congenital disorders in the infants born to treated and non-treated epileptics. The significantly increased frequency in the former group points to the teratogenic effect of anticonvulsants. The third possibility must, however, also be taken into

consideration, at least as having a modifying influence.

In the course of pregnancy, anticonvulsant treatment must be continued. During pregnancy, almost one half of the epileptics has an increased tendency, to develop seizures [17] and the consequential reduction of placental circulation may cause fetal death or mental deficiency. Besides, a sudden cessation of drug treatment might elicit a status epilepticus fatal for both the pregnant woman and her fetus. If the seizures can be controlled by barbiturates, preference should be given to this group of drugs. Taking into account the critical period for congenital disorders caused by anticonvulsants, the period from the 4th to the 10th week of gestation may be considered dangerous.

As an additional treatment, folic acid and vitamin K are recommended. The former tends to diminish or inhibit the teratogenic effect, but will increase the tendency to seizures. Vitamin K is able to neutralize the coagulation defect resulting from anti-epileptic treatment [12, 30].

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E. CZEIZEL, M. D.

Gyáli út 4.

H-1966 Budapest, Hungary

Die Eigenschaften des Gliadins und der Antikörper gegen Gliadin bei Zöliakie

Von

M. SZABOLCS, S. CSORBA, MÁRIA KÁVAI, I. FRANCIA und B. SZABÓ

Zentrales Forschungsinstitut, Kinderklinik, und Institut für Pathophysiologie der Medizinischen Universität Debrecen

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Aus dem wäßrigen Extrakt des Weizenmehls wurden mittels Gel-filtration vier Fraktionen — Fraktion A, B, C und D — isoliert.

Es wurde festgestellt, daß die Fraktion A mit dem Serum der Zöliakie-Kranken als Antigen reagiert. Die Menge der Fraktion A war im aus der Neuernste gemahlten Weizenmehl am höchsten; das Absorptionsmaximum lag bei 278 nm und die Fraktion enthielt eine Verbindung mit 1,5–2,0% igem Phosphorgehalt (Nukleinsäure und Nukleotid). Bei Zelluloseazetat-Membranelektrophorese wandert die Fraktion A eher in Richtung der Anode als bei Polyakrylamid-Gelelektrophorese. Der Glutaminsäure- bzw. Prolin-Gehalt der Fraktion A ist 27,2% bzw. 12,4%. Die mittels Nadoecylsulfat-Gelelektrophorese bestimmten Molekulargewichte von 34 000–36 000 und 56 000–60 000 Dalton und die erwähnte Aminosäure-Zusammensetzung lieferten einen Beweis dafür, daß die Fraktion A in die Gruppe der Gliadine gehört, obwohl sie durch wäßrige Extraktion (pH = 5,5–6,0) isoliert wurde.

Im Gegensatz zu den im unfraktionierten wäßrigen Extrakt des Mehles befindlichen Eiweißen wird durch das im Kaninchen erzeugten Antiserum nur die Fraktion A präzipitiert, obwohl das bei der Immunisierung angewandte Eiweißextrakt auch die Fraktionen B, C und D enthielt. Der Antikörper ist vom IgG-Typ.

Die Versuchsergebnisse führten zur Feststellung, daß das Gliadin ein proteolytisch nicht oder kaum verdaubares Eiweiß von besonderer Aminosäuresequenz ist. Demzufolge dürfte zwischen dem Pathomechanismus der Zöliakie und den physiko-chemischen bzw. funktionellen Eigenschaften des Gliadins eine enge Korrelation bestehen.

Die ätiologische Rolle des Weizenproteins Gliadin bei der Zöliakie ist bekannt [5]. Wir haben es früher bewiesen, daß unter den Eiweißen des wäßrigen Mehlextrakts die das höchste Molekulargewicht zeigende Fraktion 2–3, die im Laufe der Polyakrylamid-Gelelektrophorese in der Nähe der Katode bleibt, mit dem im Serum der Zöliakie-Kranken be-

findlichen Antikörper in eine antigenartige Reaktion tritt [6].

In vorliegender Arbeit wollen wir unsere Untersuchungsergebnisse in bezug auf die Identifizierung der aus dem wäßrigen Mehlextrakt isolierten Fraktionen, vor allem der sich antigenartig verhaltenden Fraktion sowie unsere Hypothese hinsichtlich des Pathomechanismus der Zöliakie erläutern.

METHODIK

Herstellung des Eiweißextrakts

1 g des Weizenmahlprodukts wurde in 20 ml 0,005% NaN_3 -haltigem, ionfreiem Wasser von 2–4°C suspendiert. Nach 24–36 Stunden langer Umrührung im kalten Zimmer wurde die Suspension in einer MSE-25 oder Beckmann L3–50 präparativen Ultrazentrifuge mit 50 000 g 60 Minuten lang zentrifugiert. Das Präzipitat wurde verworfen, das Extrakt (Supernatant) lyophilisiert, und das lyophilisierte kalte Extrakt im Vakuumexsikkator aufbewahrt.

Eiweißfraktionierung auf Sephadex G-75 Säule.

600 mg des kalt, unter Vakuum aufbewahrten, lyophilisierten Extraktes wurden in 4 ml ionfreiem Wasser gelöst und gegenüber 0,005% NaN_3 -haltigem ionfreiem Wasser dialysiert. Zunächst wurden 4 ml des Extrakts (80 mg Eiweiß) zwecks Fraktionierung auf eine Sephadex G-75 Säule (Durchmesser 1,8 cm, Höhe 51 cm, Volumen 130 cm³) aufgetragen und mit 0,005% NaN_3 -haltigem, ionfreiem Wasser bei +4°C eluiert. Die Elutionsgeschwindigkeit betrug 20–22 ml/Stunde, das Volumen der eluierten Fraktionen belief sich auf 5 bzw. 2,5 ml. Die Extinktion dieser Fraktionen wurde im Spektrophotometer PM2 DL Opton gemessen.

Polyakrylamid-Gelektrophorese

Das Extrakt und die gewonnenen Fraktionen wurden unter Anwendung von 7% iger Polyakrylamidgel-Lösung und einem Trisglyzin-Puffer (Ionenstärke 0,05, pH 8,3) elektrophoriert. [6].

Na-Dodecylsulfat-Polyakrylamid-Gelektrophorese bei pH 7

Die 50–100 µg Eiweiß enthaltende Probe wurde im Verhältnis 1:1 oder 2:1 mit einer aus 0,01 M Na-phosphat (pH 7,0), 5% Na-dodecylsulfat, 1% Merkaptoethanol, 0,005% Bromphenolblau und 40% Glycerin

bestehenden Unterschichtlösung versetzt, sodann bei 100°C 5 Minuten lang inkubiert. Hiernach wurden die inkubierten Proben quantitativ, unter einem Elektrodenpuffer auf die Gelsäule aufgetragen. Die Elektrophorese wurde auch mit der Methode von Weber und Osborn [21] durchgeführt, mit dem Unterschied, daß die Gelsäulen nur 5% Akrylamid enthielten. Stromstärke: 7 mA/Rohr, Laufzeit: 5 Stunden. Nach der Elektrophorese wurden die Gelsäulen mit Coomassie-Brillantblau gefärbt und der überflüssige Farbstoff mit einem aus Essigsäure, Methanol und Wasser bestehenden Gemisch ausgelöst. Als Standard-eiweiße (zum Vergleich dienende) wurden Bovin-Serumalbumin (Molekulargewicht: 68 000 Dalton), Gammaglobulin (Molekulargewicht: 50 000 bzw. 23 000 Dalton) und Ovalbumin (Molekulargewicht 42 000 Dalton) angewandt.

Na-Dodecylsulfat-Polyakrylamid-Gelektrophorese bei pH 8,3

Die 50–100 µg Eiweiß enthaltende Probe wurde im Verhältnis 1:1 oder 2:1 mit einer aus 0,06% Tris, 0,29% Glycin, 5% Na-dodecylsulfat, 1% Merkaptoethanol, 0,005% Bromphenolblau und 40% Glycerin bestehenden Unterschichtlösung versetzt und bei 100 °C 5 Minuten lang inkubiert. Hiernach wurde die Probe quantitativ unter einem Elektrodenpuffer auf die Gelsäule aufgetragen. Die Elektrophorese wurde nach Peterson und Strohmman [15] bei 1,5 mA/Rohr mit 2 Stunden Laufzeit durchgeführt, die Säule enthielt jedoch nur 5% Akrylamid. Färbung usw. geschahen wie bei pH 7. Nach Auslösung der überschüssigen Farbe wurde das Gel mit einem, an das Zeiss-Schnellphotometer angeschalteten GIBI Kompensographen densitometriert.

Zelluloseazetat-Membran Elektrophorese

Auf eine vorangehend mit Veronalnatriumazetatpuffer (pH 8,6) durchtränkte, 2,5 × 16 cm große Zelluloseazetat-Membranfolie (Schleicher-Schüll) wurden mit

einer Pipette 10 μ l (70–100 μ g Eiweiß) Untersuchungsmaterial aufgetragen. Zwecks Markierung kam Bromphenolblau zur Anwendung. Zunächst wurde bei 0,4–0,5 mA Stromstärke/cm Streifenbreite 2 Stunden lang elektrophoriert, und danach die Folie gefärbt und gewaschen, getrocknet, mit Paraffinöl transparent gemacht und mit einem, an ein Zeiss-Schnellphotometer angeschalteten GIBI Kompensograph densitometriert.

Herstellung des Immunserums

Das lyophilisierte Weizenextrakt wurde in Wasser gelöst und der reine Supernatant mit soviel NaCl versetzt, daß die Endkonzentration des Kochsalzes 0,9% ausmachte. Mit dieser Eiweißlösung (Eiweißkonzentration 1–1,2%), die mit kompletten Freund-Adjuvant (Difco) im Verhältnis 1:1 vermischt wurde, wurden Kaninchen immunisiert. Sechs Tage nach der letzten Injektion wurden die Tiere entblutet, die Seren bei 56°C 30' lang inaktiviert und bei –18°C im Tiefkühlschrank aufbewahrt.

Agardiffusion

In 50–55°C warmem Wasser gelöste 3%ige Agarlösung (Bacto Agar Difco) wurde mit 8- oder 16fach verdünntem Antiserum im Verhältnis 1:1 rasch vermischt und danach 2,3 ml auf Objektträger pipettiert; am nächsten Tag wurden in das Agar Löcher von 4 mm Durchmesser verfertigt, und in die Löcher aus dem Mehlextrakt bzw. den Sephadex Fraktionen je 10 μ l pipettiert. Diese Manipulation wurde nach 24 Stunden wiederholt. In der Zwischenzeit wurden die Objektträger in der Feuchtkammer bei Zimmertemperatur aufbewahrt. Nach 48 Stunden Inkubation wurden die an der Bildung des Immunpräzipitats nicht beteiligten Eiweiße aus dem Agar mittels physiologischer Kochsalzlösung ausgewaschen, die Agarschicht getrocknet, das Eiweiß mit Säurefuchsin gefärbt und differenziert.

Aminosäureanalyse

1 ml des Untersuchungsmaterials (Extrakt bzw. seine Fraktionen), dessen Eiweißkonzentration 1,5 mg/ml ausmachte + 1 ml 38%ige HCl-Lösung wurden in Ampullen zu 2 ml gemessen. Die Ampullen wurden nach Durchblasen mit N₂ abgelötet, sodann 48 Stunden lang bei 105°C aufbewahrt. Es folgte Entsäuern bei 80°C in der Anwesenheit von KOH und P₂O₅, im Vakuumtrockenschrank. Zur Bestimmung der Aminosäurezusammensetzung des entsäuerten Hydrolysats diente ein Aminosäureanalysator LYZ 75 (Chinoin).

VERSUCHSERGEBNISSE

Unsere früheren Untersuchungen führten zur Feststellung, daß sich im Laufe der Speicherung des Weizens als Mahlgut die Menge des mit Wasser extrahierbaren, antigenartigen Eiweißes ändert. Demnach richteten sich unsere Untersuchungen vor allem auf die Klärung der Frage, ob sich im auf drei verschiedene Weisen behandelten Weizenmehl – 1. bei Zimmertemperatur 1 Jahr hindurch, in Form von Mahlgut gespeicherten 2. 1 Jahr hindurch in Samenform gespeicherten und nur vor der Extraktion gemahlten und 3. im aus Neuernte gemahlten Weizenmehl – die extrahierbare Gesamteiweißmenge, bzw. die darin befindliche Antigenmenge ferner die bei einer Eiweißkonzentration von 1,0 mg/ml, bei 280 nm, in einer 1 cm Küvette gemessene Extinktion des Extraktes im Laufe der Speicherung ändern (Tab. I).

Aus Tabelle I geht hervor, daß sowohl die mit Wasser extrahierbare

TABELLE I
Wasserextrahierbarer Gesamteiweiß- und Antigengehalt

Lagerungszeit und -form	Extrahiertes Eiweiß mg/-Mehl g	Antigen mg%/-Mehl g	$E_{280}^{0,1\%}$ nm
1 Jahr, gemahlten	11,3	1,1	3,00
1 Jahr, Korn, gemahlen vor Extraktion	15,1	2,25	1,980
Neuernte, gemahlen vor Extraktion	17,2	3,25	1,90

* Mit Gelfiltration gemessene Werte

Eiweißmenge, als auch ihr Antigengehalt im aus Neuernte gemahlten Weizenmehl am höchsten sind. Andererseits sind in diesem Mehl auch die Eiweiße intakter, da ihr $E_{1\text{cm}}^{0,1\%}$ -Wert am niedrigsten ist.

Angesichts dieser Ergebnisse untersuchten wir die Eigenschaften der im Wasserextrakt des aus Neuernte gemahlten Mehls befindlichen Eiweiße.

Die Eiweiße des Wasserextrakts können auf Sephadex G-75 Säule in 4 Komponente separiert werden;

diese Fraktionen bezeichnen wir mit A, B, C und D. Abbildung 1 zeigt das Elutionsdiagramm einer Gelfiltration.

Die im Laufe von je 3 Gelfiltrationen gewonnenen Fraktionen A, B, C und D wurden separat vereinigt und lyophilisiert. Wie wir darüber bereits berichteten, spielt sich zwischen den in der Fraktion A befindlichen Eiweißen und dem im Serum der Zöliakie-Kranken anwesenden Antikörper eine antigenartige Reaktion

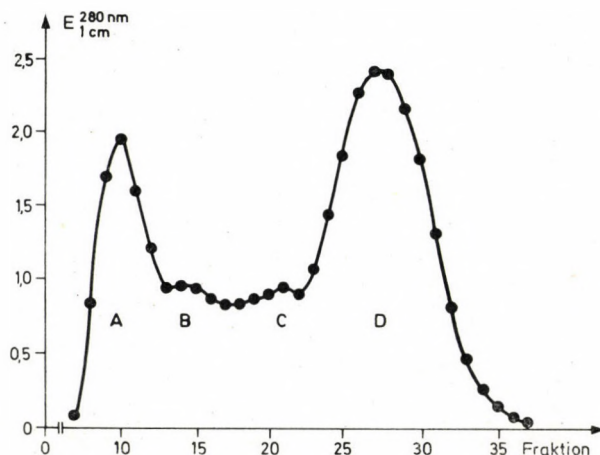


ABB. 1. Elutionsdiagramm der Eiweiße des Mehlextrakts, anlässlich Gelfiltration auf Sephadex G-75 Säule. Das Volumen der Fraktionen beträgt 5 ml.

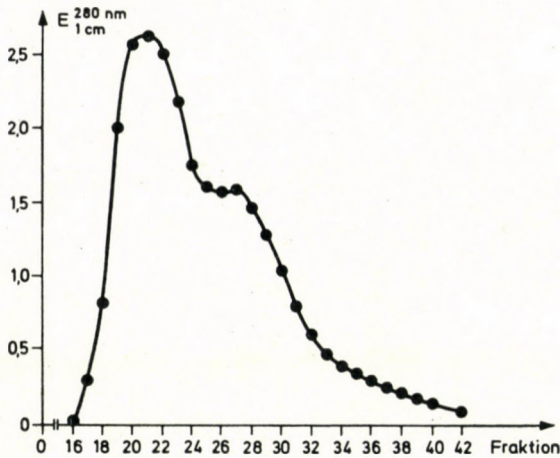


ABB. 2. Elutionsdiagramm der Fraktion A des Mehlextrakts anlässlich wiederholter Gelfiltration. Das Volumen der Fraktionen beträgt 2,5 ml.

ab [6]. Unseres Erachtens bietet die genauere Kenntnis der Eigenschaften der Fraktion A eine Möglichkeit zur weiteren Klärung der Pathogenese der Zöliakie.

Da laut der Polyakrylamid-Gel-Elektrophoretogramme vereinigten Fraktionen A auch die Eiweißkomponenten anderer Eiweißfraktionen enthalten, wurde die Fraktion A auf Sephadex G-75 Säule wieder gelfiltriert (Abb. 2). Wie aus Abbildung 2 ersichtlich, kann die Fraktion A in 2 Komponenten separiert werden. Wie die Polyakrylamid-Gelelektrophorese zeigte, entsprach die zweite Komponente der Fraktion B, d. h. daß sie als Verunreinigung in die Fraktion A gelangte. Da sich die einzelnen Fraktionen bei der Gelfiltration überlappen, haben wir die Fraktionen B, C und D auf Sephadex G-75 Säule wiederholt gelfiltriert. Nach der Gelfiltration kam es zur

Untersuchung des Absorptionsspektrums dieser gereinigten Fraktionen (Abb. 3).

Das Absorptionsmaximum der Fraktionen A, B und C betrug 278 nm, das der Fraktion D lag bei 260 nm. Der Quotient der bei 280 nm und 260 nm gemessenen Extinktionen $E_{280 \text{ nm}}^{1 \text{ cm}}/E_{260 \text{ nm}}^{1 \text{ cm}}$ liefert bekanntlich eine Aufklärung darüber, ob die Fraktionen Nukleinsäure oder Nukleotide enthalten. Bei den einzelnen Fraktionen ergab der Wert des $E_{280 \text{ nm}}^{1 \text{ cm}}/E_{260 \text{ nm}}^{1 \text{ cm}}$ -Quotienten 1,18 (Fraktion A), 1,19 (Fraktion B), 1,15 (Fraktion C) und 0,73 (Fraktion D). Das bedeutet, daß die Fraktion D eine bedeutende Nukleotidmenge enthält. Einen weiteren Beweis für diese Feststellung lieferte die Bestimmung der anorganischen Phosphatmenge (P_i) in den einzelnen Fraktionen nach Zerstörung mit Perchlorsäure und Wasserstoffperoxyd. Auf 1 mg Eiweiß bezo-

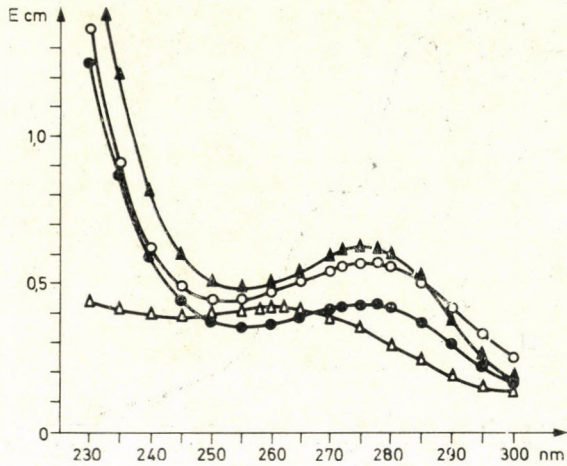


ABB. 3. Absorptionsspektrum der mittels Gelfiltration wiederholt gereinigten Fraktionen A, B, C und D.: ○—○ Fraktion A, 0,35 mg/ml.; ▲—▲ Fraktion B, 0,40 mg/ml.; ●—● Fraktion C, 0,25 mg/ml.; ▷—▷ Fraktion D, 0,10 mg/ml. Lösungsmittel: 0,005%ige wässrige Natriumazidlösung.

gen enthielt die Fraktion A 17 μg P_i , die Fraktion B 16 μg P_i , die Fraktion C 20 μg P_i und die Fraktion D 170 μg P_i . Die Gegenüberstellung der Eigenschaften der gereinigten Fraktionen erfolgte unter Anwendung der Mancinischen-Technik (Abb. 4).

Auf den Objektträger wurde des gegen das Wasserextrakt des Mehles erzeugte, mit Ager vermischte, 16fach verdünnte Antiserum aufgetragen; in

die Löcher wurden unterschiedlich verdünnte Fraktionen gemessen. Man sieht in Abbildung 4, daß einen Präzipitationsring nur das wäßrige, unfraktionierte Mehlextrakt und die Fraktion A ergaben, bei den Fraktionen B, C und D (diese letzterwähnte ist in Abbildung 4 nicht dargestellt) diese Erscheinung dagegen nicht zu beobachten war. Insofern auf den Objektträger mit Agar vermisches, von Zöliakie-Kranken

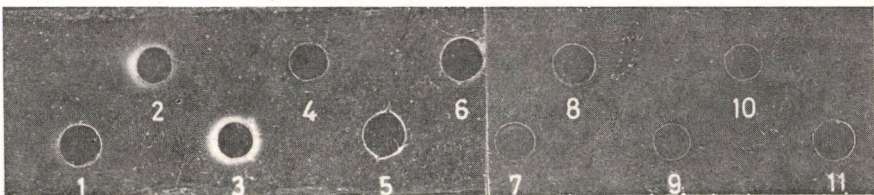


ABB. 4. Immunreaktion des Mehlextrakts und der Fraktionen A, B, C und D, gegenüber das gegen das Mehlextrakt produzierte Antiserum. Eiweißkonzentration der drei A Fraktionen (1, 2, 3): 1,75, 3,50 bzw. 7 mg/ml. Eiweißkonzentrationen der Extrakte 4, 5, 6: 3,3, 6,6 bzw. 9,9 mg/ml. Die Eiweißkonzentration der drei B Fraktionen (7, 8, 9) betragen in allen Löchern 6 mg/ml, während die Eiweißkonzentrationen der zwei C Fraktionen (10, 11) in allen Löchern 5 mg/ml ausmachten.

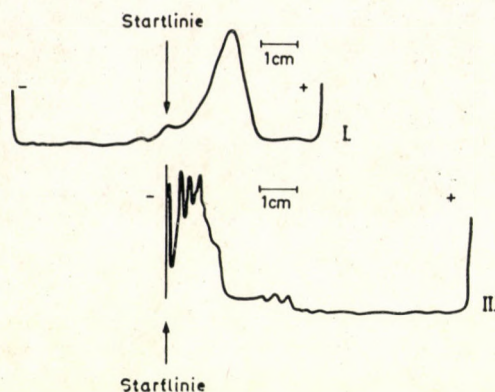


ABB. 5. Densitogramm der gereinigten Fraktion A nach Zelluloseazetat-Membran-elektrophorese (I) bzw. Polyakrylamid-Gelelektrophorese (II).

entnommenes Serum aufgetragen wurde, gestalteten sich die Ergebnisse ähnlich. Aus dem Gesagten folgt, daß bei Zöliakie nur die gereinigte Fraktion A ein antigenartiges Verhalten aufweist. Die Wanderung dieser Fraktion in Richtung der Anode

war bei der Zelluloseazetat-Membran-elektrophorese ausgeprägt, bei der Polyakrylamid-Gelelektrophorese dagegen unbedeutend (Abb. 5).

Diese Ergebnisse sind scheinbar widerspruchsvoll. Aus dem Ergebnis der Zelluloseazetat-Membran-

TABELLE II

Aminosäurezusammensetzung der Fraktion A und des Gliadins

Aminosäure	Fraktion A	Gliadin*	Aminosäure	Fraktion A	Gliadin*
Mol%					
Lys	4,40	1,50	Gly	5,90	3,00
His	1,90	1,70	Ala	6,90	3,40
Arg	3,50	1,80	Val	5,50	4,80
Asp	6,10	2,90	Met	1,10	1,10
Thr	3,70	2,10	Ile	4,20	4,20
Ser	4,40	5,40	Leu	7,30	7,70
Glu	27,20	37,50	Tyr	1,20	2,70
Pro	12,40	16,00	Phe	4,30	4,20

* Aufgrund der Aminosäurezusammensetzung der Fraktion III gerechnete Werte (Beckwith und Mitarb. [2])

elektrophorese könnte auf eine starke Elektronennegativität der gereinigten Fraktion A gefolgert werden, während die Ergebnisse der Polyakrylamid-Gelelektrophorese für eine schwache Elektronennegativität sprechen. Es muß jedoch berücksichtigt werden, daß sich das Akrylamidgel wie ein Molekularfilter verhält. Im Falle einer Substanz mit hohem Molekulargewicht wird die Bewegung der Molekeln im elektrischen Kraftfeld nicht nur durch die Ladung des Molekels sondern auch durch seine Masse beeinflusst.

Laut der mittels Ultrazentrifuge durchgeführten Analyse ist die gereinigte Fraktion A etwas polydispers, ihr Sedimentationskoeffizient beträgt $S_{20,v} = 4,0$ Svedberg-Einheiten. Die Ergebnisse der Aminosäure-Analyse haben wir in Tabelle II zusammengefaßt, in der vergleichshalber auch die in der Literatur für Gliadin angegebenen Ergebnisse der Aminosäure-Analyse ersichtlich sind [2]. Aus den Angaben der Tabelle

II geht hervor, daß sowohl die gereinigte Fraktion A, als auch das Gliadin große Glutaminsäure- und Prolinmengen enthalten. Der hohe Glutaminsäuregehalt darf als ein Beweis dafür angesehen werden, daß sich die Fraktion A bei der Zelluloseazetat-Membranelektrophorese elektronen-negativ verhält.

Zur Bestimmung des Molekulargewichts der Polypeptidkette der in der Ultrazentrifuge etwas polydispersen Fraktion A diente die mit Natriumdodecylsulfat durchgeführte Polyakrylamid-Gelelektrophorese (Abb. 6).

Falls die Bestimmung nach WEBER und OSBORN [21] bei pH 7,0 durchgeführt wird, enthält die Fraktion A zwei Polypeptidketten mit unterschiedlichem — 61 000 und 36 000 Dalton — Molekulargewicht. Die nach PETERSON und STROHMAN [15] mit geringer Modifikation bei pH 8,3 vorgenommene Bestimmung ergab ebenfalls zwei Polypeptidketten mit unterschiedlichem Molekulargewicht: 56 000 und 34 000 Dalton.

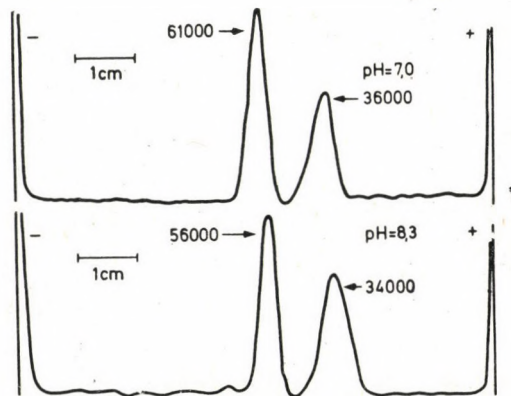


ABB. 6. Densitogramm der gereinigten Fraktion A nach mit Natriumdodecylsulfat durchgeführter Polyakrylamid-Gelelektrophorese.

BESPRECHUNG

Seitdem es nachgewiesen wurde, daß bei der Zöliakie die Eiweiße der Getreidesorten eine Rolle spielen, steht diese Frage nicht nur in der Lebensmittelindustrie und Ernährungswissenschaft, sondern auch auf dem Gebiet der Immunologie im Mittelpunkt des Interesses. Mit den sich in dem letzten anderthalb Jahrzehnt verbreiteten zeitgemäßen Untersuchungsverfahren (Ultrazentrifuge, Gelfiltration, Ionenaustausch-Chromatographie, Stärke-Akrylamid-Gelelektrophorese) fand zwecks Klärung bzw. Identifizierung der physikochemischen Eigenschaften der in Wasser bzw. Salzlösungen löslichen bzw. unlöslichen Weizenweiße eine Reihe erfolgreicher Untersuchungen statt [2, 9, 10, 12, 13, 22, 23].

Die Gliadine und die Glutenine des Weizens sind in Wasser oder neutraler Salzlösung bekanntlich unlöslich, während sie sich in 50–70%iger Alkohollösung, dünner Säure oder Lauge einwandfrei lösen. ROSIPAL und PALM [16] haben im wäßrigen Extrakt des Weizenmehls mit Akrylamid-Gelelektrophorese 12–14 Eiweißfraktionen nachgewiesen, unter denen die in der Nähe der Kathode liegenden 2–3 Fraktionen mit dem Serum der Zöliakie-Kranken eine Präzipitation ergaben. Wir vermochten diese 2–3 Eiweißfraktionen in unserer Fraktion A zu finden [6]; ihre Menge war im aus Neuernte gemahlten Weizenmehl am größten (Tab. I). Das Absorptionsmaximum (Abb. 3) der mit wiederholter Gel-

filtration gereinigten (Abb. 2) Fraktion A — die zu etwa 1,5–2,0% phosphorhaltige Verbindungen (Nucleinsäure und Nucleotid) enthält — liegt bei 278 nm. Die anhand der Zelluloseazetat-Membranelektrophorese (Abb. 5), der Aminosäurezusammensetzung (Tab. II) und der SDS Polyakrylamid-Gelelektrophorese bestimmten Molekulargewichte von 34 000–36 000 und 56 000–61 000 Dalton verwahrscheinlichen es, daß die Fraktion A Gluteneiweiße, vor allem Gliadin enthält. Die von zahlreichen Verfassern [1, 2, 7, 17, 22] in essigsäure- und ureahaltigen Lösungen mit Gelfiltration und Ionenaustausch-Chromatographie hergestellten verschiedenen Gliadinfraktionen (anhand der bei freier Elektrophorese gezeigten Beweglichkeit Fraktionen α , β , γ , ω bzw. ihre Subfraktionen, z. B. γ_1 , γ_2 , γ_3) sind hinsichtlich ihrer Aminosäurezusammensetzung, besonders aber ihres Molekulargewichtes der von uns Fraktion A genannten ähnlich. All dies spricht dafür, daß im Laufe der Extraktion der Mehleiweiße mit ionenfreiem Wasser im pH-Bereich 5,7–6 nebst anderen Eiweißen auch die Gliadine in Lösung gelangen.

Durch das gegen die Mehleiweiße im Kaninchen produzierte Antiserum wird nur die Fraktion A präzipitiert (Abb. 4), die übrigen Fraktionen B, C und D, aber nicht, obwohl das bei der Immunisierung angewandte Eiweißextrakt auch diese Fraktionen enthielt. In bezug auf die gegen Gliadin erzeugten Antikörper wurde früher bereits festgestellt, daß

diese IgG-, IgA- und IgE-Typen sind [14]. Laut unseren Versuchen ist der zirkulierende Antikörper gegen Gliadin vom IgG-Typ [11]. Im Zöliakie-Serum kann kein spezifisches IgE nachgewiesen werden, angesichts der hochgradigen Zytophilie des IgE kann aber die Möglichkeit nicht ausgeschlossen werden, daß dieses Immunglobulin in zellgebundener Form auch im Serum der Zöliakie-Kranken vorkommen kann.

Laut BEYREISS und Mitarb. [3] sind Zöliakie und Sprue mit Darmzottenatrophie einhergehende Resorptionskrankheiten, die annehmbar durch eine hereditäre Empfindlichkeit gegenüber Kleberproteinen herbeigeführt werden. Wenn also die Gluteneiweiße, vor allem das Gliadin durch Trypsin und Chymotrypsin nicht oder nur teilweise abgebaut werden, können die erwähnten Eiweiße oder ihre größeren Fragmente durch die verletzten Darmzotten leicht in den Kreislauf gelangen, und dieser Prozeß muß zur Antikörperproduktion führen. Nach unseren Ergebnissen läßt sich der Antikörper gegen Gliadin – zwar in geringerem Titer als im Serum der Zöliakie-Kranken – auch bei gesunden Personen nachweisen. In diesen Fällen kann das nicht oder nur teilweise abgebaute Gliadin durch den, wegen irgendeiner anderen Ursache geschädigten Dünndarm in den Kreislauf gelangen. BEYREISS und Mitarb. [3] haben darauf hingewiesen, daß einige Medikamente, besonders die Antibiotika und Zytostatika auf den Dünndarm unter Umständen toxisch

einwirken. Die Anwesenheit des Gliadins im Kreislauf und die darauffolgende Antikörperproduktion könnten somit erklärt werden. Eine Frage bleibt aber weiterhin offen, namentlich die Ursache dessen, daß das Gliadin nicht oder nur teilweise abgebaut wird. Die möglichen Ursachen sind: 1. Enzymmangel, 2. verringerte Proteaseaktivität, und 3. ein besonderer struktureller Aufbau dieser Eiweiße, der den Abbau durch Protease entweder nicht, oder nur zum Teil ermöglicht [19].

ad 1. Bei gesunden Personen kommt annehmbar kein Enzymmangel vor, Antikörper können aber in niedrigem Titer auch bei Gesunden gemessen werden.

ad 2. Früher haben wir im Wasserextrakt des Mehles bzw. in seinen Fraktionen eine Proteaseinhibitor-Aktivität nachgewiesen. Durch den mit der Nahrung in den Darm gelangenden Trypsininhibitor könnte die Eiweißverdauung gehemmt werden [6].

ad 3. Mais- und Reisfütterung führen zur raschen Regeneration der Dünndarmschleimhaut, obwohl das Maiskorn auf das Gewicht des getrockneten Korns bezogen mehr Pro-lamin (5 % Zein) enthält als das Weizenkorn (4,2 % Gliadin) [4]. Sowohl das Zein, als auch das Gliadin gehören zwar in die Gruppe der Pro-lamine, der sich in ihrer Wirkung manifestierende Unterschied hängt annehmbar mit ihrer Aminosäurezusammensetzung bzw. Aminosäurereihenfolge zusammen. Wie aus Tabelle II ersichtlich, verfügt die

von uns isolierte Fraktion A über einen hohen Glutaminsäure- und Prolingehalt. Bekanntlich werden dagegen durch Trypsin die in der Nachbarschaft der basischen Aminosäuren liegenden Peptidbindungen d. h. die den Lysin- und Arginin-Kettengliedern entlang befindlichen Peptidverbindungen hydrolysiert. Die Lysin-Prolin- und Arginin-Prolin-Peptide sind der Hydrolyse gegenüber resistent; Lysin-Glutaminsäure und Arginin-Glutaminsäure mit Peptidbindung zeigen eine partielle Resistenz. Durch Chymotrypsin werden die aromatische Aminosäuren enthaltenden Eiweiße oder Peptide der Karboxylgruppe der aromatischen Aminosäuren entlang gespalten. Die Tyrosin-Prolin- bzw. Phenylalanin-Prolin-Peptidbindungen sind ebenfalls resistent.

Unsere Hypothese wird durch die Angaben von FRAZER [8] unterstützt, laut deren die Gluteneiweiße – und so auch die Gliadine gegenüber Pepsin und Trypsin resistent sind. Die Gluteneiweiße weisen aber nicht nur gegen die Proteasen, sondern auch gegenüber Wärme eine Resistenz auf. Wir konnten es nämlich nachweisen, daß die Gluteneiweiße durch Wasser- oder Essigsäureextraktion – nebst Beibehaltung ihres Antigencharakters – sogar aus dem Brot isoliert werden können. [20].

Laut SINGH und KAY [18] spielen die Gluteneiweiße auch bei der Schizophrenie eine Rolle. Der Zöliakie ähnlich ist der Wirkungsmechanismus auch in diesem Fall ungeklärt, nur soviel liegt fest, daß der genetischen

Prädisposition eine Bedeutung beizumessen ist.

Anhand der angeführten Argumente vertreten wir die Ansicht, daß die Untersuchung der Struktur, der physikochemischen und funktionellen Eigenschaften der Gluteneiweiße einen weiteren Schritt zur Klärung des Pathomechanismus der Zöliakie, der Sprue und vielleicht auch der Schizophrenie bedeuten wird.

Unser herzlicher Dank gebührt Herrn Dr. M. Hauck für die Aminosäureanalyse und Frau I. Korom, sowie Fr. M. Debreceni für die technische Hilfe.

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Dr. M. SZABOLCS

Zentrales Forschungsinstitut Pf. 3.

H-4012 Debrecen, Ungarn

Recensiones

Parent-Infant Interaction. A Ciba Foundation Symposium. Elsevier—Excerpta Medica—North Holland, Amsterdam—Oxford—New York 1975. Dfl 53,00

The book discusses a complex subject, the consequences of the early parent-infant relations in animals and human beings.

The first contact of human mothers with their newborn infants in different cultures strongly suggests that this event initiates a regular series of interactions which have biological roots powerful enough to cut across divergent cultures and might thus be considered species-specific. Within this general pattern there are remarkable individual differences which appear to be the result of cultural values and constraints imposed by hospital routines and regulations (Klaus et al.). The timing and duration of the contact between mother and infant that the hospital allows in the first few postnatal days can affect the relationship for months and even years. Separation of the mother from her prematurely born baby appears to have an adverse effect on the whole family unit. (Kennel and Leidermann).

Human studies suggest that shortly after birth there is a sensitive period which appears to have long-lasting effects on maternal attachment and which may ultimately affect the child's development (Kennel et al).

Neonates use smell to locate a food source and they can differentiate between their mother and other women on the

basis of smell. Application of lanolin and deodorants to mothers may make the infant's task more difficult (Macfarlane). Play interaction between mother and infant over periods of time measured in microseconds and minutes have revealed the existence of a dance-like synchrony of movements, facial expressions and vocalizations (Hinde et al).

The type and amount of social interaction between a human mother and her infant in the immediate postpartum period can influence the mother's subsequent behaviour and attitude towards the infant. Separation of a mother from her infant for as short a time as three weeks in the immediate postpartum period can lead to lowered feelings of maternal competency and decreased amounts of attachment behaviour, sometimes continuing for as long as a month. Follow-up of these mothers and infants at 11, 12 and 15 months showed that the effects of separation on maternal attitude and behaviour have disappeared, except that non-separated mothers continued to touch their infants more often than separated mothers (Leidermann and Seashore). Finally, Oppé underlines that developmental psychology may contribute to the prevention of paediatric illnesses if it can discover the processes responsible for the failure in the early parent-infant relationship.

The book will be of real interest for psychologists, behaviourists and all those who care for mothers and their babies.

A. GEIGER

DECKER, K., BACKMUND, H.: *Paediatric Neuroradiology*. VIII + 184 pages with 345 illustrations. Georg Thieme Publishers, Stuttgart 1975. DM 88,—

This book is the English version of the really outstanding monograph that appeared in German in 1970 and has been reviewed in this periodical 12, 86 (1971). The only sentence the reviewer can add is that the excellent and useful work is still up-to-date and fully deserves to become known in every country.

J. SZÉNÁSY

H. LOEW, P. MELLIN, H. OLBBING: *Nephrologie — Urologie*. Springer Verlag, Berlin, Heidelberg, New York 1975. XII + 170 Seiten mit 28 Abbildungen DM 28,—

Die rapide Spezialisierung der vergangenen Jahrzehnte und die hochgradige Entwicklung der sich auf die Nieren- und Harnwegskrankheiten beziehenden Kenntnisse und therapeutischen Möglichkeiten erfordert, daß die Gesamtheit dieser Daten dem praktizierenden Arzt stets zur Verfügung stehe. Die Betreuung der an einer nephrologischen oder Harnwegskrankheit leidenden Patienten ist ein wichtiges Problem. Die rechtzeitig gestellte Diagnose, die Einweisung der Patienten in ein entsprechendes Fachinstitut sind auf diesem Gebiet von ausschlaggebender Bedeutung, was ebenfalls für die Notwendigkeit der Fachbildung der praktizierenden Ärzte spricht. Diesem Ziel dient in vorzüglicher Weise dieser Band.

Der erste Teil des Taschenbuchs ist den aktuellen Fragen der internistischen bzw. pädiatrischen Nephrologie gewidmet. Anamnese und die breite Skala der zur Verfügung stehenden diagnostischen Möglichkeiten werden in Tabellen anschaulich erläutert. In den nächsten Kapiteln finden Ätiologie, Diagnostik und Klinik der häufiger vorkommenden internistischen Nierenkrankheiten eine Besprechung. Im Zusammenhang mit der Erörterung der Harnwegs-

infektionen und innerhalb deren der akuten Pyelonephritis findet man wertvolle Ratschläge in bezug auf die ambulante Betreuung dieser Kranken. Die folgenden Kapitel befassen sich mit den seltener vorkommenden Nierenkrankheiten (wie z.B. angeborene Nephritis, Nephronophthisis juvenilis familiaris, usw.), den diagnostischen und Betreuungsproblemen der an akuter und chronischer Niereninsuffizienz leidenden Patienten, wobei auch auf die modernen klinischen therapeutischen Möglichkeiten (Hämodialyse, Transplantation) eingegangen wird.

In dem die pädiatrischen nephrologischen Krankheiten darlegenden Kapitel wird auf die diagnostischen Schwierigkeiten, die Häufigkeit dieser pathologischen Prozesse und auf die prognostische Bedeutung der Frühdiagnose hingewiesen. Ein besonderes Verdienst des Bandes ist, daß man bei den einzelnen Krankheiten auch die therapeutischen Möglichkeiten findet.

Der zweite Teil enthält die urologischen Probleme der Erwachsenen bzw. der Kinder. Entwicklungsanomalien, diagnostische und therapeutische Fragen werden kurz und in einer in der alltäglichen Praxis gut anwendbaren Weise besprochen.

Das Taschenbuch erhebt keinen Anspruch auf Vollständigkeit, es bietet aber dem praktizierenden Arzt wertvolle Kenntnisse über die praktischen Aufgaben der sich ständig entwickelnden Nephrologie und Urologie.

L. TURAI

D. BERG: *Schwangerschaftsberatung und Perinatologie* 2., überarbeitete und erweiterte Auflage. XIV + 218 Seiten mit 55 Abbildungen und 50 Tabellen. G. Thieme Verlag, Stuttgart 1976. DM 15,80

Das Taschenbuch wendet sich an Geburtshelfer und Neonatologen. Es schildert die im Verlauf der Schwangerschaftsberatung und Geburtsleitung angewandten zeitgemäßen Maßnahmen, deren Indikationen und therapeutische Konsequenzen, ferner

die Möglichkeiten und Grenzen der Methoden.

Durch die praktische Anwendung der Kenntnisse der modernen Technik und Biochemie hat die Geburtshilfe im letzten Jahrzehnt eine tiefgreifende Wandlung erfahren. Diese modernen Methoden werden in den Lehrbüchern entweder noch nicht oder nur ganz kurz erwähnt. Das Ziel des Autors war, eben diese Lücke mit der vorliegenden zweiten erweiterten Auflage seines Buches zu füllen.

Das Buch gliedert sich in zwei Teile. Der erste, mit dem Titel Klinik, befaßt sich mit den im Verlauf der Schwangerschaft und Geburt auftretenden Komplikationen, unter anderen mit genetischen Problemen, jenen der Plazentarinsuffizienz, mit Diabetes, Morbus haemolyticus, drohender Frühgeburt und deren Diagnostik und Behandlung, oder z.B. mit Fragen des entsprechenden Zeitpunktes und Vorgehens bei der Geburtseinleitung und der primären Reanimation des Neugeborenen.

Im zweiten Teil, mit dem Titel Methodik, werden die vorangehend erwähnten diagnostische Verfahren, ja sämtliche in der Geburtshilfe heute routinemäßig oder in Spezialabteilungen vorgenommenen diagnostischen Untersuchungen eingehend erörtert.

Das besondere Verdienst des Buches ist, daß es ganz weitläufige wissenschaftliche Kenntnisse klar und kurz abgefaßt vermittelt und mit ausgezeichneten Abbildungen und Tabellen ergänzt bei der Anwendung und Bewertung der modernen geburts-hilflichen Methoden in der alltäglichen Praxis eine wahre Hilfe bedeutet.

E. VÁRADY

Perinatale Medizin Band VI. 7. Deutscher Kongreß für Perinatale Medizin, Berlin, 13. bis 17. November 1974. Herausgegeben von J. W. DUDENHAUSEN., E. SALING und E. SCHMIDT. XXIV + 352 Seiten mit 232 Abbildungen und 119 Tabellen. G. Thieme Verlag, Stuttgart 1975. DM 98,—

In dem vorliegenden Band werden die aktuellen Probleme der perinatalen Medizin im ganzen Querschnitt und in allen Einzelheiten zusammengefaßt.

Im einleitenden Vortrag über Diabetes mellitus und Schwangerschaft wird betont, daß die Zusammenarbeit vom Geburtshelfer, Diabetologen und Neonatologen zur entsprechenden Betreuung unerlässlich ist. In einem bedeutenden Teil der Fälle ist die Entbindung anhand der Kontrolle des mütterlichen Stoffwechsels, der fetoplazentaren Einheit, des fetalen Wachstums und der Reife meistens zum Termin durchführbar, welcher Umstand die Lebensaussichten des Neugeborenen sehr günstig beeinflusst. Mehrere Vorträge befassen sich mit dem latenten, Gestations- und Prädiabetes, und deren Diagnose während der Schwangerschaft und im Wochenbett. Es wird darauf hingewiesen, daß der unbehandelte Diabetes die perinatale Mortalität in negativer Richtung beeinflusst.

Das nächste Thema ist die pränatale Vermeidung respiratorischer Störungen beim Neugeborenen. Hier werden die verschiedenen Methoden der antenatalen Lungenreifediagnostik, deren Bewertung, die Möglichkeiten der RDS-Prophylaxe erörtert.

Der folgende Teil ist der Ultraschall-diagnostik gewidmet. Ihre Rolle in der Frühschwangerschaft, bei der Bestimmung der Reife, Terminierung der Geburt und der Lokalisierung der Plazenta wird geschildert. Als unerlässlich wird die zur Bestimmung der Gestationszeit zwischen der 16. und 20. Woche vorgenommene Ultraschalluntersuchung und zwecks Diagnose fetaler Retardation deren Wiederholung in späteren Stadien der Gravidität betrachtet.

Die Vor- und Nachteile der Lokalanästhesie in der Geburtshilfe sind ein folgendes Thema, wobei betont wird, das die Anästhesie die pH- und Apgarwerte des Neugeborenen nicht beeinflusst, ihre Anwendung bei intrapartalen Blutungen jedoch eindeutig kontraindiziert ist.

In den Vorträgen über den richtigen

Zeitpunkt der Geburtseinleitung bei Gefährdung des Kindes (Plazentarinsuffizienz, Diabetes, Terminüberschreitung usw.) wird darauf hingewiesen, daß die Gefährdung lediglich relativ sein darf und im entgegengesetzten Fall zum Kaiserschnitt gegriffen werden soll. Die Voraussetzung der Einleitung der vaginalen Entbindung ist, daß der Fetus belastbar sei und dies durch subpartale Diagnostik festgelegt werde und von Seiten der Mutter, daß der Uterus Geburtsbereitschaft aufweise. Als fakultative Bedingung ist die Oxytocinempfindlichkeit zu betrachten.

Ein Kapitel behandelt die neuzeitigen Gesichtspunkte hinsichtlich der Sectio caesarea, ihre Technik, Anästhesie, Indikation, ferner die maternellen und fetalen Komplikationen. Sectiokinder sollen immer als Risikokinder betrachtet und intensiv betreut werden.

Bei der Besprechung der Fragen der intensiven Neugeborenenpflege wird auf die Bedeutung der transkutanen pO_2 -Messung, des Kardiorespirogramms, der RDS-Therapie und der Frühdiagnose pränataler Infektionen hingewiesen. Ein Teil der Vorträge befaßt sich mit der Pathogenese und Therapie der Apnoe nach der Geburt und mehrere Vorträge mit der Frühgeburtprophylaxe, der tokolytischen Wirkung der Betamimetika und mit den Auswirkungen der Schwangerschaftsunterbrechung auf spätere Graviditäten.

Für den Perinatologen bietet das Buch ein großes Kenntnismaterial und auch Beistand bei der Gestaltung entsprechender Anschauungen. |

E. VÁRADY

Cancer in Children. Edited by H. J. G. BLOOM, J. LEMERLE, M. K. NEIDHARDT, P. A. VOUTE. Springer Verlag, Berlin—Heidelberg—New York 1975. XVI + 317 pages with 121 figures. DM 34,50

With the fall in mortality from infectious diseases, in the developed countries childhood cancer has become the second

commonest cause of death in the age group 1 to 14 years, being surpassed only by accidents. However, even in the countries where childhood cancer has attracted increasing interest, the disease is rather infrequent and even in large hospitals it is limited to a few cases a year. This partly explains the view that cancer and malignant tumours in childhood are practically untreatable and of fatal outcome. This view is no longer tenable; owing to the improvement of therapeutic interventions the survival rates in childhood have much increased, even with such lesions as Wilms tumour, brain tumours, rhabdomyosarcomas, Ewing sarcoma, retinoblastoma, lymphoma and leukaemia, and there is a real hope for a substantial reduction in the mortality of childhood cancer.

Treatment techniques of course vary according to the type of tumour. The high radiation doses for rhabdomyosarcoma and osteosarcoma require careful consideration of relation to the exact anatomical region and to the child's age and the same is the case with the selection of cytotoxic agents. The joint opinion of the paediatrician, surgeon, radiotherapist, oncologist and laboratory worker is decisive for the fate of the patient. These aspects have been considered by the International Union Against Cancer, UICC, founded by French physicians in Paris and including now the representatives of numerous countries. The book under review summarizes chiefly the experience of European authors, but experts from the United States, Canada and Japan too participated in the discussion of the problems.

The book is a useful practical guide for all doctors who have to deal with childhood cancer, and also for every post-graduate student as an introduction into paediatric oncology.

The general part of the book discusses aetiology, epidemiology and pathology of tumours and the general aspects of their surgery, radiotherapy and chemotherapy. Comparatively new are the questions concerning infectious diseases in children

with malignant tumours as well as those of general care. The general part ends with the problems of diagnosis and differential diagnosis and by the recommendation for up-to-date tumour registration.

Among the chapters on special tumours the first place is occupied by the problems of the tumours of the central nervous system, which shows the highest incidence. This is followed by the description of reticuloblastoma and other tumours of the eye and orbit. The tumours of the sympathetic nervous system are also described in detail. These are followed by chapters on leukaemias, lymphomas, Burkitt's sarcoma and histiocytosis, bone tumours and soft tissue sarcomas, and teratomas of the reproductive organs as well as on tumours of the kidneys, skin and liver, head and neck.

Z. ERDŐS

R. T. D. EDMOND: *Farbatlas der Infektionskrankheiten*. Ins Deutsche übertragen von W. D. GERMER. 384 Seiten mit 456, davon 407 mehrfarbigen Abbildungen. Schattauer Verlag, Stuttgart—New York 1970. DM 56,—

Als Folge der verbesserten Lebensbedingungen und der Verbreitung wirksamer präventiven Maßnahmen kommen die klassischen Infektionskrankheiten stets seltener vor. Ein bedeutender Teil der Fälle meldet sich mit atypischen Symptomen, so daß ihre Erkennung, besonders für Studenten und junge Ärzte, schwierig ist. Bei dem heutigen überfüllten Unterrichtsprogramm bleibt für das Studium und die Vorstellung dieser Krankheitsbilder nur wenig Gelegenheit, so daß die meisten jungen Ärzte in dieser Hinsicht mangelhaft ausgerüstet in ihr Berufsleben eintreten. Diese Lücke soll der vorliegende schöne farbige Atlas ausfüllen.

Das lebensstreuere Bildmaterial liefert dem praktizierenden Arzt wahrhaftig eine große Hilfe bei der Diagnostizierung der infektbedingten Krankheiten. Der die

Abbildungen begleitende Text, wenn auch äußerst kurz abgefaßt, gibt eine vorzügliche zusammenhängende Schilderung der Krankheitserreger, klinischen Eigenheiten, und Diagnostik der einzelnen Krankheitsbilder

Á. SZÉKELY

Malignant Bone Tumours: Edited by E. GRUNDMANN. VIII + 280 pages with 116 figures. Springer Verlag, Berlin—Heidelberg—New York 1976. DM 59.80

The book is introduced by a challenge for cooperation. As bone tumours are infrequent, reliable diagnostics have developed only during the last two-three decades and it is only 5 years since an international code of classification is available. It is emphasized that the diagnosis must be based on the roentgenogram beside histology and in some cases on cytological methods. In therapy, beside surgery, radiotherapy and chemotherapy, immunotherapy has acquired increasing importance.

The book presents the newest results in research and therapy of bone tumours. Experimental induction of bone tumours by ionizing radiation and viruses as well as the study of bone tumours occurring in animals are discussed in detail. It is stressed that the general use of the WHO classification is of utmost importance with regard to uniform nomenclature. For reliable diagnosis needle biopsy, cytological and cytochemical as well as histochemical and electron microscopic examinations may be necessary. A chapter of outstanding interest is that on immunology. Based on the initial results, further developments and successes may be expected.

In the chapter on therapy, the report on 900 cases of osteogenic sarcoma treated at the Mayo Clinic should be mentioned in the first place. The primary lesion must be excised without delay. Preoperative irradiation of the tumour or of the lungs is ineffective. Excision should be followed

by immunotherapy or chemotherapy or both. Pulmonary metastases must be removed; the earlier this happens, the greater the chance of an effective cure.

Z. ERDŐS

WIEDEMANN, H.—R., GROSSE, F.—R., DIBBERN, H.: *Das charakteristische Syndrom*. XVIII + 195 Seiten mit 97 Abbildungstafeln. F. K. Schattauer Verlag, Stuttgart 1976. DM. 69,—

Wer in Europa wäre heute dazu mehr berufen, einen Atlas der Syndrome zusammenzustellen, als H.—R. Wiedemann, der erste Beschreiber der Thalidomidembryopathie und des EMG-Syndroms, Mitautor der wohlbekannteren Monographie über die Knochendysplasien, Mitbeschreiber des Kleeblattschädels, usw. Man könnte noch eine lange Liste von seinen Arbeiten erwähnen, die sich auffallend klar und didaktisch mit verschiedenen Dysmorphien befassen. Das vorliegende Buch von Wiedemann und seinen Mitarbeitern beschreibt

fast 100 Syndrome, darunter auch einige neuentdeckte wie z.B. das fetale Alkoholsyndrom. Auf der jeweiligen linken Seite wird man in Schlagworten über alles Wissenswerte über ein Syndrom einschließlich Synonyme, Auffälligkeiten, ergänzende Symptome, Manifestationszeitpunkt, Ätiologie, Pathogenese, Häufigkeit, Verlauf, Prognose und Therapie informiert. Auf den rechten Seiten werden die Krankheitsbilder und ihre Zeichen in 2 bis 20 sehr charakteristischen Photographien abgebildet.

Der Untertitel des Buches ist »Blickdiagnose von Syndromen« und wer den Atlas einmal gründlich durchstudiert hat, wird sich selten irren und (treu dem Goetheschen Motto des Vorwortes) mit den Augen sehen, was vor den Augen ihm liegt. Heute, in dem Zeitalter der Genetik, wird dieser Atlas jedem Arzt, ob Kinderarzt, Humangenetiker oder Psychiater, ob Neurologe oder Orthopäde, allgemeiner Arzt oder Röntgenologe, eine unentbehrliche Hilfe leisten.

P. V. VÉGHÉLYI

E. Kerpel-Fronius

PÄDIATRIE

Den von Jahr zu Jahr wachsenden Wissensstoff der Kinderheilkunde konnte der Autor mit sorgfältiger Erwägung in einem verhältnismäßig knappen Umfang zusammenfassen. Das Werk ist in sämtlichen Kapiteln durch prophylaktische Gesichtspunkte geprägt. Zusammen mit der klinischen Problematik der Krankheitsbilder behandelt er auch die physiologischen, biochemischen, genetischen Voraussetzungen ihrer Pathogenese. Da heutzutage die perinatale Mortalität den Hauptposten der Säuglingssterblichkeit ausmacht, womit die Neonatologie in den Vordergrund gerückt ist, erachtete es der Autor für notwendig, auf die Physiologie des Neugeborenen etwas näher einzugehen. Die in den jüngsten Jahren aufgekommenen Fragen, wie die der autoimmunen Krankheitsbilder und der Stoffwechselanomalien bedachte er mit gebührendem Umfang. Zwecks Vermeidung jeglicher Weitschweifigkeit wurden die heute schon sehr seltenen Krankheiten kürzer behandelt; auch unter den unzähligen seltenen Syndromen werden vornehmlich solche erörtert, die tiefere Einblicke in physiologische oder biochemische Grundprozesse gewähren.

In russischer Sprache · 621 Seiten · 17×25 cm · Ganzleinen ·
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Acta paediatrica Academiae Scientiarum hungaricae

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A cikkek két példányban adandók be, ugyanígy a táblázatok és ábrák is. Minden szöveget kérünk dupla sorokba legalább 4 cm-es margóval gépelni (szabvány oldal 25 sor×50 betű). Máshogy gépelt kéziratokat csak akkor fogadunk el, ha azokat mi fordítatjuk idegen nyelvre. Minden oldal (táblázatok és irodalom is) folyamatosan megszámozandó.

Az irodalmi hivatkozások ábécé sorrendben megszámozandók. A szövegben csak a számokat kell feltüntetni. Az irodalomjegyzékben szerepelni kell a hivatkozott cikk minden szerzője vezetéknevének és keresztnéve(i) rövidítésének, a cikk címének, a folyóirat rövidített nevének, a kötetszámnak, az oldalszámnak és a megjelenési évnek. Szerzők neve helyett nem szerepelhet et al. A folyóiratok nevének rövidítése a WHO World Medical Periodicals szerint történjék. Könyvekre való hivatkozásnál szerepelni kell a szerző(k) vezetéknevének és keresztnéve(i) rövidítésének, a könyv címének, kötetének, kiadási sorszámának, a kiadó nevének, a városnak, a kiadás évének és a hivatkozott rész oldalszámának. Például:

Kerpel-Fronius, E., Gács, G.: Serum insulin values. *Acta paediat. Acad. Sci. hung.* **16**, 197 (1975).

Crosse, V. M.: *The Preterm Baby*. 7th ed. Churchill Livingstone. Edinburgh and London 1971, P. 165.

Detter, J. C.: *Biochemical Variation*. In: *Textbook of Human Genetics*, ed. G. Fraser, O. Mayo. Blackwell Scientific Publications, Oxford 1975, P. 115.

A cikkben csak kongresszusnyelven megjelent munkákra lehet hivatkozni.

A cikknek rövid kivonattal kell kezdődnie. Ennek tartalmaznia kell azt, hogy mit vizsgáltak, milyen módon, valamint a vizsgálat eredményét és az esetleges következtetést egy mondatban. E kivonatból beadandó egy magyar verzió is két példányban; ennek tartalmaznia kell a cikk címét és összes szerzőjét.

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Two complete copies of the manuscript including tables and illustrations must be supplied. All material should be double-spaced with margins at least 4 cm wide. Material typed otherwise will be returned for retyping. Pages should be numbered consecutively.

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Kerpel-Fronius, E., Gacs, G.: Serum insulin values. *Acta paediat. Acad. Sci. hung.* **16**, 197 (1975).

Crosse, V. M.: *The Preterm Baby*. 7th ed. Churchill Livingstone, Edinburgh and London 1971. P. 165.

Detter, J. C.: *Biochemical Variation*. In: *Textbook of Human Genetics*, ed. G. Fraser, O. Mayo. Blackwell Scientific Publications, Oxford 1975. P. 115.

Authors are requested to begin their paper with an abstract and to add an alphabetical list of any unusual abbreviations used, with meanings.

Illustrations must be identified by number and author's name, and the top should be marked. Their place should be indicated in the text. Legends for figures should be written on a separate sheet.

Tables must be comprehensible to the reader without reference to the text and accompanied by headings.

Drugs must be referred to by their WHO code designation (Recommended International Nonproprietary Name); use of proprietary names is unacceptable.

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РЕЗЮМЕ

ДЕЙСТВИЕ ВЫЗВАННОГО
ХЛОРИСТЫМ АММОНИЕМ
МЕТАБОЛИЧЕСКОГО АЦИДОЗА
НА ВЫДЕЛЕНИЕ КАЛЬЦИЯ
В РАННЕМ ГРУДНОМ ВОЗРАСТЕ

Э. ШУЙОК

Автор определял изменения, наступающие в выделении почками Ca^{++} и H^+ под влиянием однократной нагрузки 2,8 мэкв/кг хлористого аммония, а также изменения, наступающие в кислотно-щелочном равновесии в крови. Определения проводились:

а) у 48 новорожденных с весом при рождении в 1000—4380 г на 7 день жизни, б) у 11 преждевременно родившихся детей с весом при рождении в 1000—1970 г на 7 день и затем на протяжении 6 недель еженедельно.

Полученные результаты автор сравнил с таковыми у здоровых грудных детей в возрасте от 3 до 11 месяцев. Он установил, что:

1. в однонедельном возрасте под влиянием нагрузки хлористым аммонием метаболический ацидоз всех новорожденных усиливался, но в случае грудных детей с весом при рождении меньше 2000 г, это увеличение было достоверно большее, чем у новорожденных с большим весом при рождении.

Ацидоз преждевременно родившихся детей после дачи хлористого аммония, во всех возрастах повышался приблизительно в одинаковой мере и степень этого повышения не зависела в значительной мере от степени ацидоза перед нагрузкой.

2. В однонедельном возрасте повышалось выделение почками, как H^+ , так и Ca^{++} с повышением веса при рождении. В результате нагрузки у всех новорожденных выделение почками H^+ и Ca^{++} повышалось, у таковых с весом при рождении свыше 2000 г это повышение было достоверно большее.

3. В случае преждевременно родившихся детей, выделение почками Ca^{++} под влиянием вызванного хлористым аммонием ацидоза, вопреки повышению розта, остается без изменения и выражая это в процентах величин перед нагрузкой, наблюдается выражено уменьшающаяся тенденция. В вышеуказанный период наступает значительное повышение выделения H^+ почками.

Из результатов автор делает тот вывод, что

а) буферная роль костной системы уже в ранний послеродовой период является важным фактором сохранения кислотно-щелочного равновесия, б) повышенная склонность к ацидозу у преждевременно родившихся детей объясняется отчасти понижением этой функции.

ПЕРИДУРАЛЬНЫЙ ЛИПОМАТОЗ

И. ВЕСПЕР, Е. МЕЗЕР, К. Й. НЕЙМЕРКЕР

За период с 1965 по 1974 гг. авторы наблюдали у 15 больных перидуральный липоматоз. Все случаи были оперированы. В 1975 году проводилось повторное обследование указанных больных. В 5 случаях авторы наблюдали выраженное улучшение состояния, 4 случая остались без изменения, а в 6 случаях состояние ухудшилось, из них в 2 случаях и на верхних конечностях развилась мышечная атрофия.

ПСИХИЧЕСКОЕ ИССЛЕДОВАНИЕ
ДЕТЕЙ В ШКОЛЬНОМ ВОЗРАСТЕ,
ОПЕРИРОВАННЫХ ПО ПОВОДУ
ВОДЯНКИ ГОЛОВЫ

Л. ВЕКАШИ, Э. ПАРАИЦ

1. Оперированные по поводу гидроцефалии дети обладают хорошим интеллектом, они поддаются воспитанию и препо-

даванию, они в состоянии к самостоятельному ведению жизни. Из наблюдавшихся авторами 30 детей, находящихся в школьном возрасте, 17 посещают общеобразовательную школу 8 посещают дефектологические школы, 2 посещают классы с малым числом учащихся и 3 освобождены от посещения школы.

II. Эти дети обладают хорошим контактом, их групповое положение и интерперсональные связи хорошие, наблюдаются аффективные колебания.

III. Эти дети эмоционально лабильные, особенно при умственно-физической нагрузке наблюдаются эти отклонения, они в значительной мере зависят от семьи, у них сильные эмпатические потребности.

IV. Оперированные по поводу гидроцефалии дети показывают трудности по отношению к новым, неожиданным раздражениям. Двигательные и вегетативные их свойства лабильные, внимание колеблющееся, они быстро утомляются, предпочитают темы о болезни.

V. Следовало бы предоставить школам и родителям должные сведения об обращении с этими детьми, так как этим можно было бы способствовать процессу ресоциализации детей, оперированных по поводу гидроцефалии. Еще нет педагогических учреждений и специалистов, которые проводили бы на оперированных по поводу водянки головы детей работу, объединяющую задачи нескольких дисциплин и это является большим недостатком.

ОТДАЛЕННЫЙ ПРОГНОЗ ПОСТОПЕРАЦИОННЫХ ПОСТОЯННЫХ АТРИО-ВЕНТРИКУЛЯРНЫХ БЛОКАД III-ЕЙ СТЕПЕНИ В ДЕТСКОМ ВОЗРАСТЕ

А. КИШ, Я. КАМАРАШ

Авторы наблюдали за период с 1965 по 1975 гг. 15 случаев постоянной постоперационной полной атрио-вентрикулярной блокады. 12 детей через 2—11 лет после операции находятся в живых. Имплантация кардиостимулятора имела место в 5 случаях, из них 3 больных вопреки этому умерли. В 1 случае синусовый ритм восстановился, в дальнейших 5 случаях наблюдалось улучшение проведения импульсов, но в 2 случаях это оказалось лишь временным. Авторы сообщают о терапевтических и прогностических наблюдениях в связи с этой болезнью.

ДЕЙСТВИЕ АСФИКСИИ ПРИ РОЖДЕНИИ НА СОДЕРЖАНИЕ СВОБОДНЫХ АМИНОКИСЛОТ В ПЛАЗМЕ У ПРЕЖДЕВРЕМЕННО РОДИВШИХСЯ ДЕТЕЙ

К. ШУЛЬЦ, Й. МЕШТЯН, Д. ШОЛТЕС

Авторы сравнивали содержание аминокислот в плазме в послеродовой период у 16 преждевременно родившихся детей, перенесших перинатальную асфиксию и у 13 интактных преждевременно родившихся детей. К молочнокислому ацидозу, вызванному асфиксией, присоединилась выраженная гипераминоацидемия. Из отдельных аминокислот концентрация ланина, пролина, таурина, глутамата, валина, метионина и лизина была достоверно выше. Особенно бросалось в глаза повышение концентрации аланина, которое показывало достоверную линейную корреляцию с содержанием лактата в крови ($p < 0,001$).

Подобная связь наблюдалась между остальными потенциально гликогенными аминокислотами и содержанием лактата в крови. Аминограмма плазма преждевременно родившихся детей, перенесших асфиксию, похожа на таковую гипогликемических атрофических новорожденных, у которых можно предполагать, что накопление аминокислот-прекурсоров глюкозы вызывается пониженной активностью гликогенетических ферментов.

ДЕЙСТВИЕ СРОКА БЕРЕМЕННОСТИ И ВНУТРИУТРОБНОГО ПИТАНИЯ ПЛОДА НА СОДЕРЖАНИЕ СВОБОДНЫХ АМИНОКИСЛОТ В ПЛАЗМЕ НОВОРОЖДЕННЫХ

К. ШУЛЬЦ, Д. ШОЛТЕС, Й. МЕШТЯН

Авторы сравнивали изменение содержания аминокислот в плазме и содержания сахара в крови в послеродовой период у евтрофических и у атрофических преждевременно родившихся детей. Среднее содержание сахара в крови было достоверно ниже ($p < 0,001$) в группе атрофических преждевременно родившихся детей. Среднее общее содержание аминокислот в плазме и содержание трех важнейших гликогенных аминокислот (аланина, глицина, пролина) не отличалось в указанных двух группах. Концентрация лейцина, фенилаланина и аспаргата достоверно ниже ($p < 0,05$), а концентрация глутамата достоверно выше ($p < 0,05$) в группе атрофических новорожденных. Между содержанием сахара в крови и содержанием главных гликогенных аминокислот не было связи. Если комбинировать полученные при настоящем исследовании данные с таковы-

ми, полученными в ходе преждей серии исследования данными евтрофических и атрофических новорожденных, то из 17 аминокислот плазмы только в случае аланина удалось установить связь со сроком беременности.

На основании вышеуказанных наблюдений к гипогликемии атрофических преждевременно родившихся детей — в противоположность к атрофическим зрелым новорожденным — не присоединяется гипер-аминоацидемия. Причиной гипер-аминоацидемии, раннее описанной у атрофических зрелых новорожденных, предположительно, является пониженная гликонеогенетическая активность печени. Причина разницы между атрофическими преждевременно родившимися детьми и атрофическими зрелыми новорожденными, вероятно, та, что продолжительность внутриутробного расстройства питания влияет на созревание печеночного гликонеогенеза новорожденных. Непродолжительное неблагоприятное состояние внутриутробного питания еще не приводит к запаздыванию послеродовой активности гликонеогенеза.

ТЕРАТОЛОГИЧЕСКАЯ ОЦЕНКА АНТИЭПИЛЕПТИЧЕСКИХ СРЕДСТВ

П. ЛАКОШ, Э. ЦЕЙЗЕЛ

В вводной части своей работы авторы дают обзор данных, указывающих на повышение частоты врожденных аномалий развития у новорожденных от матерей, страдающих эпилепсией и они приводят типы этих аномалий. Частота детей, родившихся с расщеплением губ и нёба по сравнению с частотой этой аномалии среди общей популяции, в 4—7 раза большая. Авторы исследовали потребление матерями детей, родившихся в Венгрии с 1970 года с расщеплением губ и нёба, с расщеплением задней части нёба и в качестве контроля, детей, родившихся с анэнцефалией и с расщеплением позвоночника. Опять подтвердилось, что противозипептические средства, в первую очередь производные дифенилгидантоина, оказывают тератогенное действие. В отношении фенилбарбитуратов и диазепам (седуксена) авторы не обнаружили тератогенности.

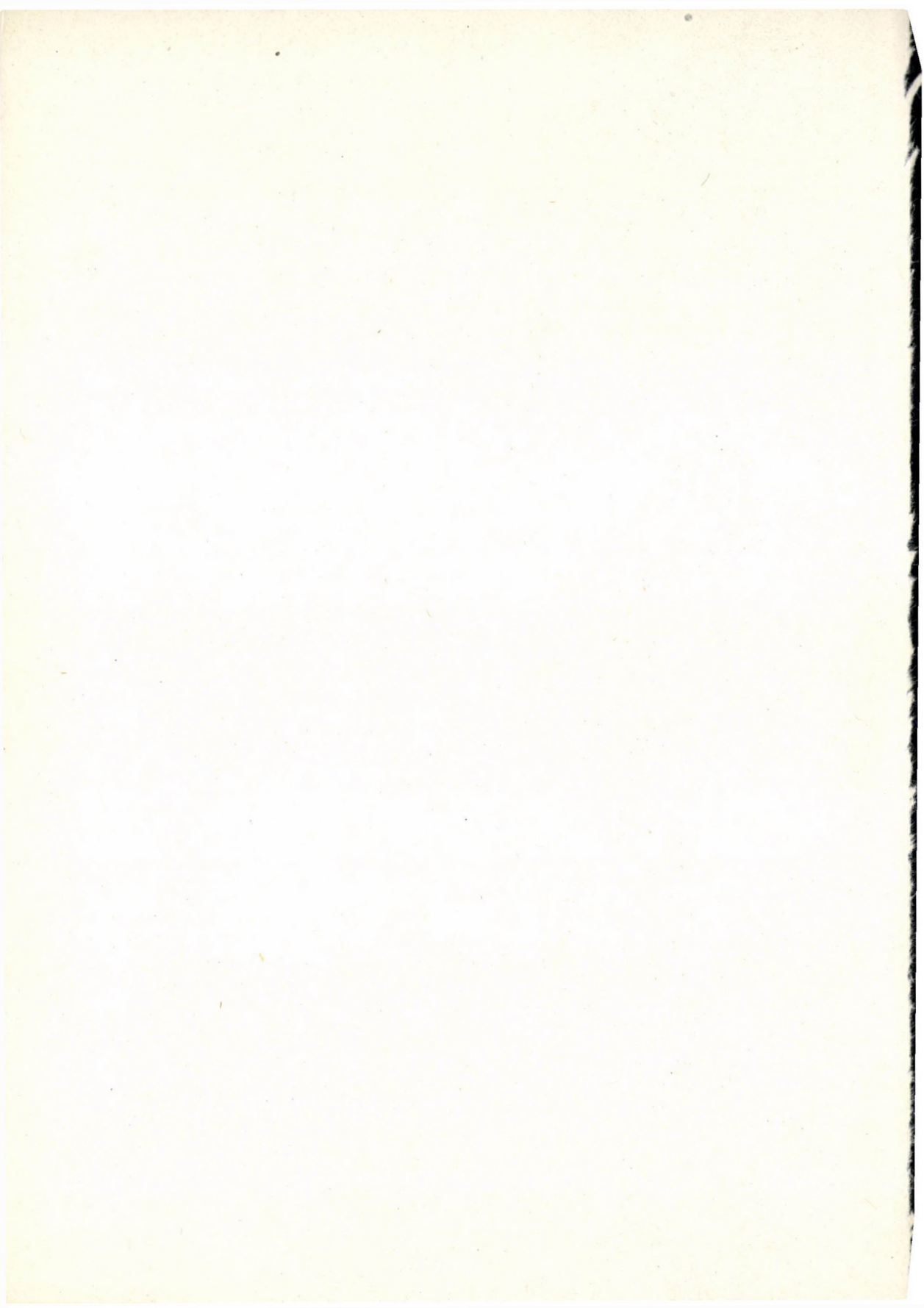
СВОЙСТВА ГЛИАДИНА И ОБРАЗОВАННЫХ ПРОТИВ НЕГО ПРИ ЦЕЛИАКИИ АНТИТЕЛ

М. САБОЛЧ, Ш. ЧОРБА, М. КАВАИ,
И. ФРАНЦИЯ

Авторы изолировали из водной вытяжки пшеничной муки, путем гелевой фильтрация на столбе Сефалекс Г-75 фракции А, В, С, D. Они установили, что фракция А реагирует как антиген с сывороткой больных целиакией. Количество фракции А наибольшее в пшеничной муке, молотой из нового урожая. Абсорбционный максимум ее находится у 278 нм, фракция содержит 15—20% фосфоросодержащих соединений — нуклеиновую кислоту и нуклеотиды. По сравнению с электрофорезом через целлюлозно-ацетатовую перепонку движение к аноду более быстрое, а по сравнению с таковым при полиакриламидно-гелевом электрофорезе более медленное, что объясняется действием гелевых молекулярных фильтров. Содержание глутамина и пролина в фракции А высокое: 27,2% и 12,4%. Определенный при помощи додецилсульфатно-гелевого электрофореза молекулярный вес в 34—36 000 и 56 000—60 000 и упомянутый аминокислотный состав доказывают, что изолированная автотами фракция А относится к группе глиадинов, вопреки тому, что они получили ее водной экстракцией (рН = 5,5—6,0).

В противоположность к белкам, находящимся в водной, нефракционированной вытяжке муки, кроличья антисыворотка преципитирует только фракцию А, а остальные: В, С, D не преципитирует, хотя белковая вытяжка, применявшаяся при иммунизации, содержала и эти фракции. Антитело носит тип ИгГ.

На основании результатов исследования и литературных данных авторы пришли к тому выводу, что глиадин, по своему аминокислотному составу, является протеолитически не- или почти непереваримым белком с особой аминокислотной секвенцией. В результате этого между патомеханизмом и физико-химическими, функциональными особенностями глиадина может существовать тесная связь.



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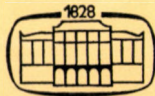
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Az *Acta paediatrica Academiae Scientiarum hungaricae* angol, francia, német és orosz nyelven közöl értekezéseket a gyermekgyógyászat és határterületei köréből. Megjelenik negyedévenként; 4 füzet képez egy kötetet.

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Patterns of neonatal bacterial infection in the 1970's

By

M. E. SPEER, L. H. TABER, A. J. RUDOLPH and J. URTEAGA

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Department of Pediatrics, Baylor College of Medicine and the Neonatology
Service at Jefferson Davis Hospital, Houston, Texas, U. S. A.

A retrospective study was carried out in a large city-county hospital nursery over the two-year period 1973-1974, to determine the incidence, mortality rate, and etiologic agents of neonatal septicemia and meningitis. One hundred of 18,465 infants admitted to the nursery service had septicemia alone and an additional 20 infants had meningitis for an incidence of 5.1 and 1.0 per 1000, respectively. In the group with septicemia the mortality rate was 38/100 (38%) and in those with meningitis 12/20 (60%). Group B streptococcus was the most frequently isolated organism, being present in 28/100 (28%) of septicemia cases and in 13/20 (65%) of those with meningeal infection. Gram positive coccal organisms comprised 47/100 (47%) of the etiologic agents of septicemia while Gram negative enteric bacilli were found in 42/100 (42%). In patients with meningitis, Gram positive cocci were present in 13/20 (65%) all being Group B streptococci; Gram negative enteric bacilli were found in 4/20 (20%). The data demonstrate the increasing incidence of Gram positive coccal organisms, primarily Group B streptococci, as the predominant cause of neonatal infection.

Septicemia with or without meningitis continues to be a significant cause of neonatal morbidity and mortality. With the advent of neonatal regional intensive care facilities, infants who may formerly have died are now evaluated and treated for prolonged periods of time in a potentially hostile bacterial environment.

A study designed to determine the incidence, mortality, and etiologic agents of septicemia/meningitis (S/M) in a large city-county hospital nursery with regional neonatal intensive care facilities was conducted over the two-year period 1973-1974.

METHODS

A total of 18,465 infants were admitted to the nursery service at Jefferson Davis Hospital (JDH) in 1973-1974; 2,111 of these were low birth weight. The hospital records of all infants with either positive blood and/or cerebrospinal fluid (CSF) cultures during the study period were reviewed and the data recorded on a standard form. Criteria for diagnosing patients as having septicemia or meningitis were strict. No patients with neural tube defects were included in the study. All blood cultures were obtained by peripheral venipuncture. Cerebrospi-

nal fluid cultures were performed by directly inoculating culture media at the time of lumbar puncture. The infections reported here represent only those occurring while the infants were in the nurseries.

RESULTS

One hundred and twenty of these 18,465 infants had either positive blood and/or CSF cultures. One hundred had septicemia alone and 20 infants had meningitis with or without associated bacteremia. Of these 120, 105 were born at JDH and 15 were transferred from other institutions. The incidence of septicemia was 5.1 per 1000 infants (100/18,465). If the outside births were excluded the inci-

dence was 4.6 per 1000 live births (85/18,314). Twenty infants had meningitis, one of whom was a transfer from another hospital, for an incidence of 1 per 1000 live births. Fifty of 120 infants died, 10 of whom were born at other hospitals, for an overall mortality rate of 50/100 (41.7%), and a mortality rate of 40/105 (38.1%) for those infants born at JDH. Of the group with septicemia the mortality rate was 12/20 (60%). If the outside births are excluded, then the mortality rate falls to 33.7% and 57.9%, respectively.

The culture results are shown in Table I. Group B streptococcus was the most frequently isolated organism and was found in 28/100 (28%) of the cases with septicemia and 13/20

TABLE I
Etiologic agents of septicemia/meningitis
1973-1974

Organism	Septicemia		Meningitis	
	Number	Percent	Number	Percent
Group B Streptococcus	28	28	13	65.0
<i>Escherichia coli</i>	17	17	1	5.0
<i>Klebsiella sp.</i>	19	19	0	—
<i>Staphylococcus aureus</i>	17	17	0	—
<i>Speudomonas sp.</i>	4	4	1	5.0
<i>Proteus sp.</i>	2	2	1	5.0
<i>Enterobacter sp.</i>	0	—	1	5.0
<i>Haemophilus influenzae</i>	1	1	1	5.0
<i>Listeria monocytogenes</i>	1	1	1	5.0
Enterococcus	2	2	0	—
Bacteroides sp.	1	1	0	—
Candida sp.	2	2	1	5.0
Mixed	6	6	0	—
Total	100		20	

(65%) of the patients with meningeal infection. Twenty-four of the streptococcal isolates were subsequently serotyped as Group B streptococci. The remaining 17 streptococcal isolates were not available for serotyping, but as their biochemical and morphologic characteristics were identical to the serotyped strains, they also were felt to be Group B streptococci. *Klebsiella sp.* and *Escherichia coli* were the most common Gram negative bacilli isolated from the blood and accounted for 19/100 (19%) and 17/100 (17%), respectively, of the cases of septicemia. However, only in one instance was *Escherichia coli* isolated from the CSF and in no instance was *Klebsiella sp.* isolated from the CSF. *Staphylococcus aureus* was the etiologic agent in 17/100 (17%) of the patients with septicemia but caused none of the cases of meningitis. All of the staphylococci were sensitive to methicillin and kanamycin, but only two of these isolates were sensitive to aqueous penicillin G. Other bacterial species found with less frequency included pseudomonas, proteus, enterobacter,

H. influenzae, *Listeria monocytogenes*, enterococci, and *Bacteroides fragilis*. Three patients had systemic candida infection, one of whom had meningeal involvement. Six instances of septicemia represented mixed infection (Table II). Two were due to Group B streptococcus and *Klebsiella*, 1 to Group B streptococcus and *Escherichia coli*, 1 to Group B streptococcus and *Staphylococcus aureus*, 1 to *Escherichia coli* and enterococcus, and 1 to *Staphylococcus aureus*, and enterococcus.

Gram positive coccal organisms comprised 47/100 (47%) of the etiologic agents of septicemia while Gram negative enteric bacilli were found in 42/100 (42%). In those patients with meningitis, Gram positive cocci were present in 13/20 (65%) and all were Group B streptococci. Gram negative enteric bacilli were found in only 4/20 (20%).

Early onset infection (less than 5 days of age) occurred in 88/120 (73.3%) of the cases; 49/88 (56%) of these were due to Gram positive coccal organisms and 30/88 (34%) to Gram

TABLE II
Etiologic agents of mixed infections

Organism	Number
Group B Streptococcus and <i>Klebsiella sp.</i>	2
Group B Streptococcus and <i>Escherichia coli</i>	1
Group B Streptococcus and <i>Staphylococcus aureus</i>	1
<i>Escherichia coli</i> and enterococcus	1
<i>Staphylococcus aureus</i> and enterococcus	1
Total	6

negative bacilli. The remainder of the cases 9/88 (10%) represented mixed infection or other types of organisms. In those infants who became infected after 5 days of age, 20/32 (62.5%) of the causative organisms were either Gram negative enteric bacilli, of which 13/20 (65.0%) were resistant to kanamycin, or a species of candida.

Premature infants comprised 85/120 (70.8%) of the total group, and 13/20 (65%) of the infants with meningitis. No significant difference in the age of onset of disease existed between term and premature infants. Forty-two out of fifty (84%) of the deaths occurred in the early onset group, and 30 of these 42 deaths occurred within 48 hours of birth.

Twenty-seven per cent of the mothers had received no prenatal care prior to delivery and 74.2% of the mothers had some form of obstetric complication either during pregnancy or during labor and delivery. Prolonged rupture of the fetal membranes greater than 24 hours occurred in 21/120 (17.5%) of the patients.

There was a male to female ratio of 1.7 : 1 (63 males and 37 females) in the group with septicemia and a ratio of 1.5 : 1 (12 males and 8 females) in the meningitis group.

DISCUSSION

The incidence of neonatal septicemia has been reported from 1/500 to 1/600 live births [9, 12, 13], and neonatal meningitis has been found

in approximately 0.4/1000 live births [11, 15].

It is difficult to explain why the incidence of S/M should be so much higher than that found in previous studies. Several factors may account for this apparent discrepancy. The population served by JDH has a large percentage of high risk deliveries. Fully 25% of the mothers who deliver at JDH have no prenatal care and all belong to a low socio-economic group. As previously noted, maternal complications were frequent in the study group and there was a high incidence of prematurity. Both factors have been related to increased risk of neonatal infection [13, 16, 19]. Because of the improved life support systems now available, many premature infants are exposed to resistant bacterial flora within the hospital for prolonged periods of time thus increasing their risk of becoming infected. It is nursery policy to obtain blood, urine and cerebrospinal fluid cultures on any infant who is judged to be at risk and whose clinical course suggests infection, regardless of any other disease entity felt to be primarily responsible for the infant's condition. This policy would be expected to increase the number of infants identified as infected.

The increased role of the Group B streptococcus in neonatal infection is probably related to the increased incidence of maternal and neonatal colonization. Baker et al. found that 25% of all mothers and infants in our hospital had Group B streptococcal colonization at the time of deliv-

ery [1]. Similar rates of colonization also have been noted in studies involving middle-class college students in the northeastern portion of the country [3]. Why this high colonization rate exists is not known at present.

The increase in the incidence of septicemia due to *Staphylococcus aureus* is unexplained. Most of these infants were symptomatic early in life and represented early onset infection (14/17). No increase in staphylococcal colonization was noted during the study period nor were bathing or cord care policies altered (Unpublished data).

Late onset infection is often equated with nosocomial infection. Several authors have related acquisition of resistant organisms to prior antibiotic treatment and prolonged hospitalization [2, 6, 8]. Our data support this in that resistant Gram negative bacilli were frequently found in those infants with late onset disease.

Prior to the mid 1940's beta-hemolytic streptococci were the predomi-

nant organisms isolated from infected neonates [7, 14]. Beginning in the late 1940's and progressing through the mid 1960's an increasing proportion of neonatal infections were due to Gram negative enteric bacilli [5, 9-11, 14-16]. In the late 1960's and early 1970's this pattern has again changed with Gram positive coecal forms, particularly Group B streptococcus, becoming increasingly prevalent [1, 17, 18]. A further shift is demonstrated by our data with over 47% of the patients with septicemia and 65% of those with meningitis having Gram positive coecal organisms isolated, primarily Group B streptococci, and only 42% and 20%, respectively, having infections due to Gram negative coliform organism.

Thus a periodicity or "wave form" effect becomes apparent regarding the various bacterial pathogens implicated in neonatal infection (Figs 1, 2). Although the reasons underlying this phenomenon are unclear, recent work by Baker and Kasper may offer a

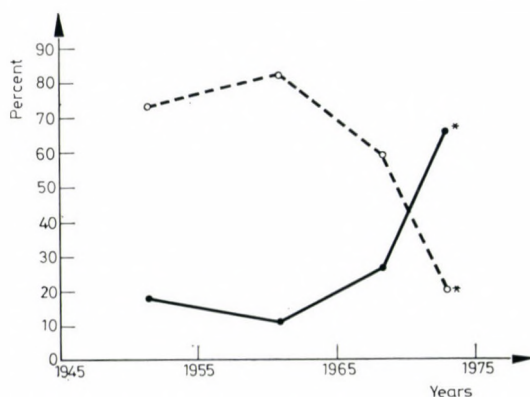


FIG. 1. Incidence of Gram positive coecal (—) vs Gram negative enteric bacilli (- - -) in neonatal septicemia [7, 9, 10, 14, 17]. *Jefferson Davis Hospital

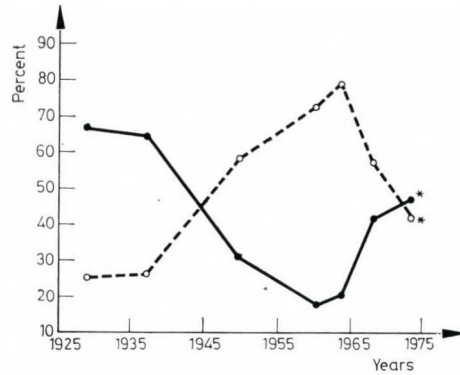


FIG. 2. Incidence of Gram positive coecal (—) vs Gram negative enteric bacilli (- - -) in neonatal meningitis [5, 16, 17]. *Jefferson Davis Hospital

possible explanation [4]. Their data suggest that transplacental transfer of maternal antibody protects infants from invasive Group B streptococcal infection with Type III strains. If maternal colonization and subsequent neonatal infection by pathogenic bacteria can be related to the maternal immune experience and subsequent production of protective levels of transplacental IgG antibody, then a mechanism explaining the observed periodicity can be hypothesized. As maternal antibody levels rise or fall in response to colonization by individual bacteria then the incidence of neonatal infection would be expected to change in a cyclic manner.

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M. E. SPEER, M. D.

Department of Pediatrics,

Baylor College of Medicine,

Houston, Texas 77030, U.S.A.

The influence of maternal diabetes on dental development of the non-diabetic offspring in the stage of transitional dentition

By

P. ADLER,* K. D. FETT,** and L. BOHÁTKA*

* Department of Stomatology, University Medical School, Debrecen, Hungary

** Dental Service, Zentralinstitut für Diabetes »Gerhardt Katsch«
Karlsburg, GDR

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Dental development was studied in some 150 to 170 non-diabetic, 6 to 15 year-old children of diabetic mothers. As compared to standards from Hungary, and partly from the GDR, no conspicuous differences were found as to median age at loss of the individual deciduous, and at eruption of the individual permanent teeth, as well as in the numbers of erupted permanent teeth, in yearly cohorts of boys and girls. Dental development was furthermore assessed individually by comparison to a USA standard and expressed by a single figure ("character number"). The influence of some filial and maternal parameters was assessed upon the mean and distribution of these character numbers in the total sample and its subgroups, *viz.* actual body weight at dental examination, birth-weight and birth-length, classification of the mothers according to White, presence and degree of retinopathy, metabolism during pregnancy, and chronological age of the examinees. The severity of material diabetes assessed according to any of the three parameters exerted some influence upon dental development in the offspring, manifesting with increasing delay, without having found statistically significant differences between subgroups formed according to the aforementioned criteria. A statistically significant delay was demonstrated in dental development of the 8.5 to 11.5-year old group as compared with children of 12.5 to 14.5 years in whom a slight advance was demonstrated. The advance of dental development was not significant statistically in the 6.5 to 7.5 years old children. Some influence was exerted upon dental development by the actual body weight of the examinees, with a slight advance in the high body weight groups. Weight and length at delivery by themselves had no obvious effect upon dental development. As to actual body weight, birth-weight, and length at delivery, the sample was significantly different from the internationally accepted standards.

In a former study of 222 poorly controlled juvenile diabetics, age-dependent differences in median age were shown at loss of the individual deciduous, and at eruption of the individual permanent, teeth [9]. By expressing the dental development of the individual children by a single figure varying between 0 and 100,

it could be demonstrated in 194 juveniles of this sample that dental development depended on the chronological age of the examinees in a statistically significant manner while the duration of overt diabetes exerted only a modifying influence; the age at which the disease was detected had no influence whatever [5]. Accord-

ingly, it was assumed that the juvenile diabetic is born with a special constitution which is apparently capable of affecting dental development prior to the manifestation of diabetes.

In order to test this assumption, a similar study was conducted in the non-diabetic offspring of diabetic mothers. This particular population was chosen for obvious reasons. If diabetes is a genetically transmissible condition, there is a 50% chance of the transmission of the particular gene or genes responsible for the aforementioned shift in dental development. Disregarding this possibility, the offspring is exposed during pregnancy to an environment characteristic of the mother's diabetic state. While in the general population up to the age of 15 yr the frequency of diabetes amounts to approximately 0.03% [7, 16], in the offspring of diabetics the frequency is about twentyfold [11, 6]. Thus, if there is a "diabetic constitution", in the offspring of diabetic mothers it should manifest itself in some way, although in this particular population not more than a few per cent are afflicted. In these children, the inherited "diabetic constitution" turns into a manifest disease, preferentially between 3 and 4, between 6 and 8, and most markedly between 10 and 11, years of age [13, 18, 23].

MATERIAL AND METHODS

In the Zentralinstitut für Diabetes »Gerhardt Katsch«, dental records were collected from 169 children who proved free from manifest or latent diabetes

detected by routine laboratory tests. Of this sample, 152 had been delivered in the Institute by mothers who stood under continuous control during pregnancy. Eight boys and 9 girls had been born elsewhere but were kept since birth together with their mothers under systematic control at Karlsburg like their institute-born age-mates and their mothers. Of these 152 children and their mothers, complete case records were available from the files of the Institute as to duration and severity of maternal diabetes, course of pregnancy, delivery and diseases of the children, etc. In a few cases some data were lacking; therefore, in the different analyses the number of examinees varied slightly. As to sex and age distribution, see Table II.

Dental development was assessed by comparing the number of erupted permanent teeth individually with tabulated cumulative percentages for boys and girls of each year with 0, 1, 2, etc. . . . 26, 27, and 28 erupted permanent teeth, in reliance on data from Hagerstown, Md. [15]. Extracted permanent teeth were counted as erupted. The mean of the upper and lower percentage limit of the cells for particular numbers of erupted teeth rounded off to the next full number was allotted to each of the examinees. In this way, their dental development was expressed by a single figure varying between 0 and 100. This figure is termed the "character number" of dental development in the individual child [8].

Median age at loss of the deciduous, and at eruption of the permanent, tooth-entities (and standard deviations) was determined graphically after conversion of the percent values of lost deciduous, and erupted permanent, units ("tooth absence" and "tooth presence" percentages, respectively) into probits. With regard to the small number of examinees in some cohorts, one third of the sum of the tooth absence or presence percentages of the particular year of age, and of the preceding and following year was taken into account (smoothing by sliding means).

Actual body weight at dental examination was chosen as another parameter of physical development. Children were grouped into seven classes in reliance on Heimedinger's figures [14]: the lowest 2.5, then up to the 10th, 25th, 75th, 90th, 97.5th percentiles, and above (actual body weight classes; in the following: WtC). Since in these tables weights are given for each half-year of age, our examinees were compared with the figures as shown for their sex and age in intervals of half-years.

As to chronological age, the last birthday was taken into account.

Weight and length of children at delivery. Since in pregnant diabetics delivery is mostly induced before term, the actual measurements of the newborn babies were compared with the corresponding standards for pregnancies of equal duration given by Lubchenco et al. [19, 20]. Accordingly, six length and weight classes (in the following: BLC and BWtC, respectively) were formed, viz. 1) children falling into the lowest 10 percentiles; 2) between >10 and 25; 3) between >25 and 50; 4) between >50 and 75; 5) >75 and 90; and 6) >90 percentile. Children of Class 6 whose length or weight exceeded by more than 10% the numerical values for the 90th percentile standard for the same sex and the same duration of pregnancy, were allotted to a special Subclass 6A.

Maternal diabetes was grouped according to White [22] into classes (WhC) A, B, C, D, and F. WhC E was disregarded. In this classification, the mother's history of diabetes as age at manifestation, duration (in the absence of retinopathy), and in Classes D, E and F, the presence of some complications such as retinopathy in Class D and nephropathy in Class E were taken into account. The presence and degree of retinopathy in late pregnancy were chosen as another basis for classification on the one hand, and the state of maternal metabolism during the whole course of pregnancy, on the other. As to retinopathy, freedom from it (R_0), and severity degrees 1, 2, 3 (R_1, R_2, R_3) and

as to maternal metabolism a "good", "fair" and "poor" state [12] were distinguished.

Standards. Besides the aforementioned normal standards [14, 15, 19, 20], findings were compared with a selected Hungarian population sample characterized by a small proportion of children with an early loss of deciduous teeth from the "support zone" [1], with findings from Karl-Marx-Stadt prior to fluoridation of the public water supply [17] and with data of the aforementioned juveniles suffering from poorly controlled diabetes [5, 9]. In most instances, subgroups of the present sample were compared with each other.

Statistical treatment. In most comparisons, distributions of the "character numbers" were relied upon, mostly into quartiles, exceptionally into quintiles. In testing significance, a well-known modification of the χ^2 test was used by which samples unequal in size can reliably be compared [10]. In a few comparisons with well-established standards that could be regarded as the "expected frequencies", the common χ^2 test was used. Exceptionally, standard errors of the mean were relied upon. As the limit of statistical significance, $p < 0.05$ was adhered to.

RESULTS

1. *Median ages* at loss of the deciduous, and at eruption of the permanent, teeth are summarized in Table I. In contrast to the poorly controlled juvenile diabetic groups, no consistent age-dependent deviations could be detected from the Hungarian and from the GDR standards.

The mean number of erupted permanent teeth in yearly cohorts of boys and girls is shown in Table II. As compared to the formerly examined diabetics, the mean was lower in the present population up to 9.5 (9 to

TABLE I

Median age at loss of the deciduous, and at eruption of the permanent, teeth in the non-diabetic offspring of diabetic mothers (in years: and months, and decimals of months)

Tooth unit	Boys		Girls	
	upper teeth	lower teeth	upper teeth	lower teeth
<i>Deciduous teeth</i>				
Central incisor	7 : 01.3 ± 1 : 01.3	6 : 02.1 ± 1 : 00.1	7 : 01.4 ± 0 : 07.7	5 : 09.2 ± 1 : 06.6
Lateral incisor	8 : 03.9 ± 1 : 03.6	7 : 00.9 ± 0 : 11.9	7 : 03.8 ± 1 : 00.8	7 : 04.0 ± 1 : 11.0
Cuspid	11 : 04.8 ± 1 : 04.7	10 : 09.4 ± 1 : 06.9	10 : 01.2 ± 1 : 10.6	9 : 04.8 ± 0 : 08.1
First molar	10 : 08.9 ± 1 : 04.9	10 : 11.0 ± 0 : 10.9	9 : 09.8 ± 1 : 10.6	9 : 11.0 ± 1 : 02.3
Second molar	11 : 00.1 ± 1 : 02.4	11 : 00.5 ± 1 : 04.1	11 : 03.8 ± 1 : 09.3	10 : 04.3 ± 1 : 04.4
<i>Permanent teeth</i>				
Central incisor	7 : 04.9 ± 0 : 09.2	6 : 00.9 ± 1 : 04.0	7 : 03.3 ± 0 : 09.6	5 : 09.2 ± 1 : 06.6
Lateral incisor	8 : 06.8 ± 1 : 01.2	7 : 02.4 ± 0 : 10.8	8 : 01.1 ± 1 : 05.8	7 : 06.4 ± 1 : 05.6
Cuspid	11 : 05.8 ± 1 : 05.5	10 : 11.6 ± 1 : 08.1	10 : 11.6 ± 1 : 07.5	9 : 05.5 ± 1 : 03.6
First premolar	10 : 08.9 ± 1 : 03.2	10 : 11.4 ± 1 : 01.7	10 : 03.0 ± 1 : 11.1	10 : 05.5 ± 1 : 08.4
Second premolar	11 : 01.8 ± 1 : 04.8	11 : 07.8 ± 1 : 02.3	11 : 02.0 ± 1 : 08.8	11 : 03.7 ± 1 : 10.2
First molar	6 : 07.6 *	6 : 08.0 *	< 5 : 09.2 *	< 5 : 09.2 *
Second molar	12 : 01.2 ± 1 : 09.3	11 : 11.2 ± 1 : 03.4	11 : 10.3 ± 1 : 08.5	11 : 04.2 ± 1 : 08.3

* Extrapolated median; the standard deviation was not assessed

For a few teeth, an earlier median age was assessed at eruption of the successional than at loss of the deciduous (predecessor) unit; in a few others, the two medians were equal. This is due to having plotted the probits of tooth absence and presence percentages, respectively, in the deciduous and permanent teeth independently from each other. In drawing straight lines for loss and eruption of the teeth, central probit values were strongly adhered to.

TABLE II

Mean number of erupted permanent teeth and, in brackets, the number of examinees, in yearly cohorts of boys and girls

Last birthday	Boys	Girls
6	3.38 (8)	4.67 (3)
7	8.10 (21)	10.59 (17)
8	11.55 (11)	11.36 (11)
9	12.25 (8)	15.63 (8)
10	17.57 (7)	21.25 (4)
11	19.86 (7)	22.43 (7)
12	25.17 (12)	25.86 (14)
13	27.31 (13)	27.83 (6)
14	27.57 (7)	27.60 (5)

10) years of age, and higher in all older cohorts. As compared to the Hungarian population, from 2 × 8 comparable cohorts, higher mean numbers occurred in the offspring of diabetic mothers in 11 instances and lower ones in only four instances, whereas the mean number of erupted permanent teeth was equal in boys of 11.5 years in these two populations.

2. *The mean character numbers of dental development* are shown in dependence on the chronological age of the examinees on the one hand, and on their actual body weight on the other hand, in Table III.

The distribution into quintiles of the total sample (disregarding age) differed significantly from that of the Hagerstown standard ($p < 0.025$).

Next, attention was focussed upon the age-changes of these mean character numbers. Erratic variations were seen that might have been due to the small sample size at some

ages. In order to have groups allowing valid statistical comparisons, more or less arbitrarily three age-groups were set up, *viz.* age-group I from the 6.5 and 7.5; age-group II from 8.5, 9.5, 10.5 and 11.5; and age-group III from the 12.5, 13.5 and 14.5 years old children, with 45, 55 and 52 examinees, respectively, in each combined group. The mean character numbers were 58.91 ± 6.86 ; 46.27 ± 4.49 ; and 56.40 ± 3.25 . The differences between any two means were not significant statistically. The distribution of the examinees in the four quartiles of character numbers was significantly different between age-groups II and III ($p < 0.05$).

3. *Physical development* of the examinees, judged in reliance on their actual body weights at dental examination, was significantly different from the Heimedinger standard ($p < 0.005$). The difference was mainly due to 15% of the children in WtC 7 (over the 97.5th percentile). Into the combined WtCs 1 and 2 (lower than the 2.5th, and 2.5 to 10th percentiles, respectively), belonged only 7.19% instead of the expected 10%. Percentages higher than in the normal standard were seen in WtC 6 also but consistently lower ones were found up to WtC 5.

The character numbers of dental development in reliance on actual body weight were not significantly differently distributed into quartiles in the combined WtCs 1–3 as compared with WtC 4, in WtC 4 as compared with the combined WtCs 5–7, whereas the difference between the

combined WtCs 1–3 against WtCs 5–7 proved to be significant statistically ($p < 0.05$).

In Table IV, the dependence on the examinees' age of the character numbers in WtC 4, the combined WtCs 1–3 and 5–6, are shown. It is seen that in the combined WtCs 5–7 there were no age-dependent differences whereas in the combined WtCs 1–3 the mean character numbers in the two younger age-groups were lower than in age-group III. While in age-groups I and III a steady rise was displayed by the mean character

number with the increase of body weight (from combined WtCs 1–3 through WtC 4 to the combined WtCs 5–7), in age-group II a lower mean character number was seen in WtC 4 than in any of the aforementioned combined WtCs. In age-group II, the quartile distribution of the combined WtCs 1–4 was significantly different from that of the combined WtCs 5–7 ($p < 0.05$).

As also shown in Table IV, the mean character numbers of WtC 7 on the one hand, and of the combined WtCs 5–6 on the other, were mark-

TABLE III

Dependence of the mean "character numbers" (of dental development) on actual body weight and chronological age

Last birthday	Actual body weight class							Body wt. record lacking	Mean of the yearly cohort
	1	2	3	4	5	6	7		
6	—	35.00 (1)	—	53.00 (4)	71.00 (1)	6.00 (1)	63.50 (2)	—	50.11 (9)
7	—	32.33 (3)	57.50 (2)	62.05 (19)	65.00 (3)	46.67 (3)	80.40 (5)	72.00 (1)	61.11 (36)
8	—	20.33 (3)	62.00 (3)	42.00 (8)	66.00 (3)	68.00 (1)	51.00 (4)	—	47.86 (22)
9	—	2.00 (1)	14.00 (1)	34.40 (5)	—	60.33 (3)	32.00 (1)	—	36.45 (11)
10	98.00 (1)	—	—	30.00 (5)	100.0 (2)	—	48.50 (2)	42.00 (1)	53.36 (11)
11	—	—	43.25 (4)	45.00 (3)	—	14.00 (1)	90.00 (2)	2.00 (1)	45.82 (11)
12	—	8.00 (1)	—	56.09 (11)	74.00 (3)	41.33 (3)	58.50 (2)	—	55.23 (22)
13	—	—	63.50 (4)	55.90 (10)	72.00 (1)	—	58.50 (2)	76.00 (1)	59.89 (18)
14	—	10.00 (1)	61.50 (4)	60.83 (6)	—	—	—	19.00 (1)	53.33 (12)
15	—	—	—	52.00 (3)	52.00 (1)	66.00 (1)	52.00 (1)	—	54.33 (6)
Wt. class mean	28.27 (11)		54.89 (18)	52.45 (74)	72.14 (14)	46.08 (13)	62.83 (23)		

In parentheses: number of examinees

TABLE IV

Summarized mean character numbers in three age-groups in different combinations of body weight classes

Age-group	Weight classes				
	1-3 combined	4	5-7 combined	5-6 combined	7
I	41.16 (6)	60.48 (23)	62.73 (15)	51.50 (8)	75.57 (7)
II	41.08 (13)	37.76 (21)	61.79 (19)	66.10 (10)	57.00 (9)
III	51.81 (10)	52.07 (27)	59.15 (13)	59.70 (7)	58.50 (6)

In age-group II, the quartile distribution of the 34 examinees in the combined weight classes 1-4 was 16 : 5 : 9 : 4, whereas in the combined weight classes 5-7 a distribution of 3 : 4 : 4 : 9 was found. The difference proved significant statistically ($\chi^2 = 8.712$, at 3 degrees of freedom, $p < 0.05$).

Including the 15-year-old examinees, in the combined weight class 1-3 a 12 : 3 : 7 : 7 distribution was found, and in the combined weight classes 5-7 the distribution was 6 : 10 : 19 : 15. The difference is significant statistically ($\chi^2 = 9.3177$, at 3 degrees of freedom, $p < 0.05$).

edly different in age-group I (75.6 against 51.5). The difference was practically negligible in age-group III, whereas in age-group II a lower mean character number was found in WtC 7 than in the combined WtCs 5-6. As to the quartile distribution, none of these differences proved significant statistically. Combining children of WtCs 6 and 7 only, instead of 5-7, in the three age-groups, mean character numbers of 61.36; 55.43; and 52.78, were found.

4. *Birth weight* in the population differed significantly from the standard [20]. While in the latter a 10 : 15 : 25 : 25 : 25 : 10% distribution prevailed, in our subjects including the 15-year group a 4 : 18 : 23 : 24 : 29 : 59 distribution was found ($p < 0.001$). Such a deviation was expected in view of the maternal diabetes. As shown in Table V, no clear trends in

dental development were obvious in dependence on birth-weight. The lowest mean, amounting to 49.73, was found in the combined BWtCs 1-2 and the highest, 63.78, in BWtC 3. In the special Subclass 6A, the mean character number was 56.84.

In order to form groups suitable for statistical comparison, BWtC. 1-2-3 on the one hand, and 4-5 on the other, were combined, while BWtC 6 was handled by itself. In Table V, the interdependence of BWtC and chronological age is shown. High mean character numbers were found in the youngest BWtC 1-3, and in the oldest BWtC 6. Within age-group II, the differences between BWtCs were small. In all three age-groups, the lowest mean character numbers were found in children in the combined BWtC 4-5. Although none of the age-group III/BWtC 6

TABLE V

Dependence of the mean "character numbers" (of dental development) on birth-weight and chronological age

Age-group	Birth-weight class							
	1	2	3	1-3 combined	4	5	4-5 combined	6
I	19.00 (2)	62.67 (6)	68.33 (9)	60.53 (17)	33.63 (8)	72.43 (7)	51.73 (15)	59.92 (13)
II	—	38.20 (5)	65.20 (5)	51.70 (10)	47.14 (7)	44.64 (11)	45.61 (18)	46.00 (26)
III	84.50 (2)	45.71 (7)	59.25 (8)	56.65 (17)	42.67 (9)	52.11 (9)	47.39 (18)	66.17 (17)
15 years	—	—	52.00 (1)	—	—	59.00 (2)	—	52.00 (3)
All ages (6 to 15 years)	51.75 (4)	49.28 (18)	63.78 (23)	—	40.96 (24)	54.65 (29)	—	52.69 (59)

In parentheses the number of examinees

had a character number lower than 26, the difference in distribution against age-group II/BWtC 6 just failed to reach the $p < 0.05$ limit of statistical significance. In no other comparison of subgroups formed in reliance on BWtCs was there a difference of quartile distribution that would have so closely approached the level of significance.

5. *Length at delivery.* The distribution of the subjects into quartiles was significantly different from the standard [19]. As seen from Table VI, no clear influence of BLC on dental development was detected when partly combined BLCs were arranged according to age. The lowest mean character numbers were seen in all three age-groups in BLC 1-3; in age-groups I and II, the number of examinees was so small that reliable statistical comparison did not seem feasible. The differences in the mean character

numbers of individual BLCs (not shown in Table VI), disregarding age,

TABLE VI

Influence of body length at birth upon dental development (mean character numbers) in three age-groups

Age-group	Birth-length classes		
	1-3 combined	4-5 combined	6
I	42.33 (3)	66.06 (17)	55.33 (24)
II	42.60 (5)	48.94 (18)	46.45 (31)
III	49.85 (13)	50.33 (21)	68.22 (18)

were small except for a markedly lower mean in BLC 3 (45.06); as compared to the other BLCs, even this failed to differ significantly in quartile distribution.

6. *Classification of mothers.* In Table VII the mean subgroup character numbers are shown, arranged accord-

TABLE VII

Dependence of the mean "character numbers" (of dental development) on the White classification of mothers and on the chronological age of examinees

A. Individual cohorts

Last birthday	White classification of mothers					Mean of the yearly cohort
	A	B	C	D	F	
6	—	41.50 (2)	46.25 (4)	61.00 (3)	—	50.11 (9)
7	82.50 (2)	63.64 (22)	50.83 (6)	62.80 (5)	16.00 (1)	61.11 (36)
8	5.00 (1)	63.13 (8)	55.20 (5)	33.29 (7)	34.00 (1)	47.86 (22)
9	—	8.50 (2)	75.00 (1)	38.17 (6)	40.00 (2)	36.45 (11)
10	—	74.25 (4)	40.33 (3)	54.50 (2)	30.00 (2)	53.36 (11)
11	—	25.00 (1)	57.75 (4)	41.33 (6)	—	45.82 (11)
12	—	65.71 (7)	50.50 (4)	50.27 (11)	—	55.23 (22)
13	—	60.18 (11)	72.00 (1)	53.60 (5)	76.00 (1)	59.89 (18)
14	—	66.33 (3)	49.86 (7)	46.00 (2)	—	53.33 (12)
15	—	55.50 (4)	—	52.00 (2)	—	54.33 (6)
All ages	56.67 (3)	60.47 (64)	51.89 (35)	47.61 (49)	38.00 (7)	

B. Combined data

Age-group	Combined maternal White classes			
	A—B	A—B—C	C—D—F	D—F
I	63.38 (26)	59.38 (36)	52.78 (19)	57.00 (9)
II	53.06 (16)	53.52 (29)	43.48 (39)	38.19 (26)
III	62.90 (21)	58.91 (33)	52.00 (31)	52.05 (19)

ing to severity classes and age. WhC was found to exert a marked, and apparently unequivocal, influence on dental development of the offspring: decreasing mean character numbers were seen in children of all ages from WhC B through WhC C and WhC D to WhC F. WhC A, with three children only, did not fit into this regular

pattern. In spite of such a marked tendency, none of the inter-WhC differences proved significant as to quartile distribution, and as to the relation of the differences of any two means to their standard errors.

Combining WhCs A—B—C on the one hand, and D—F on the other, or WhCs A—B and D—F (excluding

TABLE VIII

Mean "character numbers" (of dental development) in the offspring of diabetic mothers in different White classes, in dependence on actual body weight, on body weight and on body length at birth

Filial parameter,	White class of mothers		
	A—B combined	C	D—F combined
<i>A. Actual body weight</i>			
Class 1—3	50.67 (9)	54.00 (7)	35.62 (13)
Class 4	53.16 (31)	57.14 (21)	45.11 (19)
Class 5—7	61.00 (22)	32.29 (7)	55.05 (19)
Class 5—6	48.82 (11)	31.40 (5)	52.70 (10)
Class 7	73.18 (11)	34.50 (2)	57.66 (9)
<i>B. Weight at birth</i>			
Class 1—3	71.00 (16)	63.60 (10)	41.53 (19)
Class 4—5	51.33 (21)	47.88 (17)	49.27 (15)
Class 6	62.59 (29)	45.75 (8)	48.00 (22)
<i>C. Length at birth</i>			
Class 1—3	61.50 (6)	61.67 (6)	25.33 (9)
Class 4—5	60.78 (23)	53.17 (12)	49.29 (24)
Class 6	61.14 (37)	46.06 (16)	50.68 (22)

In parentheses the number of examinees

WhC C), and taking into account the age of examinees, yielded little additional information. In age-group II, WhCs C—D—F differed significantly in quartile distribution of the character numbers from WhCs A—B in age-group I as well as III, but not from other subgroups.

WhC being generally accepted as the most characteristic maternal parameter of diabetes, its influence on dental development was examined

additionally in relation to actual body-weight, birth-weight, and birth-length. Results are summarized in Table VIII. As to the influence of actual body weight, it was remarkable to find a very low mean character number in the WtCs 5—7 children of WhC C mothers. As in this subgroup there were only 7 children, a statistical comparison was not feasible. In the combined WhCs A—B as well as D—F, higher character numbers

TABLE IX

Quartile distribution of "character numbers" (of dental development) in the offspring of diabetic mothers in dependence on maternal retinopathy, and the state of metabolism during the whole course of pregnancy

Maternal parameter	Number of children in quartile			
	1	2	3	4
<i>Retinopathy</i>				
free of pathosis (R_0)	17	20	36	28
$R_1-R_2-R_3$, combined	16	13	15	11
R_2-R_3 , combined	8	6	5	4
<i>State of metabolism during the whole course of pregnancy</i>				
Good	13	17	33	21
Fair	14	13	17	18
Poor	5	4	3	0

were found in children who were in the upper quartile of the Heimedinger standards (WhCs 5–7) than in those with lower body weight. A rather low mean character number was found in BLCs 1–3 children of WhCs D–F mothers. The trend to lower mean character numbers was nearly regular with worsening maternal WhCs, although in a few comparisons WhC C offsprings had mean values somewhat lower than WhC D–F ones.

7. *Maternal retinopathy* was apparently connected with dental development. In the 101 offsprings of R_0 mothers the mean character number was 56.79; in the 32 children of R_1 mothers it was 48.91; and in the children of R_2 mothers only 48.34, while in the 4 children of R_3 mothers, 43.50. Quartile distributions (Table IX) were compared between R_0 and combined R_{1-3} offsprings on the one

hand, and between R_{2-3} offsprings on the other, without finding a statistically significant difference. No additional information was gained from comparison to the WhCs of the mothers. Taking into account the chronological age of the examinees, in age-group II children of R_{1-3} mothers a markedly lower mean character number (39.22) was found than in any other subgroup; in these, mean character numbers varied between 51.78 and 59.75. As to quartile distribution, this particular subsample (age-group II offsprings of R_{1-3} mothers) differed significantly ($p < 0.05$) from the age-group I and age-group III offsprings of R_0 mothers, but not from age-group II offsprings of R_0 mothers.

Retinopathy having been a criterion for the classes D and F, it was not unexpected that only two of the

WhCs D and F mothers could be classified as R_0 .

8. *Maternal metabolism* seemed to exert an influence on dental development of the offspring if the disturbance was severe. The mean character numbers were 55.73 in the 84 children of mothers in a "good", 54.23 in the 62 offsprings of mothers in a "fair" state, whereas in the 12 children of mothers with a "poor" metabolism the mean was only 36.00. None of the examinees of this small subsample had a character number exceeding 75 (Table IX). Between the two large groups formed according to maternal metabolism [12], the difference was negligible. No further connections were detected by comparisons according to age and maternal WhCs.

DISCUSSION

The influence of several parameters was examined upon dental development in the non-diabetic offspring of diabetic mothers. The parameters were classified as filial and maternal; the filial parameters were subdivided into actual (i.e. stated at dental examination) and natal ones (recorded at birth). It was shown unequivocally and proved statistically that the actual body weight, BWt and BL of our subjects was significantly different from the standards chosen [14, 19, 20]. These findings indicate that our sample was not a randomly selected group from the general population. These differences may be regarded, though with some reservations,

as consequences of the maternal diabetes.

By the maternal parameters, trends were shown only as to the influence on dental development in the offspring. Although they were rather marked, none of them proved significant statistically. The most marked influence on dental development had apparently that filial parameter which is independent of maternal diabetes, i.e. the examinees' chronological age. Children grow older independently of their mothers being free of, or suffering from, diabetes. In age-group II, the quartile distribution was significantly different from that in age-group III. All other statistically significant differences which we could demonstrate were in some way connected with this particular age-group or one of its subsamples. In age-groups I and II, the mean character numbers were practically identical with the means found formerly in the poorly controlled juvenile diabetics, whereas in age-group III a mean character number was assessed that hardly differed, if at all, from the Hagerstown standard [4]. As a tentative explanation, the preferential manifestation of "inherited" diabetes in prepubertal years is referred to [13, 18, 23]. It may therefore be supposed that in our cross-sectional study the age-group III subsample was different in composition from the subsamples of age-groups I and II. In age-group III there were subjects who passed the critical age of puberty without having turned into diabetics. Accordingly, their risk of developing

manifest diabetes at a later but still juvenile age is considerably lower than in age-groups I and II. Among these latter children who were examined before their 12th birthday, many may be expected to develop manifest diabetes in the next few years. In other words: age-group III was cleared of the children who develop diabetes at a juvenile age, whereas such children formed an appreciable part of the two younger age-groups. This tentative explanation needs to be confirmed by a closer longitudinal study of a larger group.

The age-dependent connection found between actual body weight and dental development seems noteworthy. In dental development, in age-group I the combined WtCs 1–3 children were markedly delayed as compared to their age-mates who were heavier. In this age-group, a body weight in the lowest 25 percentiles of the standard seems to be indicative of some, probably slight, impairment of physical development of which our character numbers were a partial item only. In age-group II dental development was slightly delayed as compared to age-group I, and especially III. Regarding differences of subsamples within this particular age-group, no delay was obvious in the combined WtCs 5–7 children in the uppermost quartile of the standard. These subjects were physically so well-developed that their dentition was not delayed but rather slightly advanced in comparison to the standards. In a healthy population the advance of dental development at an

early age is maintained through long periods of life [21]. Although this experience does not hold true for diabetics, as an increase of delay occurs in overt diabetics with advancing age, additional attention should be paid to the further physical development of this subsample, and generally of high weight children at prepubertal age. In age-group III, advance of WtCs 5–7 children was lower against their age-mates of WtCs 1–4 than in age-group II; nevertheless, a slight advance was demonstrated.

A shortcoming of the study was the limited size of the samples; another shortcoming was the non-random selection of examinees, and the third, its cross-sectional type. As to the selection of subjects, all children were included who visited the Karlsburg Institute for regular control during a certain time interval and who proved to have no manifest diabetes nor some disturbance of carbohydrate metabolism. Although we are not aware of any bias in having scheduled children for regular control at the institute, and accordingly our sample may justifiably be considered an unbiased one, it was not selected at random. Its small size resulted in subsamples that were hardly suitable for statistical comparison. A longitudinal study of some 100 to 150 randomly selected children of diabetic parentage would be the best means to avoid the shortcomings mentioned.

To examine the significance of differences, since the character numbers

were not distributed normally, a comparison of their actual distribution seemed preferable to comparing means and assessing standard errors. We are aware of the difference between statistical significance and clinical importance of any deviation of small subsamples from standards or from each other. By statistical methods, groups only may be compared and not individuals; and therefore, statistical tests are valid only for the groups. Accordingly, for the individual offsprings hardly any prognostic aid was obtained.

The validity of our standards may also be questioned. The character number method used is hardly suited to show an advance in dental development in the final stages of mixed dentition since the 28 teeth stage is attained — except by children with tooth agenesis (hyp- or oligodontia) — at a later age by all. The Hagerstown standards are based upon a cross-sectional study conducted some 40 years ago. In the meantime, a secular acceleration in dental development occurred [2]. Accordingly, in a pilot study consistently higher mean character numbers were found in yearly cohorts of children in Hungary than the expected standard 50 [8]. In dental development some difference may exist in different countries, but

in Caucasians such differences are negligible [3]. Nevertheless, it would be preferable to use more recent European standards for comparisons. The age differences at eruption of the individual tooth units in Europeans of various nationalities have recently been shown to be minimal [17]. Thus, the nature of our recent findings was not altered by having used 40-year-old American standards.

As to the validity of the other standards, we are aware of marked differences in comparison with more recent findings from the GDR.*

Besides, or instead of, those examined, the influence of other filial and maternal parameters could have been assessed, such as e.g. maternal age at pregnancy, intercurrent diseases in infancy and early childhood, bone age, etc. They were not examined, although some might have a profound influence upon dental development of the offspring. The parameters relied upon in our study were chosen deliberately; filial as well as maternal parameters were examined which were thought to be markedly influenced by diabetes.

In summary, the influence of maternal diabetes was shown although not in a statistically significant manner on dental development in the non-diabetic offspring.

* As to actual body weight, we refer to Oemisch, W: Die Entwicklung der Körpermaße bei Kindern und Jugendlichen in der DDR. Ergebnisse einer repräsentativen Untersuchung in den Jahren 1967/68. Akad. ärztl. Fortbild., Berlin 1970.

As to normal birth-weights and lengths, the paper by Kyank, H., Herre H. D., Kruse H. J., Löscher H., Löscher K. D. and Plesse R.: Ergebnisse einer Normalwerterhebung Neugeborener in der DDR. I. Mitt.: Geburtsgewicht, Geburtslänge. Zbl. Gynäk. 97, 129 (1975) was not yet available at the time of our analysis.

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Prof. P. ADLER,
Stomatologiai Klinika
H-4012 Debrecen

A case of 22-trisomy mosaic

By

Magda OSZTOVICS and G. IVÁDY

Laboratory of Human Genetics, National Institute of Public Health, and
Heim Pál Children's Hospital, Budapest

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An extra small acrocentric chromosome was found in 50% of the cultured blood cells of a somato-mentally retarded girl with congenital heart failure and different dysmorphic symptoms. The supernumerary chromosome proved to be chromosome No. 22.

REPORT OF A CASE

This female child was born from the second pregnancy of a 30-year-old mother and a 34-year-old father. There were no spontaneous abortions and the family history was uninformative. After an uncomplicated pregnancy the baby was delivered at term, with 3225 g weight and 52 cm length. Physical and mental development was delayed and therefore the patient was referred to us for chromosome investigation at the age of 18 months. At that time her weight was 8950 g; the length 73 cm; and the head circumference 43.5 cm. She was not able to stand without help.

Except for a congenital stenosis of the aorta, she had no visceral malformation. Dysmorphic signs were microcephaly, asymmetry of head with left frontal and parietal prominence, strabismus, beaked nose with low nasal bridge, long philtrum, slight micrognathia, gothic palate, asymmetry of the ears and hypoplastic nails (Fig. 1).

CHROMOSOME STUDY

Chromosome study revealed 46, XX karyotype in 23 investigated peripheral blood cells of the patient, while in 21 cells a 47, XX, +22 karyotype was found (Fig. 2). The parents and their first child have normal karyotypes.

DISCUSSION

Trisomy 22 seems to be a rare anomaly and the question frequently arose whether it was connected with the cat eye syndrome. Before the banding era, 22-trisomy was considered a clinical entity [6]. Its cardinal symptoms consisting of mental and growth retardation, microcephaly, micrognathia, preauricular skin tag, appendage and sinus, congenital heart defect, cleft palate, were found also in cases where chromosome identification was carried out by new chromosome techniques [1, 2, 3, 5, 8, 9, 10]. The clinical features of 22-trisomy have recently been reviewed by Begleiter et al. [3].

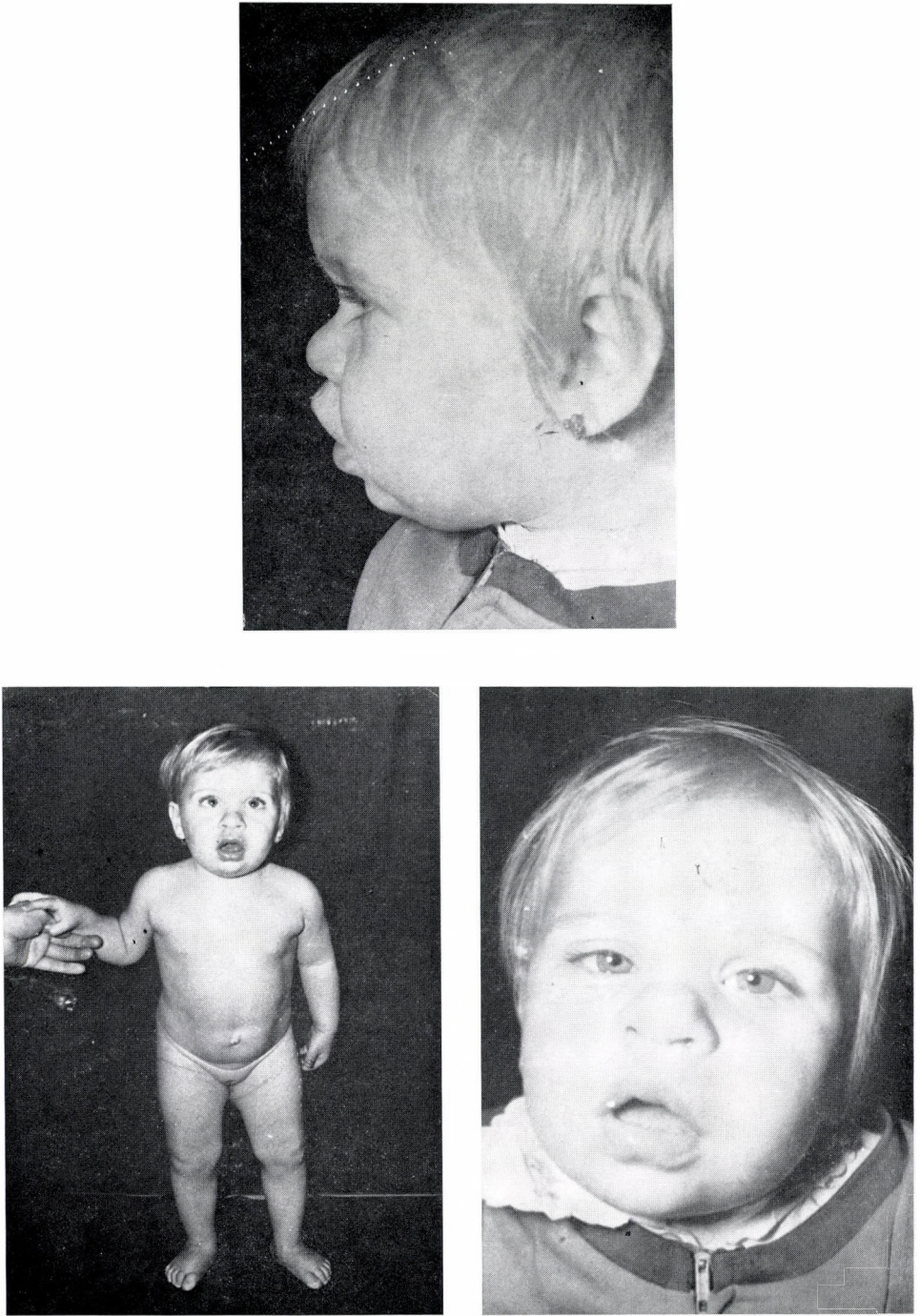


FIG. 1. The patient at 18 months of age



FIG. 2. (a) Chromosomes No. 19—22 in trisomic and normal cells; (b) karyotype in a cell with 22-trisomy. Identification by GAG technique

In a comprehensive study [7] the inconsistency of the phenotypic manifestation of the cat eye syndrome has been emphasized there having been one single case only where the supernumerary chromosome was identified as No. 22 [4]. All the other supernumerary chromosomes found in the cat eye syndrome remained unrevealed even when identification was attempted by several banding methods [7].

It has been assumed [10] that 22-trisomy and the cat eye syndrome are variants of the same entity. If this is true, the supernumerary chromo-

some must be a deleted chromosome No. 22 due in some cases to a pericentric inversion or translocation. This would explain the divergence in the clinical manifestations of the cat eye and 22-trisomy syndromes and also the experience that mental retardation is more serious in patients with 22-trisomy.

In spite of the fact that in our patient the 22-trisomy involved only 50% of the blood cells, she is severely retarded mentally and shows many symptoms of those common cases reported previously. In external appearance she resembles especially the

patients reported by Penchaszadeh and Coco [8].

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M. OSZTOVICICS, M. D.

Gyáli út 4

H-1966 Budapest

A trisomy for 10q24-qter from a familial translocation; t(4; 10) (q33; q24) in both grandparents

By

Magda OSZTOVICS and T. KASZÁS

Laboratory of Human Genetics, National Institute of Public Health, Budapest, and District Hospital, Siófok

Received February 1st, 1977

A trisomy for 10q24-qter was found in a male infant. The clinical findings of the propositus were similar to those reported by other investigators. Both paternal grandparents are close relatives, and show the same balanced translocation, t(4; 10) (q33; q24). Their reproductive history reflected an extremely severe genetic imbalance. Four out of five children died in early infancy. The only living offspring is the father of the proband who has the balanced translocation.

CLINICAL DATA AND FINDINGS

The propositus (Fig. 1) was born two years after a first pregnancy had ended in spontaneous abortion in the third month. At the proband's birth, the mother was 25 years, the father 34 years, of age. Both are normal clinically. The pregnancy was uneventful, delivery was at term and uncomplicated. Birth weight was

2700 g, length 53 cm, head circumference 34 cm.

At the age of 8 months, body weight was 8800 g, length 67 cm, head circumference 45 cm. Psychomotor development was retarded, the baby was unable to sit, contactless and dentition has not yet started.

The infant displayed a number of dysmorphic symptoms such as microcephaly, ptosis of eyelids, microphthalm-



FIG. 1. The proband at 8 months of age



FIG. 2. The abnormal chromosome No. 4 found in the proband

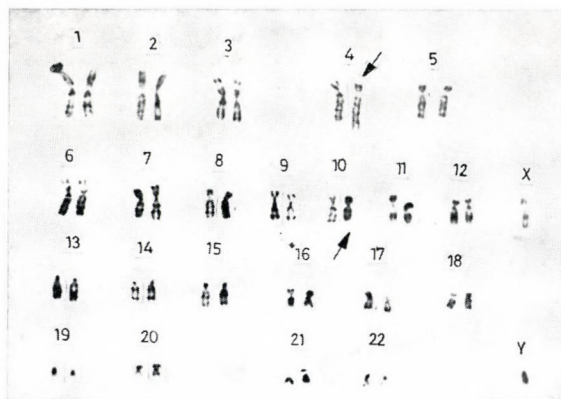


FIG. 3. The balanced translocation, $t(4; 10)$ (q33; q24) in the karyotype of the father

mia with blepharophimosis and antimongoloid slants, small nose with depressed bridge, spacious forehead, micrognathia, malformed left ear, short neck, umbilical hernia, limitation of hip movements and hydrocele on the right side. The upper extremities showed hypertonicity and X-rays revealed a thoracolumbal kyphoscoliosis. Apart from an inspiratory stridor, other findings (cardiology, EEG, kidneys, etc.) were normal.

CHROMOSOME STUDY

Chromosome studies of peripheral blood cultures revealed an abnormal chromosome No. 4 of the proband (Fig. 2). The abnormality proved to be a derivate chromosome from the

balanced translocation of the father. The father has a translocation between the chromosomes No 4. and 10, (4; 10) (q33; q24) Fig. 3). On the basis of the identification of the paternal balanced translocation, the proband's karyotype is 46,XY,der(4),t(4; 10) (q33; q24) pat. Consequently, the malformed child shows a trisomy for the segment of 10q 24—qter of chromosome No. 10.

The same balanced translocation was present in both paternal grandparents.

PEDIGREE ANALYSIS

As can be seen from the pedigree (Fig. 4), the paternal grandparents (I. 2 and I. 3) of the proband are second degree relatives and both have

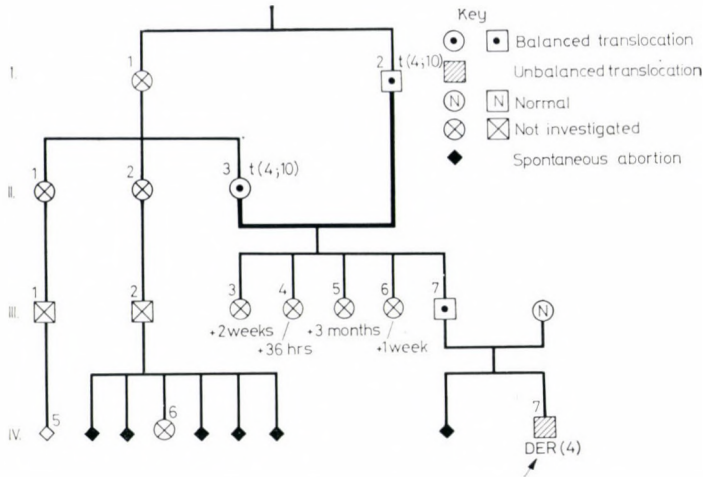


FIG. 4. The pedigree

the same balanced translocation. One may suppose that one of the parents of the grandfather and one of the grandparents of the grandmother must have had the same balanced anomaly and transmitted it to their offsprings. In this way, the chromosome anomaly must have passed through at least five generations.

Four out of five offsprings from the marriage of the grandparents (III. 3, III. 4, III. 5, III. 6) died in early infancy. They were all born at home and also died there. In this way no data could be obtained on their condition and the cause of death. It is, however, assumed that the bilateral heterozygosity had led to unbalanced chromosome abnormality in the offsprings and the cytogenetic anomaly manifested itself in fatal malformations.

The other relatives of the proband, the two sisters of the grandmother

(II. 1 and II. 2) as well as their offsprings, could not be contacted.

DISCUSSION

Partial trisomy of chromosome 10 has been reported on several instances. In most of them trisomy for the distal part of the long arm was found in the karyotypes. Only one out of the reported 16 cases of 10q trisomy was described as a *denovo* chromosome mutation [10], the others originated from familial chromosome anomalies [1-9, 11-15]. In the reported families including our case, paternal transmission occurred seven times, maternal transmission in nine cases. The familial cytogenetic aberration was pericentric inversion in one case [1], the others were familial translocations that could mostly be followed through three or more generations.

TABLE I
The main clinical symptoms found in 11 patients with 10q trisomy

	Dutrillaux et al 1973	Foraboso et al 1975	Krøyer and Niebuhr 1975	Laurent et al 1973	Mulcahy et al 1974	Prieur et al 1975	Roux et al 1974	Tavlik et al 1973	Tsuchimoto and Bühler 1974	Yunis and Sanchez 1974	Present case
Age of proband	4.5m		18y	9m	17d	2.8m		11m	2d	6y	8m
Sex of proband	M	M	F	F	M	M	M	M	M	M	M
Trisomic segment	q24-qter	q24-qter	q25-qter	q22-qter	q24-qter	q24-qter	q24-qter	q24-qter	q22-qter	q34-qter	q24-qter
Balanced carrier	mother	father	father	mother	mother	father	mother	father	mother	father	father
Familial aberration	inv(10)	t(10; 18)	t(10; 18)	t(1; 10)	t(10; 13)	t(10; 17)	t(10; 22)	t(10; 14)	t(10; 15)	t(10; 15)	t(4; 10)
Hypotrophy	+	+	+	+	+	+	+	+	+	+	+
Mental retardation	+	+	+	+	+	+	+	+	+	+	+
Hypotonia	+	-	+		+	+	-	-		+	-
Hypertonia	-	-	-		-	-	-	+		-	+
Microcephaly	-	+	+			+	+	+	+	+	+
Characteristic face	+	+	+	+	+	+	+	+	+	+	+
Skeletal anomaly	+		+					+		+	-
Scoliosis		+	+	+		+		+		+	+
Visceral malformation	-	+	-		+			+			-

The banding technique allows to identify the size of the trisomic segment. In the reported cases it was the distal half of the long arm that occurred three times in the karyotypes of the patients. This means that it is possible for the zygote carrying the trisomy of this segment to avoid the effect of prenatal selection.

The characteristic clinical manifestations of 10q trisomy are as follows [11]. Growth retardation is the rule. The facial dysmorphism is characteristic, the patients resemble each other and are often referred to cytogenetic investigation with the suspicion of Down syndrome. The main clinical features of this chromosome syndrome are,

low birth weight;

somatic and severe mental retardation;

broad, round and flat face, high forehead, ptosis, narrow palpebral fissures with epicanthal folds, microphthalmia, small nose, prominent malar region, micrognathia, low set and poorly formed ears;

joint laxity, scoliosis, congenital heart defects and kidney malformations.

The main clinical findings of patients with trisomy of the long arm of chromosome 10 reported in the literature are summarized in Table I.

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M. OSZTOVICS, M. D.

Gyáli út 4

H-1966 Budapest

Pentamidin-Behandlung der kongenitalen generalisierten Candidiasis

Von

G. TÓTH, G. MIKLÓS, A. KERÉKES, J. KATONA und D. SZARVAS

Städtisches Krankenhaus, Kecskemét, Ungarn

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Es wird über die Pentamidin-Behandlung von 7 an kongenitaler generalisierter Candidiasis und von 1 an Candida-Sepsis leidenden Neugeborenen berichtet. Das Mittel wurde sechs Tage lang in Dosen von 4 mg/Tag i. m. verabreicht. Mit dieser Therapie konnte eine rasche Heilung der auf Lokalbehandlung nicht reagierenden Hauterscheinungen erzielt werden. Nach 7-Stägiger stationärer Behandlung wurden die Patienten in geheiltem Zustand entlassen.

Die durch *Candida albicans* verursachte und sich beim Neugeborenen generalisiert manifestierende Krankheit ist keine Seltenheit. Die durch die Krankheit im allgemein betroffene Mundschleimhaut und Glutealgegend reagieren auf die Lokalbehandlung gut [1, 18]. Diese Form der Candidiasis entsteht als Folge einer intra- oder postpartalen Schädigung [5, 6, 11, 25, 38].

Die Häufigkeit der vaginalen Candidiasis schwankt zwischen 20–50% [19, 23, 26]. Der Aszension zufolge kann es, meistens nach frühem Blausprung, zu einer intrauterinen Infektion kommen [2, 4, 5, 7, 20, 23]. Bei den auf diese Weise infizierten Neugeborenen erscheinen generalisierte Symptome innerhalb von 12 Stunden nach der Geburt. Mit der kongenitalen Hautcandidiasis befaßt sich nur eine geringe Zahl der Mitteilungen [7, 9, 17, 18, 21, 24, 27, 28]. Die Krankheit tritt charakteristischerweise generalisiert auf und verbreitet sich auf die Flexuren, auf den Rumpf, den Kopf und auch auf die Extremi-

täten. Die Hautausschläge erscheinen in Form makulo-papulöser, stecknadelkopf- bis halblinsengroßer Blasen und Pusteln, die ein entzündlicher Hof umringt. Sobald die Blasen platzen, kann Exfoliation beobachtet werden. Der Nachweis des Erregers aus dem Vesikelinhalt bietet eine wesentliche Hilfe zur Feststellung der Diagnose.

Obwohl der antifungale Effekt von Pentamidin wohlbekannt ist, wird von einigen Autoren die per os bzw. lokale Anwendung von Nystatin und bei Candida-Sepsis die Verabreichung von Amphotericin B, Clotrimazol und Flucytosin empfohlen [8, 9, 10, 11, 13, 14, 15, 22, 26, 27, 28, 29, 30, 31, 32, 33, 35, 39]. Unsere mit Pentamidin gewonnenen vorteilhaften Erfahrungen veranlaßten uns zur Erläuterung unserer Beobachtungen.

MATERIAL UND METHODIK

An unserer Neugeborenen-Abteilung wurden zwischen 3.10.1974 und 31.10.1976 insgesamt 5250 Neugeborene behandelt.

In 7 dieser Fälle konnte generalisierte Candidiasis registriert werden und in einem weiteren Fall meldeten sich die klinischen Symptome 2 Wochen nach der Geburt.

In Fällen mit charakteristischen Symptomen gelang es uns, die Hyphenfaden mit Gram-Weigertscher Färbung in den Vesikeln ausnahmslos nachzuweisen. Zu Beginn kam eine lokale Behandlung zur Anwendung, wenn aber die Krankheit progredierte, wurde Pentamidin sechs Tage hindurch in Tagesdosen von 4 mg/kg i. m. verabreicht.

Im Interesse der Feststellung der wirksamen Dosis wurden in vitro Untersuchungen vorgenommen: Pentamidin wurde in verschiedenen Konzentrationen (1, 10, 50, 100, 150, 200, 250 und 500 µg/ml und 1, 2, 4 mg/ml) dem Sabouraud-Nährboden beigemischt und der Nährboden mit *Candida albicans* infiziert. Die Kulturen wurden 24 Stunden lang bei 37 °C inkubiert und dann weitere 48 Stunden lang bei Zimmertemperatur gehalten, das Ablesen erfolgte nach 72 Stunden. Die Untersuchungen führten zur Feststellung, daß Pentamidin eine von der Konzentration abhängige, wachstumshemmende Wirkung entfaltet, die bei 100 µg/ml erkennbar aber noch nicht ausgeprägt ist, während bei einer Konzentration von 2 mg/ml die Vermehrung der Pilze praktisch aufhört.

FALLDARSTELLUNGEN

Fall Nr. 1. N. L. Der Knabe kam aus einer durch Blasensprung bedingte Frühgeburt zur Welt. Die Mutter litt an Scor-Vaginitis. Plazenta und Nabelschnur zeigten keine makroskopischen Veränderungen. 10 Stunden nach der Geburt erschienen vorne und hinten am Rumpf und an den Händen stecknadelkopf- bis linsengroße Flecke und Blasen. Die Blasen konnten nur schwer aufgerissen

werden. Bepinselung mit Resorcinsalicylat blieb erfolglos, der Prozeß zeigte eher eine Progression. Aus dem Blaseinhalt wurde *Candida albicans* gezüchtet, die Pilzfäden konnten deutlich beobachtet werden (Abb. 1). Hiernach wurde Pentamidin in Tagesdosen von 4 mg/kg i. m. verabreicht. Vom 2. Behandlungstag an meldeten sich keine neuen Eruptionen und am 5. Tag zeigte die Haut nurmehr eine kleingradige Exfoliation. Am 7. Lebenstag wurde der Säugling entlassen. Die übrigen sechs Fälle zeigten einen ähnlichen Krankheitsverlauf.

Fall Nr. 2. Zs. V. Der neugeborene Knabe wurde im Alter von 2 Wochen wegen disseminierter Hautveränderungen, mit der Diagnose bullöse, generalisierte Urtikarie in unsere Abteilung eingewiesen (Abb. 2); bei der Aufnahme konnte auch mäßiger Soor oris beobachtet werden. Hämokultur auf flüssigem Sabouraud-Agar: *Candida albicans*; im Blaseinhalt Pilzfäden (Abb. 3); Züchtung des Blaseninhalts; *Candida albicans*. Da die Krankheit nach 2tägiger lokaler Behandlung mit Boraxglyzerin, und Resorcinsalicylat eher progredierte, gingen wir auf 4 mg/kg/Tag Pentamidin über. Der Zustand des an Candida sepsis leidenden Neugeborenen war am 6. Tag fast normalisiert; nach 8tägiger stationärer Behandlung wurde das Kind in geheiltem Zustand entlassen.

BESPRECHUNG

Pentamidin ist ein allgemein anerkanntes Mittel bei der Behandlung der interstitiellen, plasmazelligen

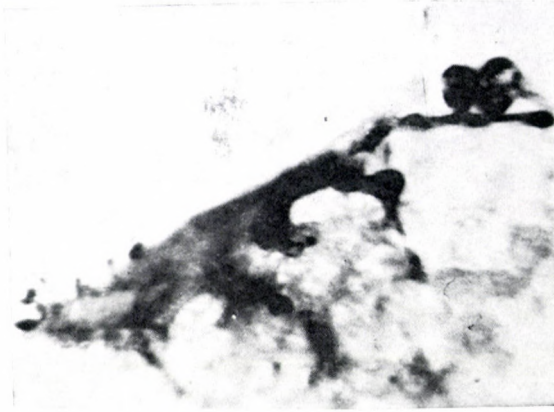


ABB. 1. *Candida albicans* im aus dem Blaseninhalt verfertigten Ausstrich. Gram-Weigert-Färbung, Ölimmersion, Vergr.: $16 \times 100/1,25$

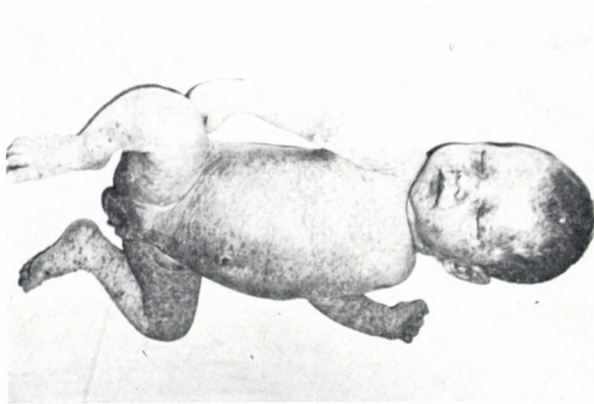


ABB. 2. Zs. V. zweiwöchiger Säugling bei der Aufnahme

Pneumonie [3, 16, 34], bei kongenitaler, generalisierter Candidiasis bzw. Candida-Sepsis fand es jedoch keine Anwendung. Die sich mit der Behandlung dieser Krankheiten befassenden neuesten Mitteilungen empfehlen die Verabreichung von Amphotericin-B, Clotrimazol und Flucytosin [8, 9, 10, 11, 13, 14, 18, 22, 26, 27, 32, 33, 35]. Die Anwendung dieser Mittel ist aber wegen ihrer unerwünschten Nebenwirkungen riskant. Die Nebenwirkungen

von Pentamidin melden sich seltener, sie sind größtenteils reversibel und weniger schwer [12, 36, 37]. Unsere in vitro Untersuchungen ergaben den Beobachtungen von IVÁDY und FRIEDRICH [15] und STENDERUP und Mitarb. [30, 31] nahestehende Ergebnisse. Einerseits diese, andererseits die befriedigende, rapide Wirkung, ohne Nebenwirkungen, die wir im Laufe der Behandlung unserer Fälle beobachteten sprechen dafür, daß Penta-

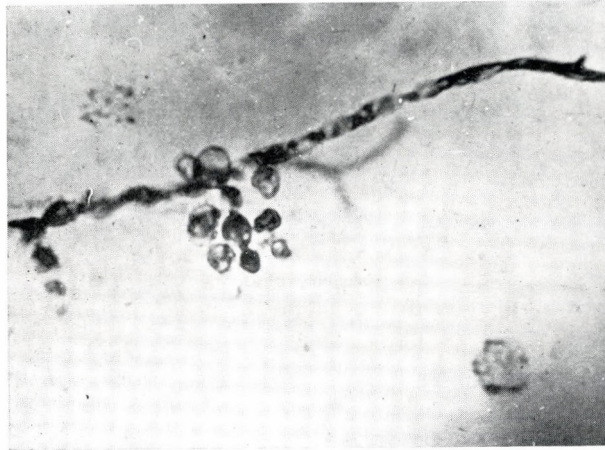


ABB. 3. *Candida albicans* im aus dem Blaseninhalt verfertigten Ausstrich. Gram-Weigert-Färbung, Ölimmersion, Vergr.: $16 \times 100/1,25$

midin in der Therapie der kongenitalen generalisierten Candidiasis und der Candida-Sepsis eine erfolgreiche Anwendung finden kann.

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Chefarzt Dr. G. TÓTH

Megyei kórház

H-6001 Kecskemét, Ungarn

Mumps meningitis: Electroencephalography and leukocyte migration inhibition by basic myelin protein

By

G. KÁLI, Ottilia UJHELYI and G. NYERGES

László Hospital for Infectious Diseases, Budapest

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In 20 patients with mumps meningitis, electroencephalography and leukocyte migration inhibition tests with basic myelin protein were carried out. Fourteen patients had mild or moderate EEG abnormalities indicative of encephalitis as well. Cellular reactivity to basic myelin protein was found in 4 cases only. The observations support the concept that mumps meningo-encephalitis is a consequence of a direct viral impact onto the nervous tissue, i.e. no neuroallergic mechanisms are involved.

In a previous study on uncomplicated measles with EEG-changes, cellular reactivity to human basic myelin protein could be demonstrated by the leukocyte migration inhibition (LMI) technique [10]. The findings were similar to those found in measles and rubella encephalitis [11].

It has suggested that the pathogenesis of mumps meningoencephalitis was different from that of the parainfectious encephalitides in the majority of cases [2]. It seemed therefore interesting to test whether a cellular reactivity to brain tissue antigen occurred in mumps meningoencephalitis and, if so, whether there was any correlation between this reactivity and the EEG-changes observed in these patients.

MATERIALS AND METHODS

Patients. Twenty 3 to 9-year-old hospitalized mumps meningitis patients were investigated. All of them had parotitis as

well. In one case the neurological symptoms appeared two days before the parotid glands had become swollen, in two cases they presented simultaneously, while in the others, nervous system involvement manifested 2 to 7 days after the onset of parotitis. The diagnosis of mumps virus infection was confirmed in each case by a rise of the complement fixing antibody titres of the patients' sera during their illness.

Clinically all patients had aseptic meningitis; mild focal signs (nystagmus, Babinski sign) were observed in five cases only. The CSF cell count ranged from 310 to 3200 per μ l; the cells were predominantly lymphocytes. The protein content of the CSF varied between 31 and 210 mg per dl, while glucose values were within the normal range. CSF-findings normalized within 2 to 4 weeks. All patients recovered without sequelae.

Electroencephalography was carried out by an Alva Reega-VIII type portable encephalograph. Fifteen electrodes were applied to the frontopolar, precentral, central, parietal, occipital and three temporal areas. Bipolar conventional leads were used. The time constant was 0.3 sec. Paper speeds were 15 and 30 mm per sec.

A three-min hyperventilation was applied in each case. The recordings were analysed visually.

EEG-tracings were carried out in all cases on the first day after admission, i.e. during the acute phase of the disease. In cases showing EEG-alterations, tracings were repeated at 3 to 5-day intervals until the EEG had normalized.

LMI tests were carried out by the method of Søborg and Bendixen [16]. Basic myelin protein prepared from human brain according to Kies [8] was used as antigen at a concentration of 100 μg per ml in the test chambers. Migration indices (MI) were calculated as described previously [11]. MI-s less than 0.8 proved significant when evaluated with Student's *t*-test and were therefore considered "positive". In previous investigations we showed that the MI values of normal persons were invariably above 0.8 when using the basic myelin protein as an antigen. Therefore no control group was included in this study.

Each patient was tested twice, once during the acute phase and once during convalescence. The shortest interval between the two tests was two weeks.

RESULTS

In the acute phase, EEG-alterations were found in 14 of the 20 patients. Twelve of them showed a slight, and two a moderate slowing of the background activity (Fig. 1). Besides, circumscribed excitement-signs were observed in one temporal or temporo-occipital area manifesting with sharp wave-inversions or abortive spikes in six cases (Fig. 2). The latter signs were seen even at the second examination in two cases. Out of the 14 altered EEG, 9 had normalized by the second, 3 by the third and 2 by the fourth examination.

MI values during the acute and convalescent periods are presented in Fig. 3. Table I shows the means, the standard deviations and the ranges. In the acute phase only 4 patients had a slightly positive MI and during convalescence all MI values were normal. Though the mean MI values for the acute and convalescent periods slightly differed from each other, the difference was not significant statistically ($t = 1.69$; $p = 0.1$).

TABLE I

MI in 20 mumps meningoencephalitis patients tested by basic myelin protein

	Acute phase	Convalescence
Mean \pm SD	0.903 \pm 0.072	0.947 \pm 0.078
Range	0.74 \pm 1.02	0.82 - 1.10

Though all of the patients with a significant MI had EEG alterations, 10 patients with EEG alterations had normal MI values.

No correlation was found between MI values and the time that elapsed between the onset of parotitis and the appearance of neurological signs. Similarly, there was no correlation between MI values and CSF changes or focal signs.

DISCUSSION

Clinically, our cases were aseptic meningitides with occasional mild focal neurological signs, while EEG changes could be found in 14 out

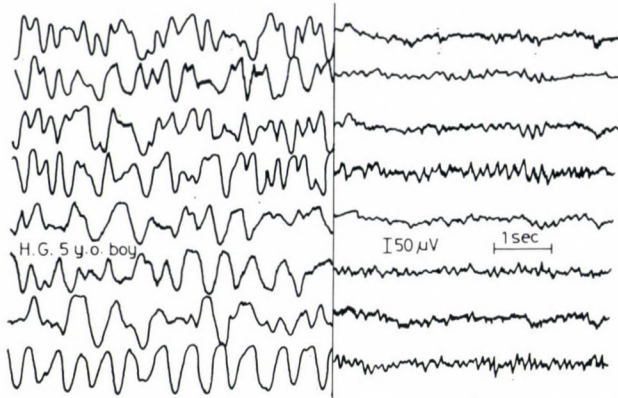


FIG. 1. H. G., 5-year-old boy. Mumps meningoencephalitis. I. EEG in the acute phase: polyrhythmic high amplitude delta and theta waves. II. EEG one month later: background activity consists of alpha waves with 7 c/s theta episodes (physiologic EEG)

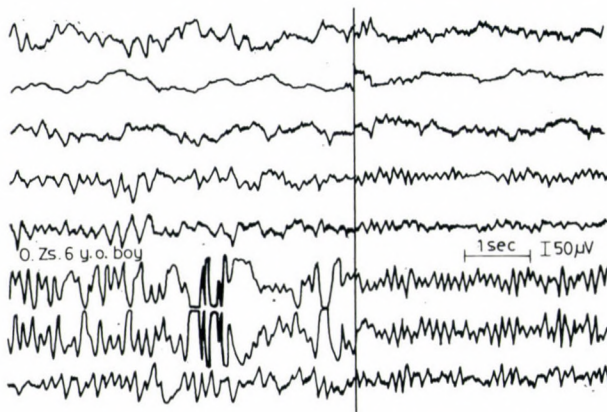


FIG. 2. O. Zs., 6-year-old boy. Mumps meningoencephalitis. I. EEG in the acute phase: slight diffuse slowing and left-sided temporo-occipital sharp and slow wave complexes. II. Ten days later: 8/sec alpha rhythm. Normal EEG



FIG. 3. MI values of 20 mumps meningoencephalitis patients tested by basic myelin protein

of the 20 patients. Schmidt and Hofmann demonstrated EEG changes in mumps meningoencephalitis even more frequently [14]. Thus, there is little doubt that EEG signs of encephalitis are more frequent in mumps meningitis than it could be expected on the basis of the clinical symptoms. This observation is similar to that found in uncomplicated measles [4, 5, 6, 7, 10, 13]. However, while sensitization to myelin, i.e. a positive LMI with basic myelin protein was observed in uncomplicated measles with EEG changes [10], this was not the case in the majority of mumps meningoencephalitis cases. Even in the few patients where a slight transient sensitivity could be revealed, the rapid and uneventful recovery makes the pathogenetic role of this sensitization very unlikely. Accordingly, our observations indirectly support the concept that mumps meningoencephalitis is a consequence of a direct viral impact onto the nervous tissue [2, 3, 9, 12, 18], i.e. no autoimmune processes are involved. In fact, demyelination has been described in a few lethal mumps meningoencephalitis cases [1, 3, 15, 17]. It would be of interest to know whether LMI tests are positive in such cases. Fortunately, no case was lethal in our material.

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G. KÁLI, M. D.

Gyáli út 5

H-1097 Budapest

Comparison of nitrite and dipslide methods for bacteriuria screening

By

G. JÓJÁRT and I. ÉDER

Municipal Hospital, Cegléd, Hungary

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The results of screening for bacteriuria by the nitrite reaction and the dipslide method were compared. The nitrite reaction was specific in 99.8%, its sensitivity was 93.1% and its reproducibility, 100%. Specificity of the dipslide method was 94.5%.

The nitrite reaction is considered most suited for screening, owing to its specificity, satisfactory sensitivity, short time requirement and low cost. The dipslide method is not suited for screening, as apart from being expensive it yielded 5.5% false positive reactions, but proved excellent for estimating the bacterial count in nitrite positive samples.

In bacteriuria the freshly voided urine has a bacterial count of 10^5 /ml or more. In urine specimens contaminated during urination the count is mostly below 10^4 /ml [21, 29]. When the bacterial count is higher than 10^5 /ml it is called significant bacteriuria to distinguish it from contaminated urine.

Bacteriuria may occur in itself, without other clinical or laboratory signs of urinary tract infection. The significance of this isolated or monosymptomatic bacteriuria is questionable [32, 36]. Urinary tract infections are often asymptomatic and their early detection is decisive for the patient's fate. Their earliest and most persistent symptom being bacteriuria, the importance of screening has been stressed [7, 21, 27].

Bacteriuria can be demonstrated by bacteriological and chemical methods. The bacteriological methods are ba-

sed on the fact that each bacterium in the urine will form a colony on a suitable medium and the bacterial count allows to conclude to the bacteriuria being significant or the result of contamination. Since the bacteria themselves are demonstrated, the method is very sensitive but needs 24 hours culturing before the result can be read. The simplest such test is the extensively applied dipslide method. The sterile slide covered on both sides with culture medium is dipped into urine and incubated in its container for 24 hours. The quantity of urine adhering to the surface of the cultures is always identical, therefore from the density of the developing colonies the bacterial count can be estimated. Serial examinations proved that the method was reliable and equivalent with the pour plate method [3, 4, 7, 17, 26]. Sensitivity of the dipslide test remains unchanged

on incubation at room temperature, only the growth of Gram positive microorganisms is then slower [3, 4].

The chemical methods demonstrate instead of the bacteria some of their metabolic products. Since the bacteria produce different metabolic substances, the chemical methods are less sensitive. Their advantage is that they supply results within a short time, they are simple and inexpensive. The great majority of bacteria causing urinary tract infection reduces urinary nitrate to nitrite. Nitrite can promptly be demonstrated in the urine without false positive reactions, but a positive finding fails to supply information on the strain and antibiotic sensitivity of the microorganism.

With both methods, freshly voided urine is needed, since on standing the number of contaminating bacteria will be increased.

In the present study we have compared the dipslide method with the nitrite reaction.

MATERIAL AND METHODS

The examinations were performed in 6 to 14 years old children of primary schools. They were told to hold their urine for 3 to 4 hours, then to urinate into a plastic container washed with tap-water. The interval before urination could not be controlled, but when a small quantity was voided, a negative nitrite reaction was not evaluated. The urinary specimens were examined immediately.

The nitrite reaction was performed with the Griess—Hosvay reagent modified by Csokonay [10], consisting of 0.4 g alpha-naphthylamine and 0.5 g sulphanilic acid dissolved in 170 ml 20% sulphosalicylic acid.

When 4 to 5 drops of the reagent are added to about 2 ml urine, in the presence of nitrite a red colour develops within 2 minutes. In the presence of protein, a clouding as in the sulphosalicylic acid test is observed. The reagent keeps at room temperature in a dark bottle for at least 6 months.

For the dipslide method Uricult® (Orion, Helsinki) slides were used. After dipping in urine, they were incubated for 24 hours at room temperature previous to reading. Sampling and reading of results were performed in each case by the same person. When the count was 10^5 or higher the microorganism cultured on the slide was identified and its antibiotic sensitivity determined.

The examinations were performed in 3 groups.

I. The urine of 628 girls was screened by both methods.

II. Dipslide screening was performed with 257 urines. These were selected from among 6000 girls screened by the nitrite reaction. Their urine was nitrite positive, or when it was negative, the girls were suspect of bacteriuria. Suspicion of bacteriuria arose when the urine was clouded and no clearing occurred on the addition of the acid nitrite reagent, or when the child had complaints like enuresis or frequent micturition.

Group III included 51 treated girls who had a reinfection. Their urine was examined by both methods.

The children in whom the dipslide demonstrated a bacterial count of 10^5 or higher, were called back for examination and their mid-stream urine was tested for nitrite reaction, dipslide count and urinary sediment.

The children were considered bacteriuric, when

1. the nitrite reaction was positive and the dipslide revealed a count $\geq 10^5$;
2. the dipslide demonstrated a $\geq 10^5$ bacterial count at least twice and on both occasions a pure culture of the microorganism was obtained with identical antibiotic sensitivity.

In one of the children the nitrite reaction was positive on four occasions: and in all the four instances a pure culture of *Staphylococcus albus* was obtained. At screening the dipslide gave a count of 5×10^3 . The child was considered bacteriuric; the low count was due to the slow growth of staphylococci at room temperature [3, 4]; visible colonies failed to develop from each microorganism.

RESULTS

Group I. Among the unselected 628 girls screened, the urine of 623 was nitrite negative and of 5 nitrite positive. The dipslide method gave a bacterial count of $\geq 10^5$ in 39 cases and one of $\leq 5 \times 10^4$ in 589 cases (Table I).

TABLE I

Dipslide	Nitrite			Total
	positive	negative		
		No.	per cent	
$\geq 5 \times 10^5$	5	17	2.7	22
10^5	—	17	2.7	17
5×10^4	—	28	4.5	28
10^4	—	44	7.1	44
$\leq 5 \times 10^3$	—	396	63.6	396
Sterile	—	121	19.3	121
Total	5	623	100.0	628
Bacteriuric	5	—	—	5

Repeated examination verified bacteriuria in only 5 among the 39 girls; the others were false positive findings. The urine of the 5 bacteriuric girls was nitrite positive.

Group II. Among the 257 selected girls a positive nitrite reaction was

obtained in 77 cases. The dipslide demonstrated a count of $\leq 10^5$ in 90 cases (Table II).

TABLE II

Dipslide	Nitrite		Total
	positive	negative	
$\geq 5 \times 10^5$	75	9	84
10^5	—	6	6
5×10^4 —	—	12	12
10^4	—	8	8
$\leq 5 \times 10^3$	1	100	101
Sterile	1	45	46
Total	77	180	257
Bacteriuric	76	6	82

Among the 77 children voiding nitrite positive urines 76 suffered from bacteriuria; among these a bacterial count of $\geq 10^5$ was found in 75. The dipslide of the girl with *Staphylococcus albus* bacteriuria was negative (5×10^3). In one girl a false positive nitrite reaction was observed.

Group III. In the 51 girls with reinfection the count was $\geq 10^5$ in each specimen, the nitrite reaction was positive in 50 cases.

Specificity of the nitrite reaction. In the three groups 132 positive nitrite reactions were observed: among these one was false positive. Thus among 804 non-bacteriuric cases only one was false positive, thus the specificity was 99.8%.

Sensitivity of the nitrite reaction. Routine screening was performed by both methods in 628 girls. All the 5 bacteriuric girls voided a nitrite posi-

tive urine, but the low number of positive cases does not permit to evaluate the sensitivity.

The summarized data of Groups I and II are already sufficient to determine the sensitivity. Among the 87 bacteriuric children, 81 had a nitrite positive urine, thus the sensitivity of the reaction in this material was 93.1%. This sensitivity would only be real if among the 6000 screened girls all those with bacteriuria would have been selected. The majority of bacteriuric urines is slightly clouded, thus the expectation may be justified that further examination of clouded urines would allow to detect almost every bacteriuric child. The 628 routine dipslide examinations also supported this high sensitivity, the number of cases, however, was too low for reliable evaluation.

Reproducibility of the nitrite reaction. Among the 82 girls nitrite positive at screening, 68 were suffering from persistent bacteriuria. One reaction was false positive, 13 girls had transitory bacteriuria. (It has been shown that bacteriuria disappears spontaneously in 15 to 30% of cases [6, 33, 38]). Repeated dipslide examination of the latter was negative. In our material the reproducibility of the reaction for persistent bacteriuria was 100%. The 6 girls included in Group II, who had false negative nitrite reactions, had a nitrite positive first morning urine at reexamination.

Specificity of the dipslide method. In the course of the routine examination of Group I, among the 623

non-bacteriuric girls 34 false positive dipslide results were obtained. The specificity of the method in this material was 94.5%. The incidence of false positivity was 5.5%.

Sensitivity of the dipslide method. According to data in the literature the method's sensitivity is satisfactory, corresponding to that of other bacteriological methods [3, 4, 7, 17, 26, 30, 31, 37].

DISCUSSION

Requirements of a satisfactory screening method for bacteriuria are an adequate sensitivity; an adequate specificity; simplicity; and low cost.

According to several authors, sensitivity of the nitrite reaction is unsatisfactory, between 40 and 70% [7, 15, 20, 23, 26, 39, 40]. This conclusion was drawn from examinations where the reaction was compared to bacteriological methods. In a number of cases it was not controlled whether the persons selected by bacteriological methods had real bacteriuria on repeated examination or the culture produced a false positive result. Other authors drew conclusions from urine samples brought to the laboratory after an unknown interval.

Kass [22] described that when midstream urine was examined after careful washing, in 20% of the women with a bacterial count of $\geq 10^5$ the repeated examination was negative. According to other data, with bacteriological methods the ratio of false positive reactions is even higher. By screening tests 1.5 to

13.5% urine specimens may be false positive, that is 1.3 to 7.5 times as much as the number of persons with real bacteriuria [1, 5, 11, 12, 13, 14, 16, 21, 24, 25, 32, 34, 36, 42]. The specificity of bacteriological methods is rather uncertain; in our screening examination it amounted to 94.5%. Thus, the above results reflect the low specificity of bacteriological methods rather than the low sensitivity of the nitrite reaction.

In our examinations the sensitivity of the nitrite reaction reached 93.1%.

Alwall and Lohi [2] reported on a similarly satisfactory sensitivity of the nitrite reaction: in their adult urological patients they found a sensitivity of 95%. Among clinical patients it was 70%, but the basis of comparison was a bacteriological method, without excluding the possibility of false positive reactions. Examining the first morning urine of adult women, Czerwinski et al. [8, 9] found a sensitivity of 92 to 94%, Fritz [14] 89%, Wallmark et al. [41] 84%, at 5 hours after voiding. According to Randolph and Morris [35], among female children the sensitivity of the nitrite reaction in the first morning urine is 92.8%. The two false negative girls had megacystis and the false negative reaction was due to urine retention.

When the interval after previous micturition is short, sensitivity of the reaction in adults is 25 to 50% [2, 8, 9]. The nitrite reaction is of high sensitivity only in those cases where the examination is carried out following an urination interval of 3

to 4 hours. After an appropriate interval between micturitions, all our 6 false negative patients voided nitrite positive urines.

The specificity of the nitrite reaction is satisfactory; according to the literature it exceeds 99% [2, 8, 15, 39, 41]; in our material it was 99.8%. The specificity of the dipslide method, similarly as that of other bacteriological methods depends on urine sampling. When many subjects are screened, due washing will considerably prolong the examination, but without washing there will be a number of aspecific reactions.

Both the nitrite and the dipslide tests are simple to carry out. The nitrite test supplies immediate results; the child can be ordered back promptly for reexamination. The dipslide result, on the other hand, takes 24 hours before it can be read and requires more manipulation and administration.

Finally, against the relatively high cost of the dipslide test the cost of the nitrite reaction is negligible.

Thus, for screening for bacteriuria we recommend the nitrite reaction carried out in urine voided at least 3 to 4 hours after the last micturition. The most appropriate is the first morning urine. In positive cases the bacterial count should be determined by the dipslide method. The cultured organism is then identified and its antibiotic sensitivity is determined. The positive children should report for reexamination after 3 days. When the control result is again positive, treatment should be started.

Suspect for bacteriuria are the turbid or clouded urines which do not clear up on the addition of the nitrite reagent. Large floating parts indicate the presence of vaginal exudate, whereas in the case of bacteriuria the urine is finely clouded. When such urines yield a bacterial count $\geq 10^5$, a control examination should be carried out.

Owing to its high cost and low specificity, with the 5.5% incidence of false positive results, the dipslide method is not suited for screening examinations, in agreement with the opinion of Manners et al. [28]. On the other hand, the method is excellently suited for estimating the bacterial count in nitrite positive urines suspect of significant bacteriuria.

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G. JÓJÁRT, M. D.

Városi Kórház

H-2701 Cegléd, Hungary

LDH-Isoenzymaktivität der peripheren T- und B-Zellen bei Neugeborenen mit unterschiedlichem Gestationsalter

Von

L. KARMAZSIN, Hedvig CSERNYÁSZKY, Anikó MAKAY und Margit SZÖVETES

Kinderklinik und Pathophysiologisches Institut der Medizinischen
Universität Debrecen, Ungarn

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Die Separierung der T- und B-Lymphozyten gesunder, reifer Neugeborenen und Frühgeborenen (Gestationsalter: zwischen der 23. und 33. Woche) erfolgte anhand der LDH-Isoenzymaktivität der Zellen. Die Erfahrungen zeigten, daß sich die Methode zur Ergänzung bzw. zum Ersatz der auf Oberflächenmarker beruhenden Techniken eignet. Zwischen reifen Neugeborenen und Frühgeborenen konnten gewisse Unterschiede erkannt werden: Bei den Frühgeborenen war die Aktivität der LDH-1 Fraktion der B-Zellen und der LDH-5 Fraktion beider Zelltypen insbesondere aber der B-Zellen höher als bei den reifen Neugeborenen. Die Methode hat sich zur Erschließung der sich in der fötalen Periode differenzierenden Zellen als brauchbar erwiesen.

Bekanntlich können zwei Populationen der peripheren Lymphozyten separiert werden, namentlich die T- oder Thymus dependenten Zellen sowie die B- oder Thymus independenten Zellen. Der Identifizierung der beiden Zellpopulationen liegt der Charakter der Oberflächen-Immunglobuline zugrunde. Auf der Oberfläche der B-Zellen befinden sich mindestens drei Oberflächen-Rezeptoren: der modifizierte komplementbindende Rezeptor, der aggregierte IgG-bindende Rezeptor und der Immunglobuline bindende Rezeptor.

Zum Nachweis der komplementbindenden Rezeptoren eignen sich zahlreiche Methoden [1, 13, 11, 5]. Die Oberflächen-Immunglobuline bindenden Rezeptoren werden mit Fluoreszein konjugierten Antiimmunglobulinen nachgewiesen; neuestens bot sich auch zur Anwendung der Anti-

körper gegen die Schwer- und Leichtketten der Immunglobuline eine Möglichkeit [5, 2, 3]. Die zum Nachweis der mit den aggregierten Immunglobulinen reagierenden Rezeptoren dienende neue Methode wurde von DICKLER und Mitarb. [4] ausgearbeitet.

Zur Separierung der T-Zellen eignet sich der von WYBRAN und Mitarb. [16] sowie JONDAL und Mitarb. [5] ausgearbeitete E-Rosettentest.

Laut der an menschlichen Föten durchgeführten Untersuchungen erscheinen die die B-Lymphozyten charakterisierenden Marker in den hämopoetischen Zellen und Lymphoidgeweben zwischen der 9,5. und 22. Woche. Unter diesen Merkmalen können die die IgM- und IgG-bindenden Rezeptoren tragenden B-Zellen in der Leber und auch die ausschließlich IgM positiven B-Zellen in der Leber

und in anderen Zellen in der 9. Woche nachgewiesen werden. Die IgA-positiven Zellen lassen sich zuerst im 11,5-wöchigen Fötus nachweisen. Unter Anwendung der direkten Fluoreszenz-Antikörpertechnik wurde bewiesen, daß die die Immunglobuline sezernierenden Zellen in der Mitte der 14. Woche erscheinen, wenn die Konzentration der B-Zellen bereits für den erwachsenen Zustand charakteristisch ist. Diese Untersuchungen wiesen ferner darauf hin, daß die T- und B-Zellen zum selben Zeitpunkt erscheinen.

Angesichts dieser Daten erhob sich die Frage, ob uns in der fötalen Lebensperiode, wenn die Entwicklung der Oberflächenmarker der T- und B-Zellen noch nicht beendet ist bzw. in anderen Zuständen, in denen der Nachweis dieser Gebilde wichtig wäre, irgendwelche entsprechende Methoden zur Verfügung stehen, die ohne Ermittlung der Oberflächenrezeptoren zur Selektion der zweierlei Zellpopulationen eine Hilfe bieten würden.

Die Abnahme der Aktivität der in den Lymphozyten von an chronischer lymphatischer Leukämie leidenden Patienten vorhandenen LDH-1-Fraktion der in Richtung der Unreife zeigenden Dedifferenzierung der malignen Zellen verläuft parallel [9, 14]. PLUM und RINGOIR [8, 10] versuchten, die Eigentümlichkeiten der T- und B-Zellen der Lymphozyten von fünf gesunden Erwachsenen anhand ihrer Isoenzymaktivität zu charakterisieren; die Separierung der Zellpopulation haben sie auch aufgrund der Oberflächenmarker durchgeführt (E- und

EAC-Rosettentechnik). Die LDH-Isoenzyme können bekanntlich in sämtlichen Zellen des Organismus vorgefunden werden. Mittels Elektrophorese können — unter Anwendung der das LDH-Molekül aufbauenden zweierlei Untereinheiten, d. h. die Kombination von H—M — fünf Fraktionen der LDH-Isoenzyme separiert werden. Im Laufe der von den Autoren angewandten Zellseparierungsmethode konnten fünferlei Zellpopulationen separiert werden. Aus den separierten Zellen wurde mittels Elektrophorese und spezieller Färbung ein Zymogramm verfertigt; anlässlich der Darstellung dieses Zymogramms mit einem Quick-Scanner-Gerät (Helena Laboratories) wurde das prozentuale Vorkommen von fünf Fraktionen der LDH-Isoenzyme demonstriert. Diese Untersuchungen führten zur Feststellung, daß die T-Lymphozyten auf dem Gebiet der LDH-1-Fraktion, im Vergleich mit den B-Zellen eine signifikante Aktivität zeigen, was gleichzeitig auch soviel bedeutet, daß die Bestimmung der LDH-Isoenzyme die zur Erschließung der Oberflächenmarker gebräuchlichen Methoden ergänzt oder nötigenfalls auch ersetzt.

MATERIAL UND METHODIK

Unser Material bestand aus 10 reifen, gesunden Neugeborenen und 10 Frühgeborenen (zwischen der 28. und 33. Gestationswoche), von denen zur Untersuchung im Laufe der ersten 3 Lebensmonate Blutproben entnommen wurden. Die Zellseparation erfolgte mit der in Abb. 1 schematisch dargestellten Me-

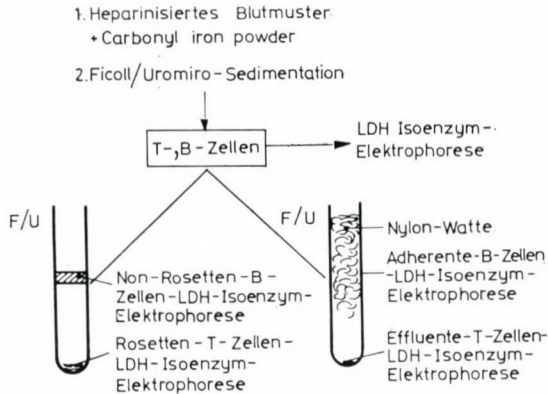


Abb. 1. Schematisch dargestellte Zellseparierungstechnik für fünf Fraktionen

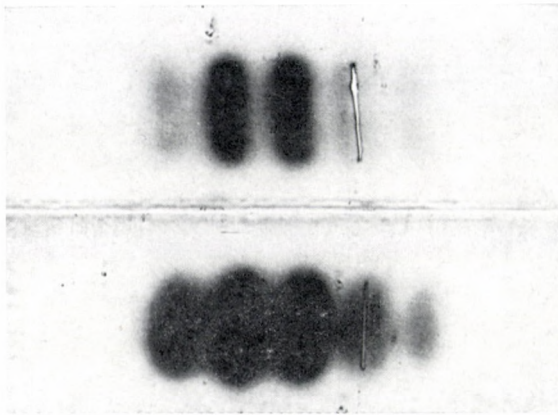


Abb. 2. LDH-Zymogramme unseparierter Lymphozyten: oben: B-Zellen, unten: T-Zellen

thode [8]. In allen fünf Lymphozytensuspensionen wurde die Zahl der E- und EAC-Rosetten bestimmt und auf einem Objektträger auch die Agarose-Gelelektrophorese (30 min, 150 V) durchgeführt; zur Färbung kam das Verfahren von Van der Helm zur Anwendung: Im Laufe der sich in Richtung der Brenztraubensäure abspielenden Reaktion wird der farblose Tetrazolium-Farbstoff durch Phenazinmetosulfat zu farbige, unlösbare Formasankörnchen reduziert und an der Aktivitätsstelle ausgefällt. Das elektrophoretische Bild der Zellpopulationen B und T veranschaulicht Abb. 2 Zur Auswertung des gewon-

nenen Zymogramms diente das Quick-Scan-Gerät (Abb. 3). Die angewandte Zellsuspension jeder einzelnen Fraktion enthielt 2×10^6 /ml Lymphozyten; zur Elektrophorese kamen je 5 Mikroliter dieser Suspension zur Anwendung.

ERGEBNISSE UND KONKLUSION

1. Die von PLUM und RINGOIR [8] beschriebene Methode läßt sich leicht reproduzieren; die mit der Separierung gewonnenen Zellen verfügen über eine befriedigende Vitalität.

TABELLE I
LDH-Isoenzymaktivität der T- und B-Lymphozyten bei reifen Säuglingen

Zellen	LDH-1	LDH-2	LDH-3	LDH-4	LDH-5	Rosetten-Prozent (%)	
						T	B
Nicht separierte Zellen	8,5 ± 3,37 (10-5)	29,75 ± 3,3 (35-29)	38,5 ± 4,43 (44-30)	18,25 ± 1,8 (23-19)	3 ± 1,35 (7-2)	53	42
T-Fraktion, Rosetten- Sedimentation	20,92 ± 3,6 (25-17)	27,79 ± 2,1 (35-26)	30,8 ± 2,29 (36-29)	15,03 ± 1,14 (19-14)	6,27 ± 1,1 (8-4)	68	34
B-Fraktion, Rosetten- Sedimentation	6,93 ± 1,5 (8,7-2)	30,91 ± 2,1 (30-26)	36,06 ± 2,0 (40-35)	21,3 ± 1,36 (24-19)	3,5 ± 0,59 (7-2)	30	60
T-Fraktion, Nylon effluens	15,1 ± 1,7 (20-13)	34,7 ± 2,35 (37-26,2)	33,08 ± 1,9 (36-29)	21,73 ± 1,73 (23-17)	2,76 ± 0,2 (4-1,5)	59	28
B-Fraktion, Nylon adherens	1,45 ± 1,07 (3-0,5)	29,29 ± 2,2 (35-25)	43,3 ± 1,25 (48-40)	22,0 ± 2,34 (25-20,2)	3,71 ± 0,72 (7-3)	30	47

Durchschnitt %
Streuung des Durchschnitts ±
() = Grenzwerte

TABELLE II

LDH-Isoenzymaktivität der T- und B-Lymphozyten bei Frühgeborenen

Zellen	LDH-1	LDH-2	LDH-3	LDH-4	LDH-5	Rosetten-Prozent (%)	
						T	B
Nicht separierte Zellen	13,1 ± 4	27,6 ± 3,35	24,5 ± 1,9	21 ± 2,2	12 ± 2,42	61	22
	(14-9) + 4,5	(36-25) + 2,15	(25-19) - 14	(26-19) - 2,75	(16-10) + 9,0	42	20
T-Fraktion, Rosetten-Sedimentation	13,8 ± 1,25	30,9 ± 1,98	32,4 ± 2,17	17,2 ± 1,85	7,3 ± 1,28	51	15
	(20-11,3) - 7,12	(39-29) + 2,11	(38-30) + 1,6	(22-12) + 1,9	(10-3) + 1,03	35	14
B-Fraktion, Rosetten-Sedimentation	11,1 ± 1,33	32,4 ± 2,21	29,4 ± 2,41	17,7 ± 1,43	9,6 ± 1,55	10	23
	(17 ± 10) + 4,17	(34-26) + 1,49	(36-27) - 6,6	(23-16) - 3,6	(12-6) + 6,1	31	18
T-Fraktion, Nylon effluens	17,92 ± -	31,2 ± 1,30	28,93 ± 2,15	17,0 ± 1,33	3,62 ± 0,87	46	7
	(23-15) + 2,82	(37-28) + 0,5	(37,6-26) - 4,15	(23-12) - 2,73	(7-4) + 0,86	38	12
B-Fraktion, Nylon adherens	10,4 ± 1,86	30,26 ± 1,36	35,55 ± 1,85	16,56 ± 1,01	6,78 ± 1,36	20	14
	(11-6,8) + 8,95	(34-28,1) + 3,91	(43-30) - 7,8	(20-15) - 5,44	(10,8-2) + 3,07	7	33
						28.	Gestationswoche
						32.	

Durchschnitt %

Streuung des Durchschnitts ±

() = Grenzwerte

Abweichung: in Vergleich mit den Kontrollmustern (absolute Zahlen)

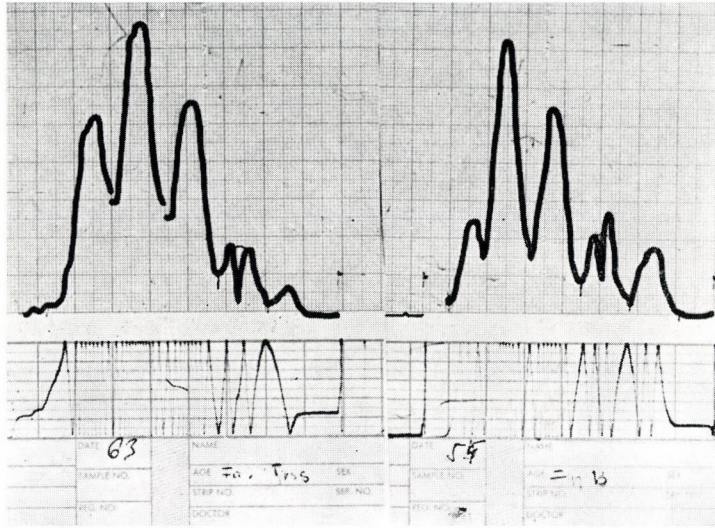


ABB. 3. Links: T-Zellen, rechts: B-Zellen

2. Da die LDH-1 Isoenzymaktivität der T-Zellen gesunder, reifer Neugeborenen im Vergleich zu den entsprechenden Werten der B-Zellen signifikant höher ist, kann die Separierung wahrscheinlich auch auf diese Weise durchgeführt werden.

3. Interessanterweise lag die LDH-1 Isoenzymaktivität der B-Zellen der Frühgeborenen höher als die der reifen Neugeborenen

4. In den Lymphozyten der Frühgeborenen war die Aktivität beider Zellpopulationen, vor allem aber die der LDH-5 Fraktion der B-Zellen erhöht.

Die ausführliche Darstellung unserer Daten ist in Tabellen I und II ersichtlich.

Unsere Untersuchungen erlauben die Feststellung, daß die Bestimmung der LDH-Isoenzyme zur Separierung der T- und B-Lymphozyten mit den Rosettenmethoden brauchbare ergän-

zende Daten liefert und auch über die Anwesenheit der T- und B-Zellen in jenen Reifep perioden, in denen die Entwicklung der Oberflächenmarker noch nicht beendet ist, eine Aufklärung bietet. Die Methode eignet sich zum weiteren Nachweis der sich in der fötalen Periode differenzierenden Zellen.

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Prof. Dr. L. KARMAZSIN

Pf. 32

H-4012 Debrecen, Hungary

Circulating antibodies in coeliac disease

by

Maria KÁVAI, M. SZABOLCS, S. CSORBA, B. SZABÓ and L. FÉSŰS

Institute of Pathophysiology, Central Laboratory and Department of Paediatrics, University Medical School, Debrecen, Hungary

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Antibodies produced against gliadin were demonstrated in the sera of patients suffering from coeliac disease as well as of immunized rabbits and rats. In the patient sera the specific antibodies proved to be of the IgG type. IgE may have a role in sensitization against gliadin only in the cell-fixed state.

In the serum of coeliac patients, precipitins and haemagglutinins produced against gliadin have been demonstrated [1]. Later these antibodies were shown to be of the types IgG, IgA and IgE [8, 10]. The present experiments were aimed at establishing whether IgE or IgG antibodies played the more important role in coeliac disease and whether the presence of IgA antibody was frequent.

MATERIAL AND METHOD

The serum of 28 coeliac patients aged between 2 and 8 years was studied with the inverse agar diffusion technique of Mancini and passive haemagglutination [12]. The antigen was extracted from wheat-meal with water at 2-4 °C, during 34 to 36 hours, then it was centrifuged at 50,000 *g* for 60 minutes [4]. The aqueous extract was fractionated on Sephadex G-75. As a positive control, rabbits were

immunized with the whole aqueous extract, giving the antigen with complete Freund's adjuvant. In this case the rabbits produced an IgG type antibody.

IgE content in the patient sera was demonstrated with the RIST technique [9]. For the demonstration of specific IgE we utilized the property of human IgE to sensitize passively the mast cells of the rat; under the action of homologous antigen, histamine is released from the cells [11]. As positive controls, rats were immunized with aqueous extract, with *Bordetella pertussis* adjuvant to enhance IgE production. With 0.5 ml serum of the animals and patients the mast cells (3.5×10^5) obtained from untreated animals were sensitized passively. The sensitized cells were incubated at 37 °C for 30 min, with 20 µg fraction A homologous antigen and the quantity of histamine released from the cells was measured by fluorimetry [5].

Finally, the serum of patients was absorbed with anti-human IgG and anti-human IgA. The antibody content of sera was determined by immune diffusion; unabsorbed serum served as the control.

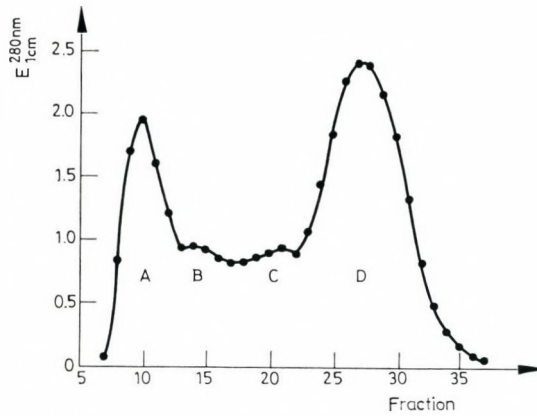


FIG. 1. Elution diagram of water soluble wheat-meal in Sephadex G-75 column. Fraction peaks marked with A, B, C, D

RESULTS

The water soluble wheat-meal was fractionated on Sephadex G-75 column. Fig. 1 illustrates the distribution of fractions marked A, B, C and D. With the technique of Mancini, fractions A showed the most distinct antigenicity against the immune serum of rabbits. After repeated fractionation this component was used as antigen, which, on the basis of its amino acid composition, could be considered to

be gliadin. With the technique of Mancini the anti-gliadin content of immune serum of rabbits was between 1.75 and 2.00 mg/ml. Table I summarizes the antibody content of human serum determined with the technique of Mancini and passive haemagglutination. In the serum of the same patient we demonstrated the IgE level with the RIST technique. Finally, following passive sensitization of mast cells of rats, we studied the specific IgE content on the basis of

TABLE I
Antibody titre of the serum of coeliac patients

Determination	Number of patients		Antibody titre
	patients	+ patients	
Mancini	28	28	> 1 : 16–1 : 64 serum dilution
Haemagglutination	28	28	> 1 : 8 serum dilution
RIST	28	9	200–601 IU/ml
RIST	28	2	601–1000 IU/ml
Histamine release	11	1	> 20% histamine release

+ patients = with increased antibody titre

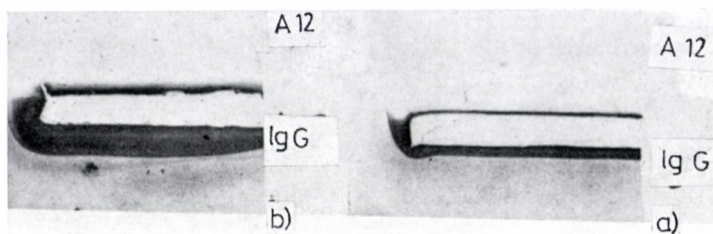


FIG. 2. Double immune diffusion of patient sera. (a) above: antigen A; middle: serum absorbed with anti-human IgG; below: anti-human IgG; (b) above: antigen A; middle: patient serum, below: anti-human IgG

histamine released from the cells on the effect of homologous antigen (fraction A). Table II illustrates the specific IgE level in patients and immunized rats.

TABLE II

Specific IgE content of antisera on the basis of histamine released from the mast cells

	Histamine release (%)
Rat: sensitized (8)	48.85 ± 2.06
control (10)	23.60 ± 1.81
Human: patient (11)	17.61 ± 1.72
control (10)	16.50 ± 1.43

In brackets, number of individuals

From both the qualitative and quantitative points of view, the results obtained with passive haemagglutination supported the quantity of antibody in the serum of coeliac patients demonstrated with the inverse technique of Mancini. IgE was present in a smaller quantity in the serum of the 11 patients. In these cases, specific IgE was not demonstrable. On the other hand, the immunized rats showed a specific IgE level.

The sera of patients absorbed with anti-human IgG did not present a precipitation curve against antigen A; the concentration decreased in accordance with the absorption (Fig. 2a). On the other hand, the unabsorbed sera of patients showed a precipitation curve with anti-IgG and accordingly reacted with antigen A (Fig. 2b). Absorption with anti-IgA did not influence the reaction with the antigen.

DISCUSSION

The technique used for the demonstration of specific IgE is equivalent to the RAST technique [11]. The results excluded the presence of circulating specific IgE in the patient sera. Considering the high cytophilic ability of IgE, in coeliac patients it seems to occur bound to cells [3]. Our observations indicate that the circulating antibody produced against gliadin is of the IgG type.

The disturbed absorption in the background of coeliac disease may be associated with a lack of tissue proteases [7]. To this contributes the

absence of IgA demonstrable locally. These circumstances may cause that gliadin is converted into an antigen. As the antigen persists in the patients, an opportunity may present itself in a certain phase of the disease for the formation of an immune complex. Following jejunal biopsy it was possible to demonstrate the presence of IgG, IgM and C₃ in the epithelial basal membrane [6] and this may be regarded as an evidence of immune complex deposition.

Thus, a mechanism more complex than the atopic one might explain the immunologic manifestation in coeliac disease [2].

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M. KÁVAI, M. D.

Pf. 32

H-4012 Debrecen, Hungary

Glukoseverwertung und Insulinsekretion beim Neugeborenen

Von

P. AMENDT, M. ZIEGLER und P. WULFERT

Zentralinstitut für Diabetes »Gerhardt Katsch«, Karlsburg, DDR

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Es werden basale und glukosestimulierte Konzentrationsverläufe von Glukose, Glyzerin, Insulin und Proinsulin bei Neugeborenen diabetischer, gestotischer und stoffwechselgesunder Mütter mitgeteilt. Neonaten von Müttern mit Schwangerschaftsdiabetes oder monosymptomatischer Gestose zeigten im Vergleich zu einer stoffwechselgesunden Kontrollgruppe statistisch signifikant erhöhte basale Insulinmeßwerte. Neugeborene von Müttern mit einem insulinbehandlungspflichtigen Diabetes mellitus oder monosymptomatischer Gestose waren im Vergleich zu einem Kontrollkollektiv durch signifikant vermehrte glukosestimulierte biphasische Insulinfreisetzung (sog. erste Sekretionsphase bis zur 30. Minute) charakterisiert. Die Glukoseverwertung dagegen war im Vergleich zu stoffwechselgesunden Neugeborenen vermindert. Daraus wurde geschlossen, daß die Hyperinsulinämie nicht als alleinige Ursache der Neonatalhypoglykämie Neugeborener diabetischer Mütter gelten kann. Das Maximum der Insulinämie war bei Nachkommen diabetischer Mütter positiv mit der Höhe des Leihiters diaplazentar permeierter Insulinantikörper korreliert.

Diese Ergebnisse belegen die Tatsache, daß die Glukoseansprechbarkeit der B-Zelle des Pankreas erst postnatal reift. Bei abnormem intrauterinem Milieu (Einfluß von Glukose, Aminosäuren, Ketokörpern, biogenen Aminen und Insulinantikörpern z. B.) resultiert eine pränatal induzierte funktionelle Aktivitätszunahme mit basaler und stimulierbarer Hyperinsulinämie.

Die anhaltende Zunahme des Bestandes an Diabeteskranken in fast allen Industriestaaten der Erde steht nicht nur im Zusammenhang mit vermehrter Streßexposition, Herz-Kreislauferkrankungen, Fettstoffwechselstörungen oder systematischen Früherfassungsaktionen, sie ist zu einem gewissen Anteil auch das Ergebnis einer Genauslese mit Anhäufung diabetischer Erbmasse. Als Folge der heute praktisch normalen Fertilität diabetischer Frauen und der deutlich gesenkten perinatalen Verlustraten wächst die Zahl von Nachkommen diabetischer Frauen zahlenmäßig an. Hormonell-metabolische und klinische Untersuchungen dieser Risikogruppe

erbrachten deutliche Hinweise für ein 20-fach erhöhtes Diabetesrisiko bereits während des Kindesalters.

Hypothetisch könnte diese vermehrte Erkrankungshäufigkeit der Nachkommen durch den multifaktoriellen Einfluß genetischer und/oder während der Schwangerschaft intrauterin-maternell induzierter »B-Zellüberlastung« erklärt werden. Diese pränatale funktionelle Belastung des endokrinen Pankreas zu einem Zeitpunkt, der physiologisch durch eine Insulin low-response charakterisiert ist, könnte eine temporäre oder bleibende Schädigung des Inselzellsystems verursachen. Zusammen mit weiteren manifestationsfördernden Umweltfak-

toren kann es dann im späteren Leben zur Funktionseinschränkung und Diabetesmanifestation kommen.

Aus der Sicht dieser Problematik legen wir Untersuchungsergebnisse zur Glukoseverwertung und Insulinsekretion von Neugeborenen vor, deren Mütter während der Schwangerschaft unterschiedlichen metabolischen Situationen (Gestose, Diabetes mellitus) ausgesetzt waren.

MATERIAL UND METHODE

Es wurden Neugeborene insulinpflichtiger diabetischer Mütter ($n = 16$; mittleres Geburtsgewicht 3780 g), Neugeborene von Müttern mit einem Schwangerschaftsdiabetes (Gestational diabetes; $n = 3$; mittleres Geburtsgewicht 3180 g), Neugeborene sonst stoffwechselgesunder Mütter ohne hereditäre Diabetesbelastung aber monosymptomatischer EPH-Gestose ($n = 4$; mittleres Geburtsgewicht 3260 g) und Neugeborene einer Kontrollgruppe stoffwechselgesunder Mütter ohne nachweisbare Diabetes- oder Adipositheredität ($n = 18$; mittleres Geburtsgewicht 3570 g) untersucht. Gestationsalter, APGAR-Werte und Säure-Basenhaushalt waren vergleichbar und altersentsprechend unauffällig. Die Blutentnahmen zur Bestimmung von Blutglukose (BG), radioimmunologisch bestimmbar Insulin (IRI) oder Proinsulin (IRP) und Glycerin erfolgten aus der Aorta abd. mittels Polyvinylchlorid-Arterienkathetern (Katheterposition in Zwerchfellhöhe). Die Glukosestimulation, mit Ausnahme der tagesprofilartigen Messungen im Nüchternzustand über die ersten 24 Lebensstunden, wurde über die katheterisierte Nabelvene vorgenommen. Versuchsbeginn für die Stimulationsteste war die 4. postnatale Lebensstunde.

Folgende zwei Versuchsanordnungen wurden benutzt:

1. 24-Stundenprofile von BG und IRI bei 3 Neugeborenen von Müttern mit einer Schwangerschaftsdiabetes und 5 Neugeborenen stoffwechselgesunder Mütter unter Nahrungskarenz und Ruhebedingungen. Blutentnahmezeiten: Geburt, 1, 2, 4, 6, 8, 10, 12, 18 und 24 Stunden. Bei Neonaten, die eine Hypoglykämie entwickelten, wurde der Versuch abgebrochen und Glukoselösung, später Nahrung, gefüttert.

2. Glukoseinfusionstest (GIT), bestehend aus initialer Startinjektion von 0.33 g/kg innerhalb 45 sec und anschließender konstanter Glukoseinfusion von 12 mg/kg/min über die Dauer von 120 min. Dabei wurde eine $20 \pm 2\%$ ige Glukoselösung infundiert. Getestet wurden 16 Neugeborene insulinpflichtiger diabetischer Mütter, 4 Neugeborene sonst stoffwechselgesunder Mütter mit monosymptomatischer EPH-Gestose und 13 Neonaten der Kontrollgruppe gesunder, nicht hereditär diabetisch belasteter, normgewichtiger Mütter. Blutentnahmezeiten: 0, 2, 5, 15, 30, 60, 90, 120, 150 und 180 min.

Die Blutglukose wurde enzymatisch mit Hexokinase und G-6-P-Dehydrogenase im optischen Test (50 μ l Vollblut, Perchlorsäurefällung) gemessen. Es wurde die radioimmunologische Insulinaktivität (IRI) mit der Alkoholpräzipitationsmethode in der Modifikation von ZIEGLER u. Mitarb. [39] und bei Anwesenheit mütterlicher Insulinantikörper (IAK) im Blut von Neugeborenen diabetischer Mütter als total extrahierbare IRI (TIRI) nach HEDING (Aufspaltung des Insulin-Antikörperkomplexes im HCl-Milieu bei $\text{pH} < 3$ und alkoholische Extraktion des Insulins) in der Modifikation von ZIEGLER u. Mitarb. [41] bestimmt. Die Proinsulinbestimmung erfolgte in Anlehnung an das von KITABCHI u. Mitarb. angegebene Verfahren, wobei die Bezeichnung IRP (immunoreaktives Proinsulin) den IRI-Anteil ausdrückt, der nach enzymatischem Insulinabbau im Radioimmunoassay als Restinsulinaktivität meßbar ist und zum größten Teil aus Proinsulin besteht. Da an einer Insulin-Standardkurve abgelesen wurde, lautet die Dimen-

sion μE Insulinäquivalent/ml. Das Glycerin wurde nach EGGSTEIN u. KREUTZ [14] bestimmt.

Beurteilungskriterien für das Verhalten der gemessenen Stoffwechselfparameter (BG, IRI, Glycerin) unter Belastungsbedingungen waren folgende Überschreitungsflächen: Absolute Blutglukosefläche ($F - \text{BG}_{\text{abs}}$; von der Kurve eingeschlossene Fläche; Basis 0 mg/100 ml), reaktive Insulinfläche ($F - \text{IRI}_{\text{reakt}}$; von der Kurve eingeschlossene Fläche; Basis 0 min-Wert) und die Mittelwerte von BG, IRI und Glycerin.

Die statistische Berechnung erfolgte mit Hilfe des *t*-Testes.

ERGEBNISSE

Neugeborene diabetischer Mütter — Basalbedingungen

Bei tagesprofilartigen Messungen über die ersten 24 Lebensstunden (Abb. 1) war das BG-Niveau bei Neugeborenen stoffwechselgesunder Mütter höher (6^{h} und 12^{h} p. n. $p < 0,05$) als bei Nachkommen von Müttern mit einem Schwangerschaftsdiabetes. Die basalen IRI-Mittelwerte

bei Neonaten von Müttern mit gestational diabetes lagen deutlich über den Werten der gesunden Kontrollgruppe.

Neugeborene diabetischer Mütter — Glukosestimulation

Basal vor Testbeginn und unter den Bedingungen des Glukoseinfusionstestes (Abb. 2 und Abb. 3) wurden bei Neugeborenen insulinbehandelter diabetischer Mütter bis zur 60. min signifikant niedrigere BG-Werte gemessen als bei der Kontrollgruppe (0, 2, 5, 15 min $p < 0,05$). Die absolute BG-Fläche 0–60 min war gleichfalls statistisch signifikant kleiner. Im weiteren Testverlauf aber war das BG-Verhalten bei Nachkommen diabetischer Mütter im Sinne verminderter Verwertung »pathologisch«, weiter ansteigend, und 60 min nach Stimulationsende noch signifikant höher als bei dem Kontrollkollektiv (180 min $p < 0,05$).

Das im Aortenblut radioimmunologisch gemessene Insulin (Abb. 2)

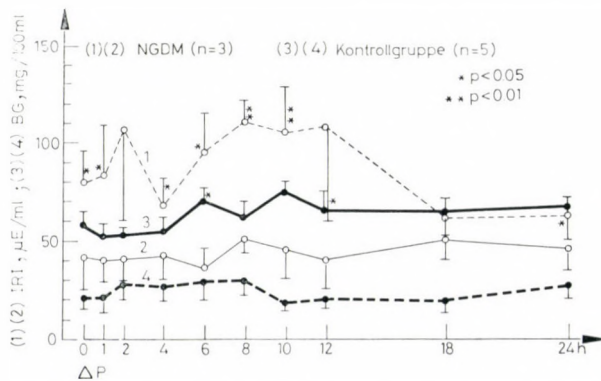


ABB. 1. Blutglukose (BG) und Insulin (IRI) im Aortenblut unter Basalbedingungen bei Neugeborenen von Müttern mit Schwangerschaftsdiabetes (IGDM) und einer gesunden Kontrollgruppe. Statistische Signifikanz: $p < 0,01$ **; $p < 0,05$ *.

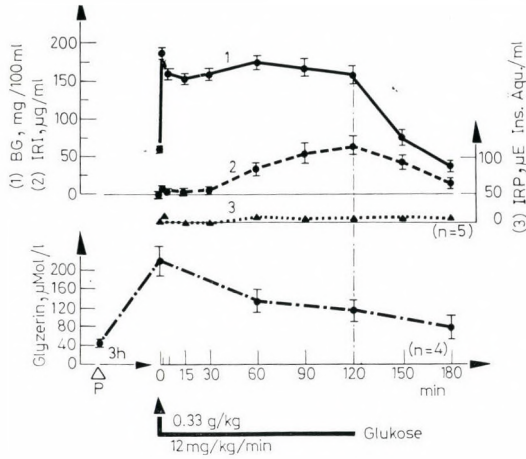


ABB. 2. Blutglukose (BG), Insulin (IRI), Proinsulin (IRP) und Glycerin bei Neugeborenen stoffwechself gesunder Mütter (Kontrollkollektiv). Glukoseinfusionstest

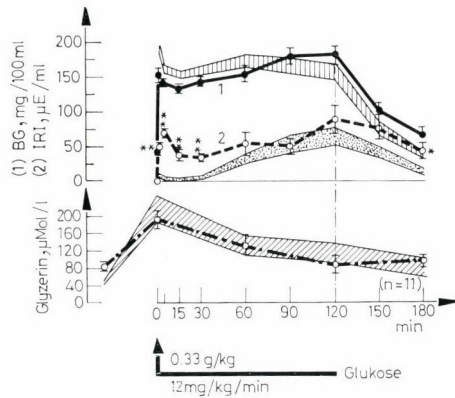


ABB. 3. Blutglukose (BG), Insulin (IRI) und Glycerin bei Neugeborenen insulinbehandelter diabetischer Mütter (ausgezogene fette Kurven) im Vergleich mit den Mittelwerten ± 1 SD der gesunden Kontrollgruppe (schraffierte Bereiche). Statistische Signifikanz: $p < 0.01$ **; $p < 0.05$ *

zeigte bei Neonaten stoffwechself gesunder Mütter eine monophasische, erst 60 min nach Glukoseinfusionsbeginn statistisch signifikant über den Basalwert ansteigende, Charakteristik. 60 min nach Stimulationsende wurden die Ausgangswerte annähernd wieder erreicht. Die radicumunologisch bestimmte Proinsulinaktivität (IRP)

schwankte statistisch nicht signifikant um den Basalwert, eine Glukosestimulierbarkeit konnte nicht festgestellt werden.

Neugeborene insulinbehandelter diabetischer Mütter (Abb. 3) hatten eine biphasische Insulinsekretionscharakteristik: 5 min nach Beginn der Glukosestimulation wurde das erste Maxi-

zum und bei Stimulationsende (120 min) der zweite Gipfel bestimmt. Die Ausgangswerte wurden bis Testende nicht wieder erreicht. Zu den Zeitpunkten 2, 5, 15, 30 und 180 min waren die reaktiven IRI-Mittelwerte und zwischen 0–30 min die reaktiven Insulinflächen (F-IRI_{reakt.} 0–5 min und F-IRI_{reakt.} 5–30 min) statistisch signifikant höher als bei der Kontrollgruppe ($p < 0,01$; 180 min-Wert $p < 0,05$).

Das Glyzerin im zentralen arteriellen Blut (Abb. 2 und Abb. 3) stieg während der Testvorperiode von den unmittelbaren postnatalen Ausgangswerten bis zum Ende der dritten Lebensstunde bei der gesunden Kontrollgruppe auf 458% und bei Neugeborenen diabetischer Mütter auf 231% der Basalwerte an (Anstieg um $171 \pm 30 \mu\text{Mol/l}$ bzw. $108 \pm 18 \mu\text{Mol/l}$). Die Ausgangswerte sofort nach der Geburt ($49 \pm 5 \mu\text{Mol/l}$ bei der Kontrollgruppe und $83 \pm 12 \mu\text{Mol/l}$ bei diabetischen Nachkommen) und das poststimulatorische Verhalten waren bei beiden Gruppen statistisch nicht different.

Neugeborene diabetischer Mütter mit unterschiedlicher Insulinbindungskapazität — Glukosestimulation

Der Einfluß diaplazentar permeierter IAK (Leihtiter) auf die stimulierte neonatale Insulinsekretion im posthepatischen Blut wurde durch statistische Bearbeitung der Versuchsergebnisse von zwei Kollektiven Neugeborener insulinbehandelter Langzeitdiabetikerinnen untersucht. Beide Kol-

lektive unterschieden sich durch die Höhe des IAK-Titers, ausgedrückt als Insulinbindungskapazität (IBC) im Gammaglobulinbereich: Niedrige IBC $< 50 \mu\text{E/ml}$ (0–50 $\mu\text{E/ml}$; $n = 5$) und hohe IBC $> 100 \mu\text{E/ml}$ (103–484 $\mu\text{E/ml}$; $n = 11$). Nach Glukosestimulation (Abb. 4) ergaben sich 5 min nach der Startinjektion von 0,33 g/kg und anschließender Glukoseinfusion bei Neonaten mit hoher IBC signifikant höhere reaktive Insulinwerte ($p < 0,01$). Im weiteren Verlauf bestanden keine sicheren Differenzen mehr. Zwischen Glukoseverwertung und IAK-Titer im Neonatalblut bestand keine Korrelation.

Neugeborene gestotischer Mütter — Glukosestimulation

Während des GIT (Abb. 5) war das Blutglukoseverhalten der Neugeborenen von Müttern mit monosymptomatischer Gestose mit der gesunden Kontrollgruppe vergleichbar. Die Insulinmeßwerte zeigten, wie bei Nachkommen diabetischer Mütter, einen biphasischen Verlauf: Erster Gipfel 5 min post injectionem, zweiter Gipfel zwischen 60–120 min. Die Mittelwerte 5 min ($p < 0,01$) und 60 min ($p < 0,05$) waren statistisch signifikant höher als bei der gesunden Kontrollgruppe. Signifikant größer als bei Neugeborenen stoffwechselfesunder Mütter waren auch die reaktiven Insulinflächenwerte (F-IRI_{reakt.} 5–30 min und 30–60 min $p < 0,05$). Bis zum Testende wurden die IRI-Basalwerte nicht wieder erreicht.

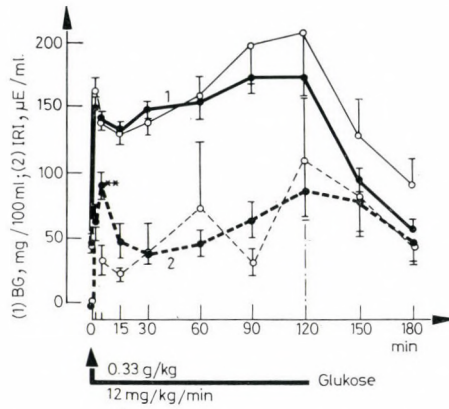


ABB. 4. Blutglukose (BG; ausgezogene Kurven) und Insulin (IRI; gestrichelte Kurven) bei Neugeborenen insulinbehandelter diabetischer Mütter mit hoher IBC (dickere Kurven) und niedriger IBC (Doppelstrichkurve). Glukoseinfusionstest. Statistische Signifikanz: $p < 0,01^{**}$

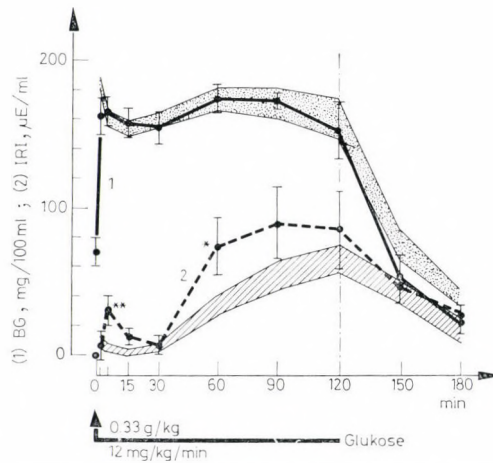


ABB. 5. Blutglukose (BG) und Insulin (IRI) bei Neugeborenen gestotischer Mütter im Vergleich zu einer gesunden Kontrollgruppe (schraffierter Bereich). Glukoseinfusionstest. Statistische Signifikanz: $p < 0,01^{**}$; $p < 0,05^{*}$

BESPRECHUNG

Insulin spielt in der normalen Fetalentwicklung eine wichtige Rolle als anaboles Hormon [3]. Parallel mit der morphologischen Reifung des en-

dokrinen Pankreas sind ab 9 cm Keimlänge Proinsulin [34] und bei 12 Wochen alten Feten Insulin [37] aus dem Pankreas extrahierbar und ab 16. Woche in der Amnionflüssigkeit nachweisbar [9]. Die früheste Insulinrelease fetaler menschlicher In-

sehn wurde in vitro ab 63. Gestationstag festgestellt [16] und ist ab 16. Woche mit Ausnahme von Glukose durch alle anderen Stimuli auslösbar [28]. Der mittlere pankreatische Insulingehalt korreliert mit Gestationsalter und Fetalgewicht [3, 16]. Die vollständige funktionelle Ausreifung der B-Zelle steht unter Kontrolle des Hypothalamo-Hypophysensystems [4].

Während des intrauterinen Lebens besteht bei gesunden Früchten unauffälliger Schwangerschaften eine relativ »glukoseinsensitive Phase« der B-Zellansprechbarkeit. Der glukosevermittelte Auslösemechanismus »reift« funktionell erst in der frühen Neonatalzeit. Der Reifungsvorgang vollzieht sich wahrscheinlich multifaktoriell und hängt eng mit der Entwicklung des Adenyl-Cyklase-Systems und dem Weg der Glukosephosphorylation zusammen [2, 10]. Die Mehrzahl der Untersucher konnten in vivo und in vitro bei stoffwechselgesunden Feten und Neonaten diesen glukosestimulatorischen »Defekt« der Insulinsekretion feststellen [5, 10, 18, 30 u. a.]. Sämtliche anderen Stimuli werden von der neonatalen und fetalen B-Zelle wie beim Erwachsenen mit sofortiger Insulinsekretion beantwortet [10, 20, 22, 29 u. a.]. Der »Defekt« kann somit nicht in der Insulinbiosynthese liegen, sondern muß im Glukoserezeptormechanismus zu suchen sein. Abweichende Literaturbefunde mit glukoseinduzierter sofortiger biphasischer Insulinfreigabe auch bei gesunden Neonaten sind durch Glukoseinfusion an die Mutter unter

der Geburt oder Vorfütterung der Neugeborenen über einen »priming effect« der Glukose [18], unterschiedliche Blutentnahmetechniken [31], differente Glukosedosen bei Dauerinfusion [32] oder Nichtausschluß monosymptomatischer mütterlicher Gestosen [1] erklärbar.

Unsere Untersuchungsergebnisse der monophasischen, verzögert ansteigenden IRI-Konzentrationserhöhung im Arterienblut bei Neugeborenen stoffwechselgesunder Mütter decken sich mit den Angaben der Literatur. Der fehlende Proinsulinanstieg unterstreicht die Auffassung von einer relativ glukoseinsensitiven Phase der Inselzellen als Charakteristikum einer ungestörten pränatalen Entwicklung.

Bei verschiedenen mütterlichen (Prädiabetes, Diabetes mellitus, EPH-Gestose) oder fetalen (hämolytische Anämie, Erythroblastose) Erkrankung wird der physiologische Reifungsvorgang gestört. Es kommt unter hypothalamisch-hypophysärer Beteiligung [17] zur Hypertrophie und Hyperplasie der Langerhansschen Inseln und B-Zellen mit unterschiedlicher Morphologie bei den einzelnen Erkrankungen. Die rein pathologisch-anatomischen Aspekte sind bereits seit 50 Jahren bekannt (Literatur bei 33), wurden später mehrfach bestätigt und von den Morphologen meist als sekundäre Folge des Hyperkortizismus gedeutet [8]. Nach heutiger Ansicht haben wir es mit einem multifaktoriellen Geschehen zu tun, bei dem die mütterliche Hyperglykämie, verschiedene Aminosäuren, biogene Amine,

Ketokörper und vielleicht genetische Einflüsse in Rechnung gestellt werden müssen.

Bei Feten und Neugeborenen prädiabetischer und diabetischer Mütter ist ein erhöhter pankreatischer Insulingehalt [4, 37] und in vielen Versuchsmodellen der basale [12, 17] und stimulierbare Hypersinsulinismus nachgewiesen worden [5, 30 u. a.]. Die in zeitlicher und quantitativer Art signifikant unterschiedliche Insulinsekretion zwischen Neugeborenen nach pathologischen Graviditätsverläufen (Diabetes, Gestose) und Neugeborenen einer unauffälligen Kontrollgruppe bestand nur für die frühe, erste oder sog. akute Sekretionsphase bis zur 30. min bei intravenösen Testen. Die zweite, mehr metabolisch gesteuerte Sekretionsphase ließ bei unseren Untersuchungen keine statistischen Differenzen erkennen.

Bisher sind diese Untersuchungen aus methodischen Gründen unter Ausschluß von Nachkommen insulinbehandelter diabetischer Frauen erhoben worden. Die mütterlichen IAK passieren die Plazentarschranke und stören die übliche Radioimmunoassays für Insulin [21, 36]. Nach Aufspaltung des IAK-Komplexes im sauren Milieu und alkoholischer Extraktion des Gesamtinsulins kann man die reaktiven Veränderungen der IRI-Konzentration im Blut der Neugeborenen von Langzeitdiabetikerinnen meßbar machen. Am Antikörper gebundenes und diaplazentar übergetretenes Insulin [21, 36] stört die Betrachtung der reaktiven Insulinämie nicht, freies Insulin soll nach Ansicht der

meisten Untersucher nicht plazentagängig sein [21].

Die Insulinantikörper sind nach bisherigem Wissen die kräftigsten Stimulatoren der Insulinsekretion [23]. Sie werden für die charakteristischen eosinophilen Infiltrate und für degenerative Veränderungen der B-Zellen und Inseln von Nachkommen diabetischer Mütter verantwortlich gemacht [15] und konnten intrazellulär fluoreszenzmikroskopisch nachgewiesen werden [7]. Der stimulatorische Effekt wurde am Tierpankreas *in vitro* nachgewiesen [40]. Bei experimentell sensibilisierten Tieren führten sie zu starker funktioneller Überbeanspruchung des Inselorgans [15]. An Hand der von uns vorgelegten Ergebnisse konnten wir eine positive Beeinflussung der glukosestimulierten ersten Insulinsekretionsphase durch IAK bei Neugeborenen diabetischer Mütter wahrscheinlich machen.

Die Deutung der verzögerten Glukoseverwertung unter Langzeitinfusion bei Neugeborenen diabetischer Mütter trotz sofortiger und vermehrter Insulinfreigabe bleibt zunächst noch hypothetisch. Dabei muß bedacht werden, daß radioimmunologisch bestimmtes Insulin nicht immer mit biologischer Insulinaktivität identisch ist. Der verminderte glukostatische Effekt könnte durch IAK-spezifische Hemmung der totalen Glukoseuptake, Glukoseoxydation und Glykogenbildung [26] und weniger durch Inaktivierung endogenen Insulins infolge Bindung oder durch Ausschüttung wenig wirksamen Insulins hervorgerufen werden. Ein zusätzlich

inhibitorischer Effekt durch Ketokörper und freie Fettsäuren ist nicht auszuschließen [6]. Beide Metabolite sind bei Neonaten diabetischer Mütter signifikant erhöht [35]. Die verminderte biologische Aktivität der glukosestimulierten Hyperinsulinämie bei Neugeborenen diabetischer Mütter kann an Hand unserer Untersuchungsergebnisse indirekt auch aus der im Vergleich zur Kontrollgruppe »relativ insuffizienten« Lipolysehemmung abgelesen werden. Im Basalzustand dagegen scheint ein funktioneller Hyperinsulinismus zu bestehen. Auch Beobachtungen anderer Autoren sprechen dafür [21], daß die Hyperinsulinämie als alleinige Erklärungsmöglichkeit für die Hypoglykämie dieser Kinder nicht ausreicht. MARTIN u. Mitarb. [27] sahen selbst in der Hypoglykämie keine Korrelation zwischen radioimmunologisch bestimmtem Insulin und Blutglukose im Neugeborenenalter. Man nimmt heute eher Abnormitäten der basalen Glukosehomeostase als pathogenetischen Mechanismus an [13, 27].

Bei der Gestose der Mutter ist histologisch eine Hyperplasie des fetalen Inselorgans gefunden worden [8]. Daraus kann sekundär auf eine funktionelle Übererregung geschlossen werden. Die resultierende biphasische Insulinsekretion im Aortenblut wurde von uns dargestellt. Wie diese vorzeitige, mature Glukoseansprechbarkeit der neonatalen B-Zelle bei mütterlicher Gestose zu erklären ist, bleibt zunächst gleichfalls hypothetisch. Denkbar wäre eine pränatale Inselzellstimulation durch Ketokörper, bio-

gene Amine oder Aminosäuren [11, 24, 38]. Auch bei den Müttern müssen ähnliche pathogenetische Mechanismen wirksam sein, denn es ist bei ihnen gleichfalls eine verstärkte Insulinausschüttung gefunden worden [25].

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Dr. sc. med. P. AMENDT
Universitäts-Kinderklinik (Charité)
DDR-104 Berlin
Schumannstr. 20/21

Transverse diameter of the chest and of the heart of infants in the course of physiological cardiorespiratory adaptation

By

J. WEISENBACH,* Aranka HAJPÁL,** S. VÁRADY,* Vera JÁSZAI,*
Margit SCHMELZER,*** K. SCHULTZ,* Lilla PAP* and Ilona RIPPL*

*Department of Paediatrics, University Medical School, Pécs, Hungary,

**Institute of Biometrics of the Hungarian Academy of Sciences, Budapest,

***Central Research Laboratory, University Medical School, Pécs, Hungary

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The morphology of the lungs and heart was analysed in 824 newborn infants with normal cardiorespiratory adaptation. Under normal conditions, the air content of the lungs became satisfactory in the first 6-12 hours and normal in all cases after 24 hours.

The values for the transverse diameter of the chest and heart were brought into correlation with birth weight, body length and gestational age. The transverse diameter of the chest and heart did not change during the early postnatal period (between 6-12 hours and 5 days). Both diameters were correlated with birth weight. The closest correlation was found in newborns under 1500 g, a varying one in those between 1500 and 2000 g and a close correlation in the category over 2000 g.

The correlation of the two diameters with body length was linear and close, without any difference between the values obtained at different times of examination. A rather loose correlation was found between the transverse diameter of the chest and heart, and gestational age.

It is a debated question in X-ray diagnostics how the lungs and heart appear and how large the cardiac shadow is in newborn infants under physiological conditions, in other words how long it takes for the respiration and circulation to adapt themselves completely to extrauterine life. In this respect, the data are conflicting. Still, their precise knowledge is of importance since the retardation of adaptation always means a pathological process, observed most frequently in post-asphyxic states. To recognize this by X-ray examination, one must be familiar with the physiological pattern.

The first X-ray examinations in infants were performed by Bamberg and Putzig [9]. Later, De Buys and Samuel [17] studied the question in 52 newborns in the first 28 postnatal hours. They found the size of the heart variable and independent of the body measurements of the newborn. The heart shadow was studied by Voss [46] and Brock [12]. Vogt [45] described the frequent occurrence of cardiomegaly in newborn age. The role of asphyxia in the phenomenon was emphasized by Weymuller et al. [50] as well as by Wasson [47]. Unfortunately, none of these investigations allowed unequivocal conclusions to be

drawn, because in most of them only few infants were examined, the roentgenograms were made with long exposition time and it was not always possible to distinguish between pathological and physiological conditions.

The transverse diameter of the chest (TTD) and that of the heart (CTD) were measured on newborn roentgenograms by Farrel [22], Dunham and D'Amico [20] and Bakwin and Bakwin [8]. These authors established the average diameters but reported different values for the size of the heart. Martin and Friedel [39] studied cyanotic and non-cyanotic newborns; they were the first to describe the cardiomegaly and atelectatic foci in the lungs in cyanotic infants. Their control group consisted, however, of infants with slight asphyxia, and the studies did not comprise all weight categories. Important anthropometric data were published by Maresh and Washburn [38] as well as by Lanzavecchia et al. [35]; these and other authors related the transverse diameters to body length, body surface or gestational age [11, 17, 29, 30, 35, 36, 38, 43].

All these observations were based on few data only, besides they failed to reveal the normal relationships that would allow pathological alterations to be recognized. It seemed therefore useful to study by X-rays in a large newborn population the relationship of TTD and CTD to a) birth weight; b) body length; c) gestational age at various points of time after birth. First of all, an attempt was made to construct a

standard that would allow the reliable quantitative evaluation of pathological alterations.

MATERIALS AND METHODS

Investigations were performed on 824 newborn infants. Their adaptation to extrauterine life was undisturbed in every case. The normal group consisted of infants with no maternal disease, undisturbed pregnancy, and normal clinical, X-ray and blood-biochemical parameters, corresponding to postnatal age [1, 2, 3, 4, 5, 6, 18, 21, 29, 31, 32, 34, 37, 42, 44, 46, 49, 51].

The method used was a retrospective analysis of data selected on the basis of roentgenograms and case records collected during the past five years.

X-rays of the chest were made under standard conditions, in supine position antero-posteriorly. In the first 24 postnatal hours lateral X-rays were also made. From the roentgenograms we determined the state of the lungs, their air content, outlines of the vessels, the form and size of the heart and the height of the diaphragm. In addition, TTD and CTD were measured.

TTD was measured from the edge of the most lateral costal line, CTD was obtained from the sum of perpendicular straight lines drawn from the median line of the most remote left and right points of the heart. In several cases, also other diameters were measured in order to determine the size and form of the chest. The changes in these values were proportional to the change of the two main diameters; therefore they were not studied in the whole material.

The infants investigated were grouped according to birth weight. Babies under 1500 g and those over 3000 g were analysed in a global way because of the low number of cases. Infants between the above two weight limits were analysed in 500 g steps.

As regards body length at birth the

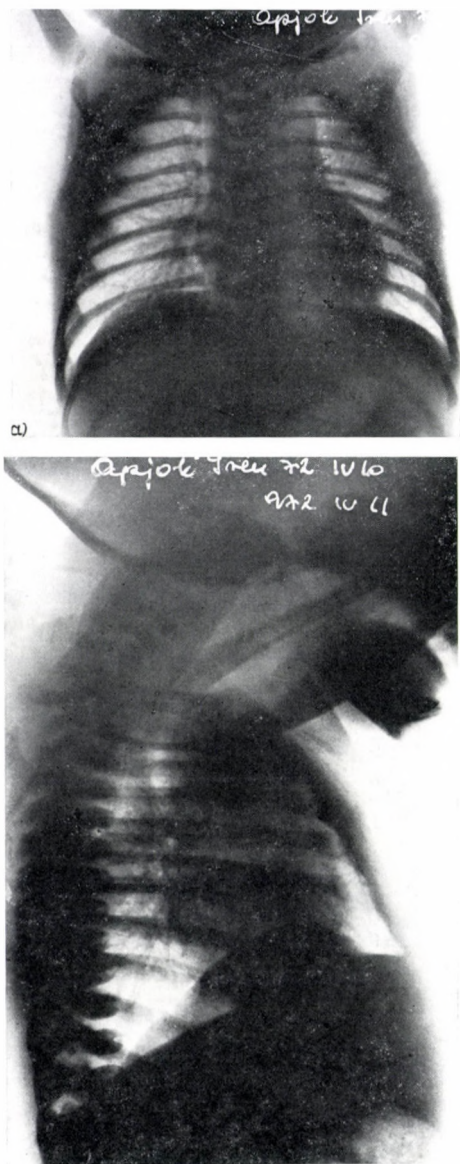


FIG. 1

infants were grouped in increasing order at one-cm steps.

As regards gestational age three groups were formed, one between 37 and 42 weeks and the two others under and beyond that period.

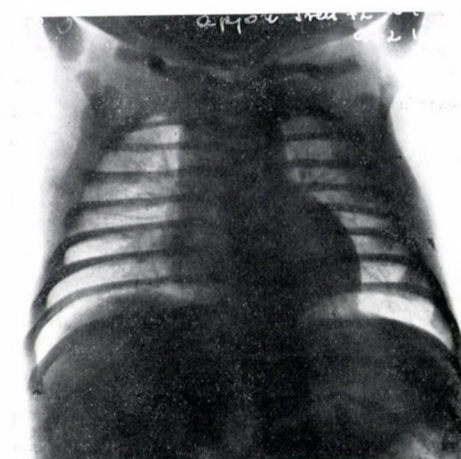


FIG. 2

As regards the time of X-ray examination, five groups were made within the mentioned categories on the basis of birth weight and length (6–12, 24, 48, 72 and 120 hours) and three groups (6–24, 48 and 72–120 hours, respectively) according to the gestational age.

The investigated relationships were

- a) relation of TTD and CTD to birth weight, birth length and gestational age;
- b) changes in the diameters during the first five postnatal days.

Standards were constructed for TTD and CTD in relation to birth weight and body length on the basis of the values corresponding to 90, 50 and 10%. These standards were plotted graphically.

Special emphasis was laid on a) the increase in pulmonary aeration; b) the changes of the chest and heart diameter during the postnatal period; c) the relation to birth weight of the size of the chest and heart.

Most authors found the adaptation of the lungs and heart to change within wide limits [14, 15, 20, 34, 39, 40, 41, 47, 50, 52]. In contrast, our observations failed to reveal any essential alteration in the appearance of the lungs or in the position of the diaphragm during the period from the 6th to 12th hour to the fifth day after birth (Figs. 1a, 1b, 1c).

TABLE Ia

Time of examination hour of life	Chest					
	Birth weight, g					
		< 1500	1500—2000	2001—2500	2501—3000	> 3000
12	n	56	43	31		
	\bar{x}	1237	1743	2275		
	\bar{y}	8.0	9.0	10.0	—	—
	r	0.70	0.22	0.71		
		P < 0.001	0.1 > P > 0.05	P < 0.001		
24	n	30	80	33	38	36
	\bar{x}	1288	1768	2238	2803	3338
	\bar{y}	8.4	9.1	9.9	10.6	11.1
	r	0.59	0.28	0.40	0.55	0.67
		P < 0.001	0.05 > P > 0.01	0.05 > P > 0.001	P < 0.001	P < 0.001
48	n	37	28	32	36	31
	\bar{x}	1269	1737	2269	2747	3420
	\bar{y}	8.2	9.0	9.8	10.6	11.2
	r	0.85	0.39	0.49	0.65	0.84
		P < 0.001	0.05 > P > 0.01	P < 0.001	P < 0.001	P < 0.001
72	n	46	31	34	31	35
	\bar{x}	1277	1768	2301	2793	3324
	\bar{y}	8.3	9.4	10.3	10.8	11.2
	r	0.81	0.69	0.61	0.62	0.62
		P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
120	n		31	38	34	33
	\bar{x}		1767	2272	2799	3270
	\bar{y}	—	9.3	10.4	10.7	11.2
	r		0.52	0.48	0.51	0.59
			0.01 > P > 0.001	0.01 > P > 0.001	0.01 > P > 0.001	P < 0.001

n = Number of subjects

\bar{x} = Mean birth weight of the given group

\bar{y} = Mean transverse diameter of chest

r = Correlation coefficient

Air content of the lungs was satisfactory in most cases after 6—12 hours and normal in all cases after 24 hours.

The size of the chest and heart did not change significantly in the individual weight groups during the period from the

6th hour to the fifth day after birth (Tables Ia and Ib).

A correlation was found between birth weight and TTD. The correlation coefficients revealed a close correlation between birth weight and TTD in infants under

TABLE Ib

Time of examination, hour of life	Heart				
	Birth weight, g				
	< 1500	1500—2000	2001—2500	2501—3000	> 3000
n	56	43	31		
\bar{x}	1237	1743	2275		
12 \bar{y}	3.8	4.3	4.5	—	—
r	0.69	0.19	0.49		
	P < 0.001	0.1 < P	0.01 > P > 0.001		
n	30	80	33	38	36
\bar{x}	1288	1768	2238	2803	3338
24 \bar{y}	3.9	4.3	4.6	4.8	5.1
r	0.38	0.26	0.47	0.40	0.61
	0.05 > P > 0.01	0.05 > P > 0.01	0.01 > P > 0.001	0.02 > P > 0.01	P < 0.001
n	37	28	32	36	31
\bar{x}	1269	1737	2269	2747	3420
48 \bar{y}	3.8	4.3	4.4	4.8	4.9
r	0.65	0.58	0.55	0.73	0.85
	P < 0.001	0.01 > P > 0.001	P < 0.001	P < 0.001	P < 0.001
n	46	31	34	31	35
\bar{x}	1277	1768	2301	2793	3324
72 \bar{y}	3.8	4.3	4.4	4.7	4.9
r	0.61	0.52	0.63	0.66	0.30
	P < 0.001	0.01 > P > 0.001	P < 0.001	P < 0.001	0.1 > P > 0.05
n		31	38	34	33
\bar{x}		1767	2272	2799	3270
120 \bar{y}	—	4.2	4.5	4.7	4.9
r		0.38	0.47	0.30	0.17
		0.05 > P > 0.1	0.01 > P > 0.001	0.1 > P > 0.05	0.1 < P

n = Number of subjects
 x = Mean birth weight of the given group
 y = Mean transverse diameter of heart
 r = Correlation coefficient

1500 g and in those over 2000 g. The correlation was less expressed in the 1500—2000 g weight group; at 6—12 hours it was not even significant statistically.

Similar results were obtained for birth weight and CTD. Here, however, the cor-

relation was not significant in the group over 3000 g by 72 and 120 hours.

The individual values for TTD and CTD in the 1500—2000 g group showed a pattern similar to the above. These values changed within wide ranges.

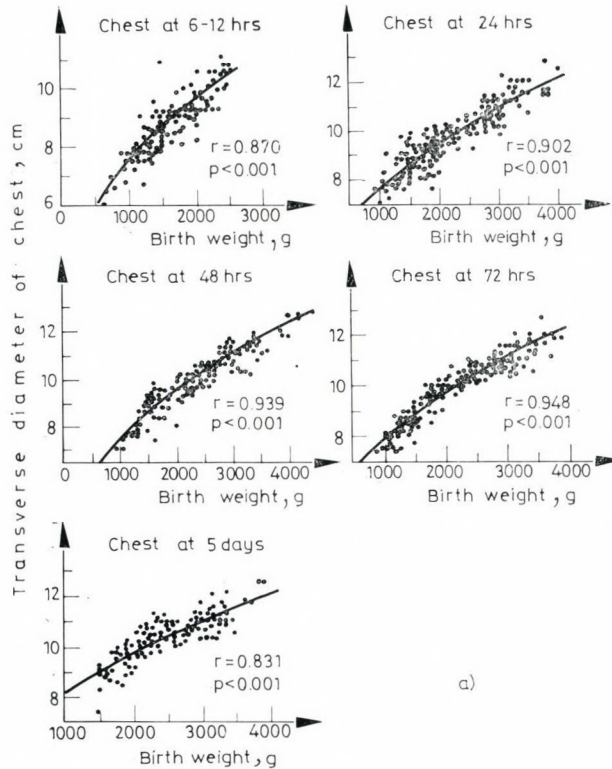


FIG. 3a

Analysis of the relationship between diameter and birth weight revealed differences in the intra-coordinate position of the hits in the groups under 1500 g and over 2000 g. The hits in the former group were mainly located around the steep regression line, when investigated in linear regression. The regression line fitted well to the hits also in the group over 2000 g, but the b value was lower than in the previous group. For the whole population their values proved significant, even though the values for the low-weight group were evidently lower than those for the mature group.

The transverse diameter of the chest in the newborn can be expressed by the simple geometric model, $d = c \sqrt{m}$, where d = transverse diameter of the chest; c = constant, m = birth weight.

Regression analysis with parabolic approach showed that the curve fitted well to the hits; this was the curve with the most significant r values (Figs 3a and 3b).

The percentual standard of the diameters was also constructed (Figs. 4a and 4b).

Examination of the relationship between body length at birth and TTD and CTD revealed a linear relation (Figs. 5a and Table II).

The b value was higher in regression equations concerning the chest than in those concerning the heart, a fact clearly mirrored by the lines in the diagram. The regression lines of the chest were steeper than those of the heart. A difference was found in the value for the coefficients concerning the CTD of infants examined after 72 hours, as well as the TTD of infants

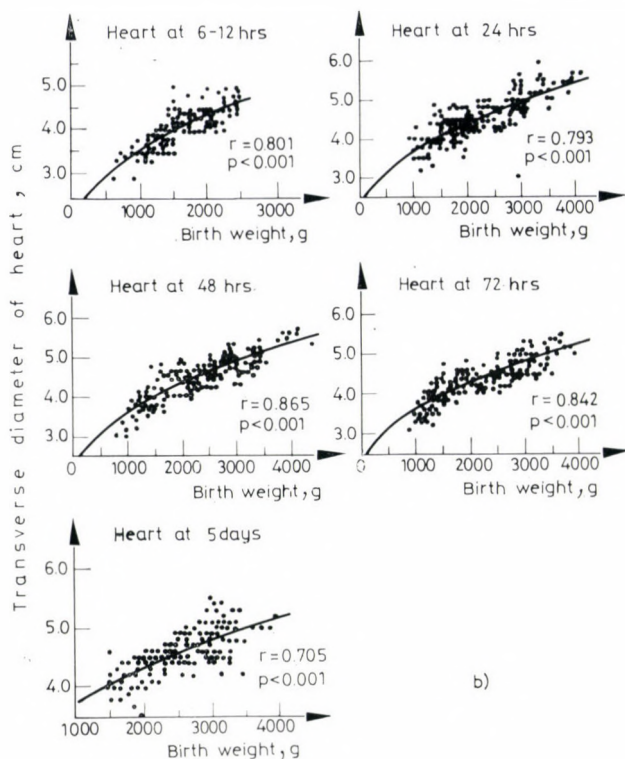


FIG. 3b

examined after five days. We cannot offer any explanation for these findings.

The percentual standard was constructed from 668 values (Figs 6a and 6b). No extra standard was constructed for the various points of time of examination because, on the basis of the regression analyses, no essential difference could have been expected between the various age groups.

TTD and CTD were studied in three groups with a gestational age under 33, between 33 and 36 and between 37 and 42 weeks, respectively. Only 449 newborns could be analysed since the time of the last menstruation was not always exactly known and thus the gestational age could not be calculated.

The correlation between transverse diameters and gestational age was not as close as in the case of birth length. In sev-

eral groups the correlation was not significant. Using multiple regression analysis, there was a good linear correlation between TTD and CTD, but it was loose in the case of gestational age vs. TTD and CTD.

As to the height of the diaphragm, in most cases it was situated at the height of the eighth rib without reaching the seventh or ninth rib.

DISCUSSION AND CONCLUSIONS

The form and shape of the chest can be characterized by various diameters. Most characteristic are the transverse and sagittal diameters. In the material of Zsebók [52] the mean TTD was 10.9 cm in boys and 10.6 cm in girls at the height of the 7th and

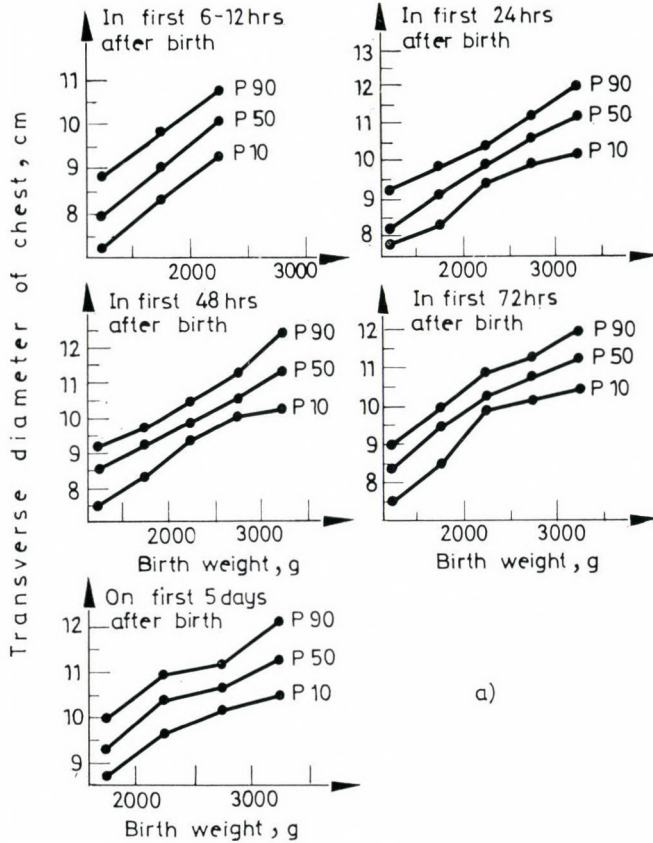


FIG. 4a

8th ribs. For these same values Farrel [22] found 9.1 cm in boys and 8.9 cm in girls. Martin and Friedel [39] observed a TTD of 9.04 ± 0.005 cm in one-day-old normal newborns, a value very close to the 9.0 ± 0.8 cm described by Bakwin and Bakwin [8]. According to Dunham and D'Amico [20] the TTD is 11.4 cm in the newborn.

We calculated mean values corresponding to birth weight groups and not to the whole material investigated. Analysis according to birth weight was justified by the fact that the two transverse diameters depend

considerably on birth weight (Tables IIa and IIb).

The changes in the size and transverse diameters of the heart were analysed by Burnard and James [15, 16]. Our previous investigations led to similar results.

We failed to find any data in the literature which would deal with the relationship between birth weight, birth length and gestational age on the one hand and CTD on the other, or, with changes within the early (first five days) neonatal period in every birth weight and length category.

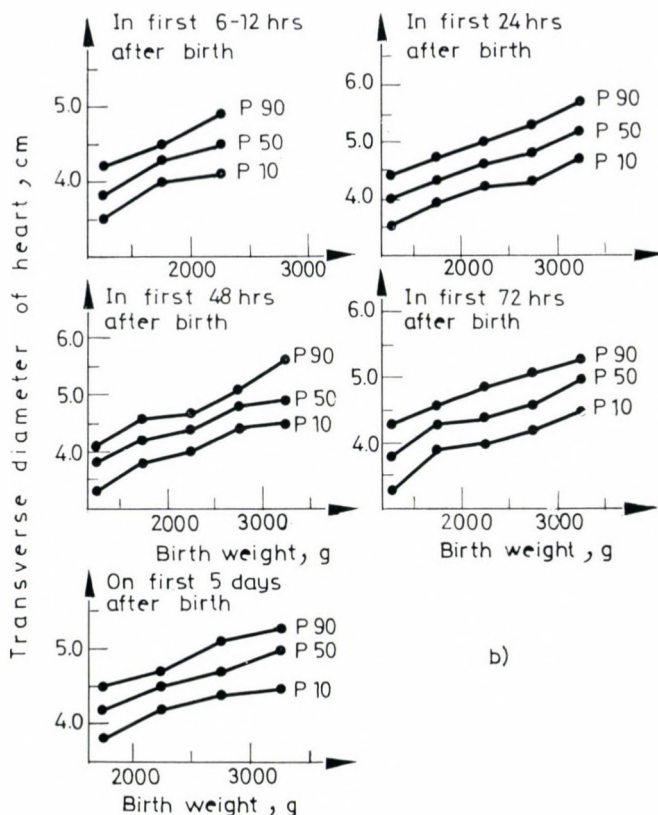


FIG. 4b

Our observations revealed a close correlation between birth weight and transverse diameters. The correlation was especially close in newborns under 1500 g. The greatest deviations were found in the category over 2000 g. These observations together with the regression shown in the parabolic curve indicate that in low-weight newborn infants weight-gain runs parallel with organ development. This parallelism is less pronounced in the category over 2000 g. Infants between 1500 and 2000 g are considered a transient group. The explanation of

this finding may lie in the functional change of the cardiovascular system. Expansion stability in this category differs qualitatively from that of other groups [26].

For practical purposes the percentual standard of TTD and CTD was also constructed. This may be of help in the individual judgement of the size of TTD and CTD in the newborn infant.

The closest correlation was found between body length at birth and transverse diameters (Figs. 5a and 5b and Tables IIa and IIb). The rela-

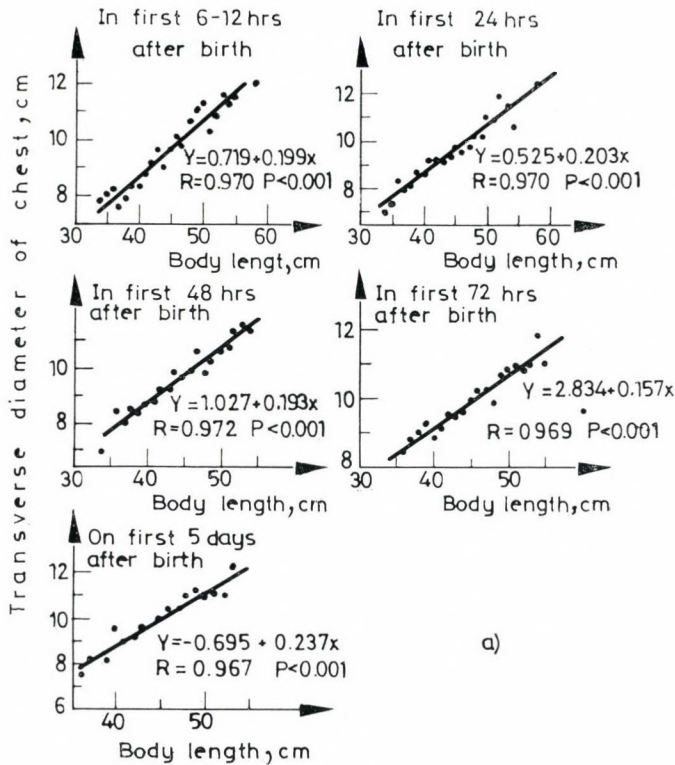


FIG. 5a

relationship was linear. No difference was found between low-weight and mature newborns.

The diameter of the heart increases in the early postnatal period. This does not, however, mean that the heart really increases during the 5 days after birth; it is due to the fact that low weight infants were examined at an earlier point of time than the infants with higher weight.

In this connection the question arises why we judge the size of the chest and heart on the basis of the transverse diameters and not on the basis of surface, volume or weight of the organs, like other authors did

[1, 33, 37]. Our simplified procedure is justified by the fact that the diameters change in a similar way as surface, volume and weight do. This method is well suited for everyday practice; on the other hand, more reliable data cannot be obtained by means of more complicated methods either.

As regards percentual standards, the values for the 90 percentage of the heart are low in the length category of 41–43 cm. Up to 50 cm, the increase in proportion to body weight is steady on the curve of the chest and of the heart.

The correlation between gestational age on the one hand and TTD and

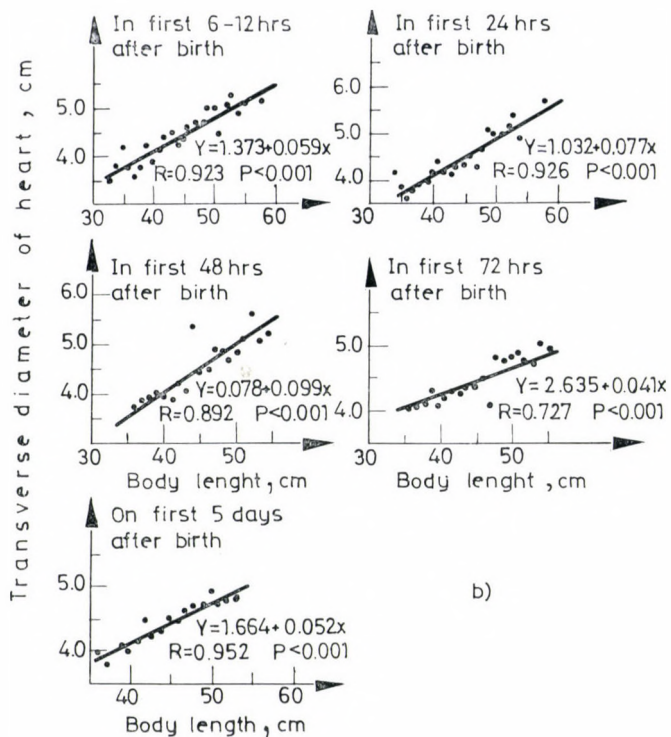


FIG. 5b

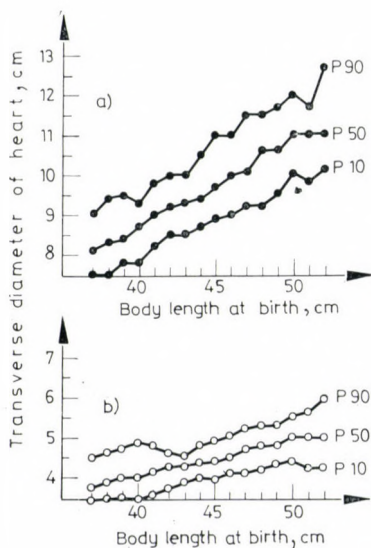


FIG. 6

TABLE II

	N	Age at X-ray investigation					
		6-12 hours		24 hours	48 hours	72 hours	5 days
		130		217	164	177	136
Mean	\bar{z}	4.305		4.412	4.494	4.554	4.602
	\bar{y}	9.236		9.546	9.662	10.133	10.472
	\bar{x}	43.077		44.370	44.613	45.847	47.140
Maximum		58		58	54.0	55	56.0
Minimum	\bar{x}	30		34	39	30	36.0
Maximum		12.5		13.2	12.4	12.6	12.5
Minimum	\bar{y}	6.1		6.8	6.5	7.7	7.5
Maximum		5.5		5.7	6.1	5.7	5.6
Minimum	z	2.9		2.8	3.0	3.4	3.5
Correlation	RYZ	0.212 $0.1 < P < 0.05$		0.740 $P < 0.001$	0.749 $P < 0.001$	0.752 $P < 0.001$	0.656 $P < 0.001$
	RXZ	0.722 $P < 0.001$		0.687 $P < 0.001$	0.615 $P < 0.001$	0.594 $P < 0.001$	0.605 $P < 0.001$
	RXY	0.845 $P < 0.001$		0.801 $P < 0.001$	0.801 $P < 0.001$	0.745 $P < 0.001$	0.745 $P < 0.001$
Deviation	z	0.498		0.551	0.665	0.47	0.422
	\bar{y}	1.257		1.184	1.162	1.025	1.063
	\bar{x}	4.696		4.76	5.815	5.228	3.918
Standard error	z	± 0.053		± 0.038	± 0.051	± 0.038	± 0.036
	\bar{y}	± 0.133		± 0.081	± 0.091	± 0.082	± 0.091
	\bar{x}	± 0.498		± 0.325	0.455	0.417	0.336
Equation		$z = 1.147 + 0.013x +$ $+ 0.280y$		$z = 0.705 + 0.030x +$ $+ 0.247y$	$z = 0.045 + 0.026x +$ $+ 0.339y$	$z = 1.021 + 0.007x +$ $+ 0.317y$	$z = 1.355 + 0.028x +$ $+ 0.183y$

 \bar{x} = Body length at birth \bar{y} = Transverse diameter of chest z = Transverse diameter of heart

CTD on the other was loose in our material. Therefore no percentual standard was constructed in this gestational age group. The correlation seems to be of less importance and, thus, hardly useful in the everyday practice. A comparison with either the standard deviation or the percentual values of our material is believed to be of help in the recognition of pathological conditions if birth weight and body length are known.

The authors quoted dealt little with the height of the diaphragm. Wasson [47] only reported that the right diaphragm was located slightly higher than the left one. Dunham and D'Amico [20] observed that the diaphragm stood higher on the 7th post-natal day than in the first hours after birth. At this age diaphragmic respiration dominates and therefore the diaphragm is less arched than in adults [45]. In our material the diaphragm was at the height of the eighth rib in the majority of cases and was located lower in few cases only.

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J. WEISENBACH, M. D.
Gyermekklinika
H-7623 Pécs, Hungary

The Poland anomalad: a clinical and cytogenetic study of seven cases

By

Liane BORBOLLA, Belkis VÁZQUEZ and Aracely LANTIGUA

Department of Cytogenetics, Paediatric Hospital "William Soler", Havana, Cuba

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Seven patients with Poland anomalad, 6 males and one female, are reported. Four were affected on the right and 3 on the left side. The clinical, radiological and cytogenetic findings in these cases are discussed. In all the patients the nipples were asymmetric, the one on the affected side was sometimes set higher or lower than the one on the normal side, in relation to the extent of the muscle defect. One patient had coloboma of the iris. There was a greater variability of the defect of the upper extremity and especially of the ipsilateral hand than of the muscle anomaly. The hand seemed almost normal in 3 cases but these cases seem to represent the variability of the malformation. All cases were sporadic. Delivery was complicated in 4/7 and one patient had a twin brother with myelomeningocele.

The Poland anomalad or Poland syndrome [2, 3, 7] is the association of a thoracic malformation, essentially an aplasia or hypoplasia of the pectoralis major muscle, especially of its sterno-costal head, with brachysyndactyly of the ipsilateral hand. Absence of the pectoralis minor muscle, hypoplasia of the serratus magnus muscle, micromelia, nipple and mammary defects have also been described. Up to 1972, somewhat less than 100 cases have been published [6].

The anomalad is usually unilateral and occurs sporadically. The incidence amounts to about 1/30,000 births or between 1/10,000 and 1/100,000 [4]. The syndrome seems to show a great variability of expression. Mildly affected patients may have almost normal hands, while others are severely

affected with dextrocardia [9] and renal anomalies [6, 10].

Recently, acute leukaemia has been reported [1, 5, 6] in patients with Poland anomalad. Accurate diagnosis is important to elucidate the relation that seems to exist between the syndrome and haematological malignancy.

To illustrate this point, we present here seven cases of the Poland anomalad and shall discuss the clinical manifestations, radiological and cytogenetic findings.

CASE REPORTS

In all the patients, we have made a clinical study with measurements of the upper extremities and hands and also a radiological examination and comparison

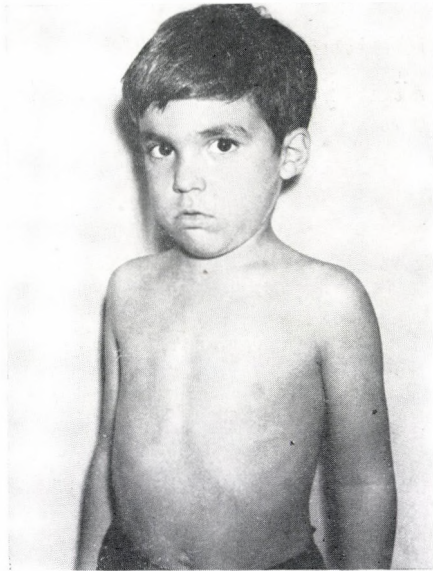


FIG. 1. Case 1. Poland anomalad on right side

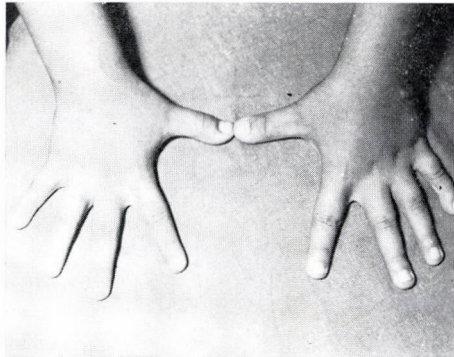


FIG. 2. The hands of Case 1: Slight webbing between fingers 2 and 3 on both sides

of the affected limb with the normal one.

Case 1. — J. A. M., a 3 8/12 year-old boy, was born 2.6.1971, after an eight-month gemellary pregnancy. The father and the mother were 27 years old at the time of the patient's birth. There was no consanguinity. Birth weight was 2.8 kg. There was no history of maternal drug habit, viral infection or X-ray exposure during pregnancy. The mother delivered twin boys by Caesarean section. The twin brother of

the propositus had myelomeningocele and died 6 days after birth. The mother had had no spontaneous abortion, but in a previous pregnancy had delivered a boy who died 3 days after birth, with dextrocardia and a single ventricle. The patient is the only child. The mother during pregnancy had had pyelonephritis and received sulphonamides, mandelamide and nitrofurantoin for more than one month. She also had a positive glucose tolerance test after the

fifth month of gestation. There was no history of diabetes in her family. A chest X-ray was made in the 7th week of pregnancy. The husband had a pararectal fistula which dated from his youth, and his father had also had one in his youth.

The child's general health had been excellent. Mental and motor development were normal. There was no history of respiratory or urinary infection. At physical examination his height was 99 cm, weight 20 kg, head circumference 52 cm. He had a slight defect of the right helix with normally set ears, mild synophrys, malocclusion of the teeth, high arched palate, short neck, hypoplasia of the right pectoralis major muscle, especially its sternocostal head, right hypoplastic nipple set higher than the left one (Fig. 1). He had a funnel chest with moderate prominence of the chondrocostal junction. Both hands appeared to be normal, but there was a slight web between fingers 2 and 3 of both hands (Fig. 2). On the right palm, there was an aberrant Sydney line, and clinodactyly of the left

5th finger. The child is lefthanded. There was no dextrocardia. Four "café au lait" spots were found on the left arm. Intelligence was normal. Laboratory data included a normal haemoglobin concentration, haematoerit and white-cell count. X-rays of the thorax, upper extremities, spine and skull showed no alterations.

Case 2. — J. N. C., a 19-month-old boy, was born 29.9.1974. The father and mother were unrelated and were 47 and 44 years old respectively. The pregnancy was uneventful. This was the mother's fourth pregnancy. She took no drugs and had no viral infection or exposure to radiation during pregnancy.

The child's birth weight was 3.4 kg. His 3 brothers, 30, 27 and 26 years old, respectively, are normal. There was no family history of congenital malformations. The propositus had had no respiratory or urinary infections. At the age of 18 months he had a throat infection with fever and generalized convulsions of five minutes duration. Physical examina-

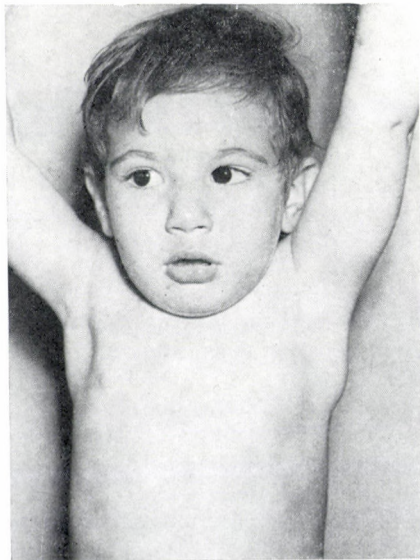


FIG. 3. Case 2. Defect of left pectoralis major muscle, hypoplastic left nipple lying lower than the right one



FIG. 4. Case 3. Coloboma of right iris

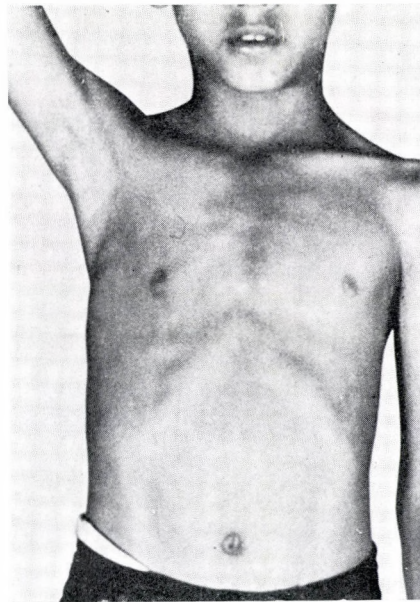


FIG. 5. Case 3. Poland anomalad on right side

tion data: height: 83 cm, weight: 14 kg, head circumference: 50 cm. There was no facial asymmetry. His neck was short and broad. The left pectoralis major muscle was almost absent. The left nipple was hypoplastic and set lower than the right one (Fig. 3). Café au lait spots were present on the anterior surface of the right hemithorax. The upper extremities were equal in size and length. The hands were normal, there was no simian crease or Sydney line on the palms. The boy had

flat feet. Laboratory data included a normal haemoglobin concentration, haematocrit and white-cell count. X-rays of the skull, spine and upper extremities and thorax showed no alterations.

Case 3. — C. A. A., a 9 1/2 year-old boy, was born at term (6-5-1966), after a normal delivery. The mother was 22 and the father 23 years old. There was no consanguinity. The child weighed 3.4 kg at birth. The mother had noted an exanthematous rash in the fifth month of preg-

nancy. There was no history of parental irradiation and the mother had no medication other than vitamins. This was her 2nd child. The 12-year-old brother is normal. The mother had 4 brothers and 5 sisters with no congenital defects.

The patient's mental and motor development had been normal. He had had pneumonia on four occasions and pyelonephritis when he was 8 1/2 years old. On physical examination, his weight was 25 kg, height 133 cm, head circumference 51 cm. Malposition of the teeth and a high arched palate were observed, as well as coloboma of the right iris (Fig. 4). He had a rather long neck. The right costal head of the pectoralis major muscle was hypoplastic in its lower part. The right nipple was set lower than the left one. There was no axillary pterygium (Fig. 5) or dextrocardia. Three café au lait spots were present, one on the right cheek, one on the chin and one on the right arm. Both upper extremities were of the same size and length, but the right hand was smaller. There was increased soft tissue webbing between all the fingers of both hands (Fig. 6), with hyperextensibility of both thumbs and a simian crease on the right palm. The boy was left-handed. There was a wide gap between the first and second toes on both feet. Laboratory data showed normal blood counts, haematocrit and haemoglobin concentration, and urine analysis. Roentgenograms of the skull, chest and spine were normal. X-rays of

the hands showed membranous syndactyly between all the fingers on both hands. The right hand was smaller, with brachydactyly and less developed carpal bones. There was also a smaller interdigital space between the right thumb and second finger. The distal phalanx of the right thumb was punitiform.

Case 4. — D. G. G., a 3-year-old girl, was born 24-8-1973. At that time, the father and mother were 36 and 41 years old, respectively. There was no consanguinity. The child was born by Caesarean section, after a normal nine months pregnancy. Her birth weight was 3.2 kg. The mother had a fall in the 5th month of gestation and denied having had viral infection or having received any medication. The mother's third pregnancy ended in a spontaneous abortion. The child had two half sisters, 27 and 20 years old. The mother is the eldest of a sibship of seven. She had four brothers and two sisters. Two brothers died, and one, 36 years old, was born with malformed feet but it was not possible to examine him.

The patient had always been in good health and her intelligence is normal. On examination, weight and height were 25 kg and 91 cm, respectively, the head circumference was 48 cm. She had normally set ears with underdeveloped lobes. Her neck was short. The sternal head of the left pectoralis major muscle was absent. She had a moderate pectus excavatum in the lower third of the sternum. There was



FIG. 6. The hands of Case 3. The right hand is smaller and there is a membranous webbing between all the fingers

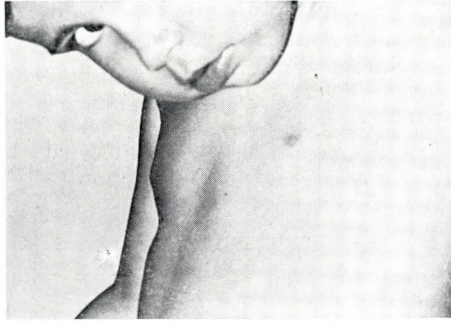


FIG. 7. Case 4. Poland anomalad on left side

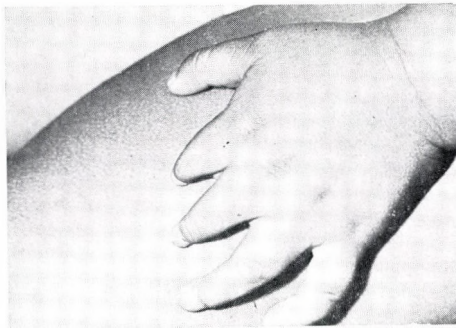


FIG. 8. Left hand of Case 4. Brachydactylic fingers and triangular shape of digits 2 and 3

asymmetry of the nipples, the left being higher than the right (Fig. 7). Both upper extremities were equal in size and length but the left hand was smaller. There was brachydactyly of all the left fingers, more marked in the 2nd and 3rd fingers. These digits had a triangular shape (Fig. 8) and the nails of the first, second and third left fingers were hypoplastic. Both thumbs were hyperextensible, clinodactyly of the fifth left finger was present as well as a simian crease on the left palm. No café au lait spots were seen. Laboratory data showed normal haemoglobin concentration, haematocrit, white-cell count and platelet count. X-rays of the chest, skull and upper extremities were normal. Roentgenograms of the hands showed that the left hand was smaller, with short 2nd and 3rd left metacarpal bones and absence of the intermediate and distal phalanges of the same

fingers. There was also brachydactyly of the left fingers with clinodactyly of the fifth. The first three fingers of the left hand had a triangular shape.

Case 5. — P. L. P., a 15-year-old boy, was born at term (22-1-1961). Maternal and paternal ages were at that time 21 years. After a fall in the fifth month of gestation, the mother had an incipient abortion. She also had cystitis. No history of drug ingestion, viral infection or X-ray exposure were mentioned. After an abnormal delivery complicated by placenta previa, the child was born with 3.1 kg.

The propositus is the oldest son; he has two healthy brothers, 14 and 12 years old. The parents are not related and the mother had had no spontaneous abortion. The patient's health had always been good but recently he had hepatitis. His intelligence is normal. On examination, his weight

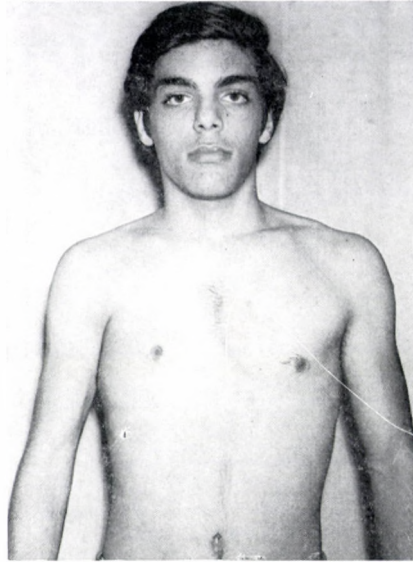


FIG. 9. Case 5. Hypoplasia of right pectoralis major muscle, the right nipple lies higher than the left one



FIG. 10. The hands of Case 5. The right hand is smaller and there is brachysyndactyly

was 60 kg, height 164 cm and head circumference 56 cm. He had a slight synophris with moderate antimongoloid slant and malocclusion of the teeth. The costal head of the right pectoralis major muscle was absent with the ipsilateral nipple set higher than the left one (Fig. 9). Dorso-lumbar scoliosis was also present. The upper extremities were of the same length but the right hand was smaller in size. There was brachysyndactyly of the

right hand (Fig. 10); the syndactyly was more marked between the 2nd and 3rd fingers but was also present between the 3rd and 4th ones. There were no café au lait spots. Laboratory data revealed a normal haematocrit, haemoglobin concentration and white-cell count. Roentgenograms of the chest and skull were normal. X-rays of the upper extremities showed that the humeri were equal in length but the right internal condylus



FIG. 11. Case 6. Poland anomalad on left side. Prominence of the chondrocostal junction

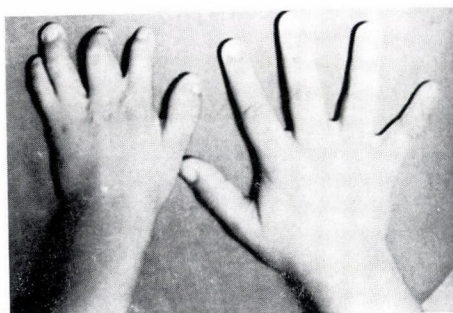


FIG. 12. The hands of Case 6. Brachydactyly with syndactyly on left side

was less developed. Radius and ulna were of the same length on both sides. There was brachysyndactyly with short metacarpal bones and the thumb was smaller than normal. There was also a dorso-lumbar scoliosis with bifid spine (S1).

Case 6. — G. T. G., a 7-year-old boy, was born 10-5-1969, to a 21-year-old mother and a 24-year-old father, after a complicated pregnancy during which two doses of progesterone were administered to the mother. At 6 $\frac{1}{2}$ months of pregnancy, the mother was hospitalized for incipient premature labour with rupture of mem-

branes. This was her first pregnancy. There is no consanguinity or congenital malformation in the family. The child had had asthma during infancy and pneumonia on one occasion. Two surgical interventions were made to repair the syndactyly.

On examination, the propositus measured 122 cm and weighed 25 kg, his head circumference was 53.5 cm. He had a moderate synophrys, a slight retrognathism, the teeth were small and separated and the neck was short. The left pectoralis major muscle was hypoplastic with asymmetry of the nipples, the left being higher

than the right (Fig. 11). He had a funnel chest with prominence of the costochondral junction on the left side. The left upper extremity and the ipsilateral hand were smaller. The left fingers were shorter and the 3rd and 4th were flexed (Fig. 12). A membranous syndactyly was present between the 2nd and 3rd, the 3rd and 4th and the 4th and 5th fingers of the hand. No nail was present on the 5th finger. The left thumb was broad and short with a hypoplastic nail and there was a simian crease on the left palm. There were surgical scars between fingers 2-3 and 3-4. No café au lait spots were detected. The laboratory data were normal and so were the chest and skull X-rays. The left metacarpal bones were shorter than the right ones and the middle phalanges of the 2nd and 4th fingers were lacking, with a rudimentary phalanx on the 3rd and 5th fingers. Distal phalanges were absent also on fingers 3-4-5. There was a punitiform distal phalanx on the left 1st and 2nd fingers and membranous syndactyly between fingers 2-3-4-5 with radial deviation of the distal phalanx of finger 2.

The left hand was undersized. The radius and ulna showed no alterations on either side.

Case 7. — O. M. A., a 4-year-old boy, was born 8-9-1972. The mother then was 26 years old and the father 35 years old. They were not related. The child was born at term after a normal delivery, with 3.4 kg. There is no history of the mother having taken drugs, having had viral infection or having been exposed to radiation during gestation. This was her 2nd pregnancy; the first ended with an artificial abortion. The child's health had been good, at examination his weight was 18 kg, the height 102.5 cm, head circumference 51.5 cm. He had small separated teeth, a short neck, the right pectoralis major muscle was lacking, the right nipple was set lower than the left one (Fig. 13). The right upper extremity was underdeveloped; length and size of the arm and forearm were smaller than normal. The right hand was hypoplastic with hyperextension of the wrist, flexed fingers and adducted thumb (Fig. 14). The thenar and hypothenar eminences were flat, a complete simian



FIG. 13. Case 7. Hypoplasia of right pectoralis major muscle

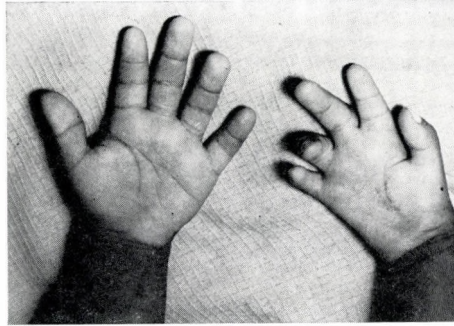


FIG. 14. The hands of Case 7. The affected hand is smaller with flexed brachysyndactylic fingers

crease was present on the right palm and an aberrant one on the left. The 4th and 5th right fingers were contracted. All the fingers were brachysyndactylic and a membranous syndactyly was present between all fingers except between the thumb and the 2nd digit. He was left handed. Haemoglobin concentration, haematocrit and white-cell count were normal. Roentgenograms of the upper extremities showed that the ulna, radius and humerus on the right side were shorter. There was an ulnar deviation of the right fingers with shorter metacarpal bones, membranous syndactyly, a shorter first interdigital space and osteoporosis. X-rays of the chest and skull were normal.

CYTOGENETIC STUDY

A buccal smear for sex chromatin yielded normal results in all the cases. Examination of metaphases from peripheral blood cultures revealed a normal set of 46 chromosomes in 5 cases. In two cases, banding of the chromosomes by trypsin solution and Giemsa staining showed no alteration.

DISCUSSION

Six of the patients were males and one was a female. According to Mace et al. [6] the Poland anomalad shows a male predominance of 3:1 and the right side is affected in about 75% of the cases. In our series the defect was on the right side in 4 and on the left in 3 children. The anomaly of the pectoralis major muscle was marked in 3 (Cases 2, 5 and 6) and slight in 3 (Cases 2, 5 and 6) and slight in 4 cases. Three children had pectus excavatum. A few small café au lait spots were present in 3 children. Asymmetry of the nipples was seen in all the cases. We have observed in our series and in the pictures of other reported cases that the nipple on the affected side was sometimes set higher and sometimes lower than the one on the normal side. This sign might be related to the extent of the pectoralis major muscle defect.

None of our patients had rib defects, herniation of the lungs or dextrocardia.

There was a greater variability of the defect of the ipsilateral upper extremity. Arm length was the least variable, being normal in 5/7. Its width was smaller in 3/7. The forearm was shorter in one but its width was less in 3/7. In one case, the hand seemed normal but was small and there was a slight membranous webbing between the fingers, which were short. This patient had also some bone alterations on X-ray examination. Another child had slight webbing between two fingers, a Sydney line on the palm and clinodactyly of the 5th finger. Case 2 had a normal hand and a normal osseous structure of the upper extremity. Brachydactyly was seen in 5/7 with syndactyly in 4/7 and without syndactyly in one. There was syndactyly alone in one case. In two cases, a flexion contracture of the fingers was present. Case 7 had a malformed hand similar to that of the case reported by David and Saad [3]. As to the brachydactyly, in Cases 4, 5, 6 and 7, the metacarpal bones were short and in Cases 4 and 6 the intermediate phalanges were missing. The distal phalanges were absent in two children. The syndactyly was slight in Cases 1, 3 and 7 and was present between all the fingers except between thumb and index in Cases 3 and 7. In Cases 5 and 6, the syndactyly was more marked and in Case 5 only between the 2nd and 3rd fingers. The patients of Mace et al. [6] showed brachydactyly on the side of the muscle defect in 4/7, absence of phalanges or digits in 3/7. One of their patients had no thumb, and syndacty-

ly was seen in 4/7. Variability was marked in the anomaly of the hand and the degree of the hand defect did not seem to be closely related to the extent of the pectoralis major anomaly. The slight malformation of the hand may be overlooked, as we showed in 2 of our patients, and it seems that in cases called unilateral malformation of the pectoralis major muscle, the hand defect may have been undetected if it was moderate. One of our patients had a malformation not reported until now, a coloboma of the iris on the same side as the muscle defect.

No attempt at abortion was mentioned in our series, in contrast to that of David [2]. Delivery was complicated in 4, and placenta previa and ruptured membranes occurred in 2 of the mothers. In Case 1, the twins were of the same sex and both had congenital defects: one had Poland anomalad and the twin who died, a myelomeningocele. Myelomeningocele is a closure defect compatible with a multifactorial/threshold explanation and this might be a possibility also as regards the Poland anomalad.

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Prof. Liane BORBOLLA
 San Francisco 10112,
 La Habana 8, Cuba

Poland anomalad: dermatoglyphic study in seven cases

By

Liane BORBOLLA, Belkis VÁZQUEZ and Aracely LANTIGUA

Department of Cytogenetics, Paediatric Hospital "William Soler", Havana,
Cuba

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A dermatoglyphic study was made in seven patients with Poland anomalad. The ipsilateral hand showed great variability of the defect. The patterns were typical when the hand was synbrachydactylic. When there was only brachydactyly, there were peculiar configurations. Though the hand on the side of the defect may seem normal, some patterns are infrequent and on the "normal" hand on the other side, rare dermatoglyphic types were found.

The clinical features of seven cases of Poland anomalad have been reported previously [3]. In this study, the dermatoglyphics of these patients are described. The variability of defects found in the hands led us to look for special patterns in cases with apparently normal hands or in hands with brachydactyly only and also to verify if the alterations described in syndactyly were present.

MATERIAL AND METHODS

Finger and palm prints of seven patients with Poland anomalad [3] were recorded by the standard ink method. The data studied were fingerprint pattern, finger ridge count, pattern intensity index, configurations in the thenar/I, hypothenar and interdigital areas II, III and IV, width of the α angle, position of the axial triradius [12] modal types of the C and D lines [4, 10] main line terminations, main line index, a—b ridge count and presence of simian crease or Sydney line.

The general morphology of the hand was also studied as well as the size of the affected hand compared with the normal one.

RESULTS

In three patients with apparently normal hands (Figs 1, 2, 3) the dermatoglyphic traits were as follows. In two patients, the axial triradius was in position t^1 and in one (Case 1) no axial triradius was found. In two, the modal type of line C was intermediate; the modal type of line D was 11 in two and 9 in the third child. There was a transversality of the ridges in two patients, a Sydney line was observed in one and a simian crease in another (Tables I and II). In all the three patients there was a medial displacement of the triradius d and in one case a distal one of the triradius b. In the girl with isolated brachydactyly (Fig. 4) four arches

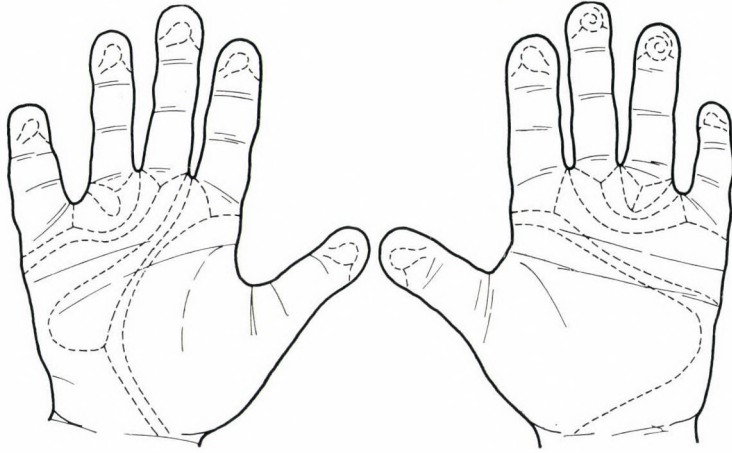


FIG. 1. Case 1. Slight webbing between fingers 2—3

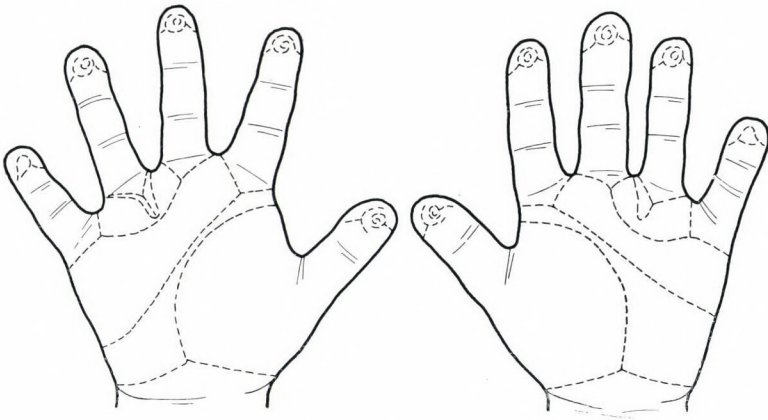


FIG. 2. Case 2

were seen on the fingers, there was an axial triradius t^1 and a low finger ridge count. The pattern intensity index was 1 and a simian crease was present. There was displacement of the subdigital triradii: medial for triradius d and distal for triradius b (Tables I and II).

Among the three patients with brachysyndactyly, in two (Cases 5

and 6) there was a zygodactylous pattern with a triradius in the third interdigital space. In Case 5, another interdigital triradius was below the first and two of the radiants formed a distal loop in the fourth interdigital space; the triradius d was displaced medially and the triradius a was absent. In Case 6, we had difficulty in locating the subdigital triradii

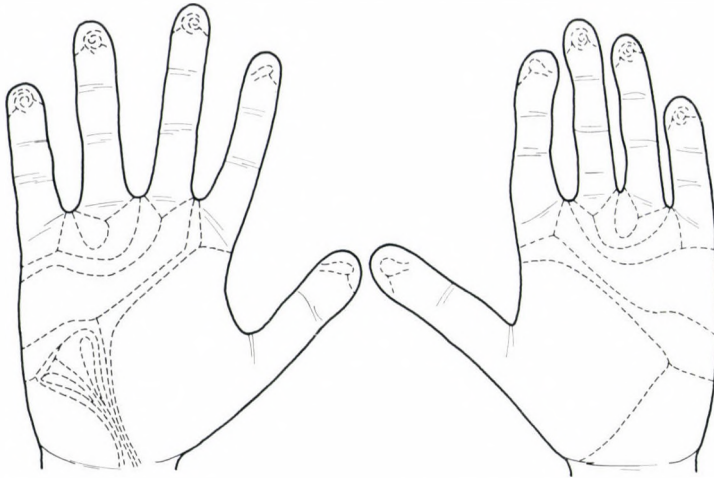


FIG. 3. Case 3. Membranous webbing between fingers 2-5 of both hands

because the child had been operated upon, and there were scars in these areas but a bc triradius was observed and triradius d was absent. Both these cases had the axial triradius in a distal position t^l and t^{ll}, true pat-

terns in the thenar/I area and arches in the fingers with low pattern intensity index and low finger ridge count. A simian crease was also present in one (Figs 5a, 5b and 6). The other child (Case 7) with a brachydactylic

TABLE I
Dermatoglyphics of the ipsilateral hand

Case No.	Digital patterns					Atd angle	Position of t	Thenar area	Hypothenar area	Interdigital		
	I	I	III	IV	V					II	III	IV
<i>Right hand</i>												
1	U	U	W	W	U	—	—	0	A ^r	0	0	0
3	U	U	W	W	W	52°	t'	0	A ^u /A ^c	0	L	0
5	A	A	A	U	U	—	t'	L ^p	A ^u /A ^c	0	t	L
7	U	W	U	W	W	43° 48° 44°	t t' t'	0	L ^c /I ^u	0	0	0
<i>Left hand</i>												
2	W	W	W	W	U	50°	t'	0	A ^u /A ^c	0	0	V
4	A	A	A	A	U	54°	t'	0	A ^u /A ^c	0	0	L
6	A	A	A	U	A	—	t''	L ^p /L ^d	A ^u /A ^c	0	t	0

TABLE II
Dermatoglyphics of the ipsilateral hand

Case No.	RC	PII	a-b ridge count	Modal type of line C	Modal type of line D	MLI	Main lines formula	Simian crease	Sydney line
<i>Right hand</i>									
1	98	7	45	intermediate	11	10	11.X.7.4	0	X
3	92	8	43	radial	11	10	11.9.7.4	X	0
5	13	2	—	—	11	—	13.0id0.0	0	0
7	73	8	45	—	—	9	1.1.1.13	X	0
<i>Left hand</i>									
2	93	9	43	intermediate	9	8	10.X.6.3	0	0
4	11	1	35	ulnar	9	5	9.7.5".1	X	0
6	11	1	—	—	—	—	0.0id0.5"	X	0

small hand had a triradius t^l with two other triradii in a proximal position: one forward in relation to the radial border, t, with a parathenar pattern and another on the cubital border t^l with a hypothenar true figure. The main line A ran a vertical course and seemed to end in position 13, whereas the main lines B, C, D seemed to end in 1. The subdigital

triradii a, b, c were displaced distally and triradius d was displaced toward the third interdigital space. A simian crease was seen and the contracted fingers 4 and 5 had no interphalangeal flexion creases. No metacarpophalangeal creases were present on fingers 2—5 (Fig. 7).

On the hand on the unaffected side, the axial triradius was in posi-

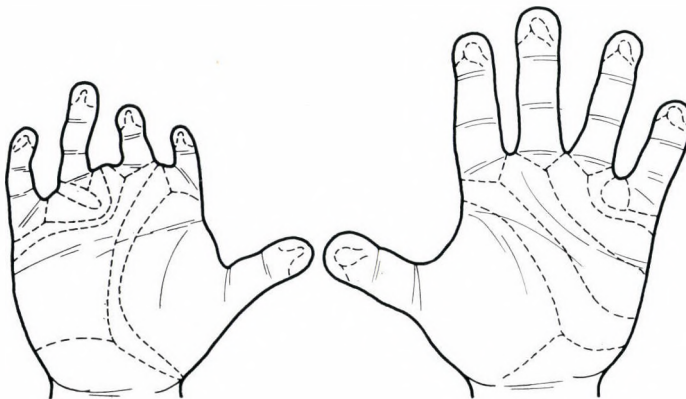


FIG. 4. Case 4. The only girl in this series. Small left hand with brachydactyly

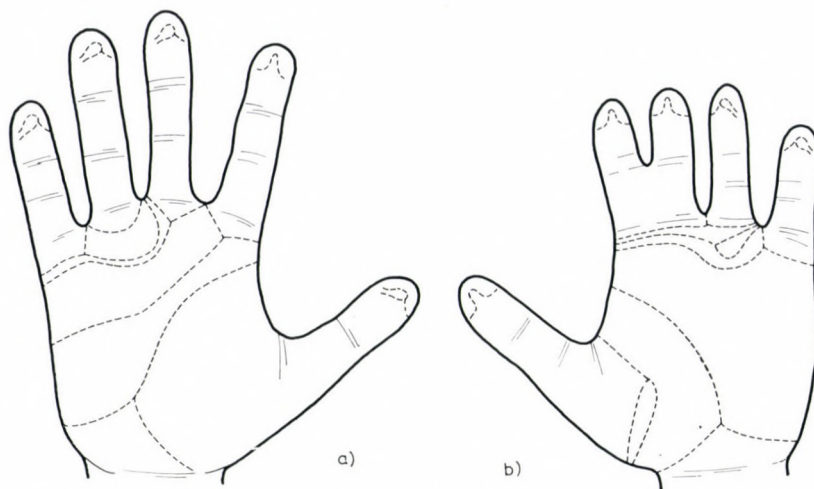


FIG. 5a. Case 5. Left hand
 FIG. 5b. Case 5. Right hand with brachysyndactyly and zygodactylous pattern

tion t^I in 5 cases and in t^{II} in 1. This case had a rare pattern on the hypothenar area, $L^c/V/A^c$. The a—b ridge count was within normal limits compared with our controls in all but one child; this patient had a high count of 52.

(In 200 male controls the mean a—b ridge count was, on the left hand, 40.86 ± 5.59 ; on the right hand, 40.18 ± 10 . In 150 female controls the mean a—b ridge count was, on the left hand, 41.74 ± 5.52 ; on the

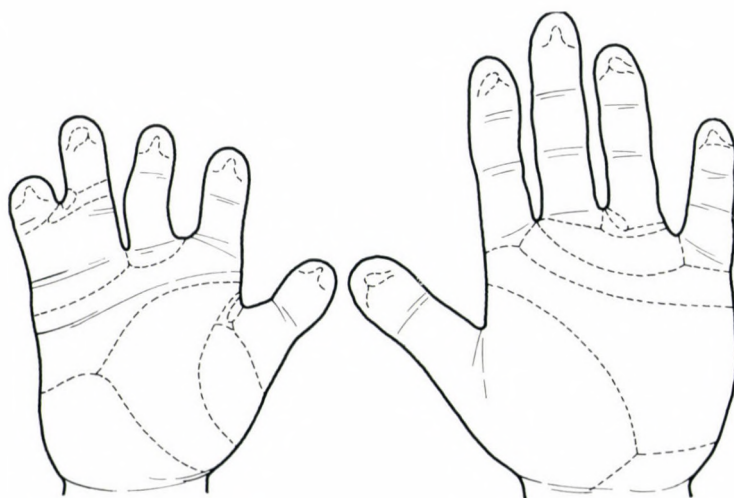


FIG. 6. Case 6. Brachysyndactyly and zygodactylous pattern

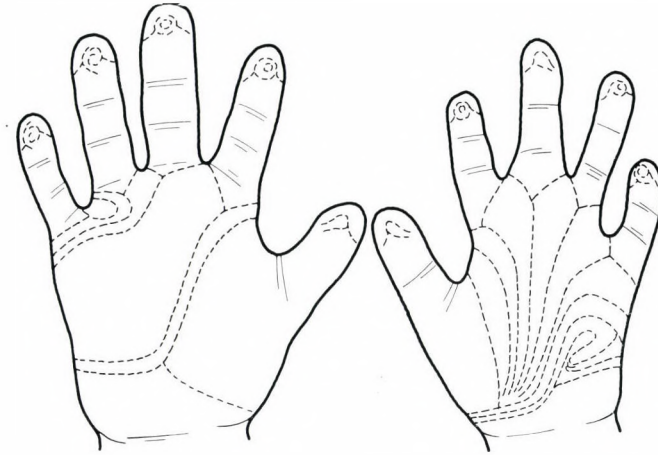


FIG. 7. Case 7. The affected hand is small, brachysyndactylic and some fingers are contracted

right hand, 40.94 ± 5.65 .) In one, the modal type of line C was absent. The pattern intensity index was high respectively low in two children each. The main line index was low in 4. The main line A ended in 1 in 2 cases; there was a Sydney line in 1 and a simian crease in another case (Tables III and IV). Medial displacement of the triradius subdigital d was found in 4; the triradius b was more distal in 2 and the triradius c more distal in 1.

DISCUSSION

The first dermatoglyphic study in the Poland anomalad seems to have been made by David [5] and Freire-Maia et al. [7]; in David's 10 cases the dermatoglyphics of the unaffected hand were entirely normal. Freire-Maia et al. described a distal axial triradius, a simian crease and an

interdigital triradius in two patients with four-finger synbrachydactyly (as in our Case 6) and another case with two arches on the fingers, a distal triradius t^1 , a subdigital triradius d by itself and a simian crease.

In these cases there was a distinct pattern with syndactyly and apart from the well-known zygodactylous pattern, mention must be made of the distal position of the axial triradius, the presence of arches and of a simian crease or a Sydney line. None of our patients had radial loops on the thumb as observed by David and Saad [6].

In cases without syndactyly, dermatoglyphic abnormalities [6] which seem to be characteristic of the Poland anomalad have been infrequent, especially on the 1st and 5th digits where in 400 controls they never occurred. In addition, there was a distal or medial displacement of the subdigital axial triradius. These peculiar features

TABLE III
Dermatoglyphics of the normal hand

Case No.	Digital patterns					Atd angle	Position of t	Thenar area	Hypothenar area	Interdigital		
	I	II	III	IV	V					II	III	IV
<i>Right hand</i>												
2	W	W	W	W	U	50°	t'	0	A ^u /A ^c	0	L	V
4	U	U	U	U	U	47°	t'	0	A ^u /A ^c	0	0	L
6	U	R	A	U	U	42°	t	0	A ^u	0	L	0
<i>Left hand</i>												
1	U	U	U	W	U	54°	t'	0	L ^f /A ^c	0	0	L
3	U	U	W	W	W	87°	t'' t'	0	L ^c /V/A ^c	0	0	L
5	A	U	U	U	U	46°	t'	0	A ^u /A ^c	0	0	0
7	W	W	W	W	W	45°	t'	0	A ^u /A ^c	0	0	L

TABLE IV
Dermatoglyphics of the normal hand

Case No.	RC	PII	a-b ridge count	Modal type of line C	Modal type of line D	MLI	Main lines formula	Simian crease	Sydney line
<i>Right hand</i>									
2	94	9	39	radial	9	10	10.9.6.5'	0	0
4	—	5	36	ulnar	7	5	7.5."5'.3	0	0
6	51	4	38	radial	11	11	11.9.7.5'	0	X
<i>Left hand</i>									
1	90	6	47	ulnar	9	5	9.7.5."1	0	0
3	92	8	39	ulnar	9	5	9.7.5."1	0	0
5	51	4	52	absent	9	9	9.0.5."5'	0	0
7	69	9	43	ulnar	7	5	7.5."5".3	X	0

were present in our cases with brachydactyly and in that with brachysyndactyly and finger contracture. As a slight membranous webbing is easily overlooked, studies of the dermatoglyphics are needed in cases with little webbing because the patterns in our cases were similar as those reported by David and Saad [6].

The "normal" ipsilateral hand of our patients also displayed some abnormalities. In a report of two patients lacking only the pectoralis major muscle, Armendares [1] mentioned an axial triradius in t^I and t^{II} in one and the equivalent of a simian crease in the other; these cases may have been Poland anomalads. The great

variability of the hand defect has repeatedly been noted [7, 9] and not all the published cases have had the typical synbrachydactyly described for the first time by Poland [11]. When the hand on the side of the muscle defect seems normal, a dermatoglyphic study may reveal peculiarities similar to those observed in our cases and it is reasonable to assume that these are valuable clues in the diagnosis of the anomalad.

Summing up, the special dermatoglyphic pattern observed in the Poland anomalad are the presence of arches or radial loops on the fingers, low pattern intensity index, low ridge count, distal displacement of the palmar (the axial and the subdigital) triradii, zygodactylous pattern or medial displacement of the subdigital triradii, their absence, a simian crease or a Sydney line. Recently, some papers [1, 2, 8, 9] have mentioned the association of Poland anomalad with leukaemia. It is interesting that the latter patients and their sibs have more Sydney palmar flexion creases than their parents or the controls [13]. We found a Sydney line in two of our 7 patients, but until now none of them had developed leukaemia.

Prof. Liane BORBOLLA
San Francisco 10112,
La Habana 8, Cuba

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Der wachsende Schädel

II. Der Gesichtsschädel: Statistische Auswertung

The growing skull

II. The face: statistical considerations

Von

K. GEFFERTH

I. Kinderklinik der Medizinischen Universität Semmelweis, Budapest
Eingegangen am 25. Februar 1977

Es wurden die Strecken und Winkel an Röntgenogrammen des Gesichtsschädels von 540 Knaben und 504 Mädchen von der Geburt bis zur Pubertät gemessen. Vom Tuberculum sellae als Ausgangspunkt gingen 3 Strecken und 3 Winkel, vom Nasion 2 Strecken aus. Eine 2-2.5 fache Zunahme der Strecken, bei Knaben deutlicher als bei Mädchen, wurde festgestellt. Den größten Zuwachs wiesen die zur Kinnschuppe ziehenden Strecken auf. Die Winkel zeigten bei beiden Geschlechtern eine mäßige, bei Knaben eine unbedeutend größere Zunahme. Manche Eigentümlichkeiten bezüglich Wachstum der einzelnen Winkel sowie hinsichtlich rassischer Unterschiede wurden festgestellt.

Distances and angles were measured on the facial X-rays of 540 boys and 504 girls of Hungarian origin from birth to late puberty. Three distances and three angles were established having the tuberculum sellae as centre and two distances from the nasion. A 2-2.5fold increase in the distances was observed; it was more pronounced in boys than in girls. The greatest increase was observed in the mandible-prosthion distance. There was a moderate increase in the angles, more in boys than in girls.

In einer früheren Arbeit [4] wurden bei Patienten im Alter von 1 Tag bis 17 $\frac{1}{2}$ bzw. 19 Jahren die Strecken und Winkel an Röntgenaufnahmen des Neurocranium abgemessen. Es wurden einige Eigentümlichkeiten des Wachstums der Strecken und Winkel beschrieben. Das Bild des wachsenden Schädels wäre jedoch ohne Auswertung des Gesichtsschädels unvollkommen: das Gesicht ist nämlich die »komplizierteste Partie unseres Körpers, sowohl in bezug auf die Zahl als auf die Art und Mannigfaltigkeit der Organe, die es einschließt« [6]. Es ist auch bekannt, sogar selbstverständlich, daß sich die Rassen-

und individuellen Unterschiede am augenfälligsten am Gesicht, und viele Krankheiten in abnormalen Gesichtszügen bzw. Proportionen äußern. Die Messung des Gesichtsschädels wäre schon deshalb gerechtfertigt. Eine Früherfassung abnormen Wachstums oder kleineren Abweichungen von der Norm sind auch nur im Besitz einer genauen Ausmessung der Norm gegeben. Zweck dieser Arbeit war, die physiologischen Längen- und Winkelmaße in den aufeinanderfolgenden Wachstumsphasen von Knaben und Mädchen an Röntgenaufnahmen gesondert festzustellen.

MATERIAL UND METHODE

Analysiert wurden jene in unserem Filmarchiv auffindbaren Schädelröntgenaufnahmen, die auch bei der Ausmessung des Neurocraniums verwendet wurden. Das Material bestand aus 540 Knaben und 504 Mädchen von der Geburt bis zur Nachpubertät. Die Gruppeneinteilung erfolgte wie in der früheren Arbeit [4]. Gruppen mit kleinen Zeitspannen erleichtern die Einordnung der zur Untersuchung kommenden Fällen in entsprechenden Kategorien und auch den Vergleich mit den Werten anderer Autoren. Die einzelnen Forscher verwendeten sehr verschiedene Einteilungen. So findet man bei SCHMID und FILTHUT [7, 8] 19 Gruppen. SINGH und SAVARA [10] untersuchten Kinder von 3 bis 16 Jahren in jährlichen Abständen, CURRARINO [3] mißt im ersten Jahr zweimonatlich, dann im Alter von anderthalb Jahren und jährlich vom zweiten Lebensjahr. BRODIE [2] machte bei seinen longitudinalen Beobachtungen Aufnahmen dreimonatlich im ersten Jahr, zweimonatlich bis zum fünften Jahr und später in jährlichen Abständen. So schien es vorteilhaft, kleine Zeitspannen in eine Gruppe zusammenzufassen, wenn auch wegen der kleinen Zahl der Fälle keine so ausgeglichenen Werte zu erwarten waren, wie bei größeren Gruppen.

Es kamen auch diesmal Strecken und Winkel zur Auswertung. Bei Festlegung der Orientierungspunkte wurden möglichst solche gewählt, die am besten über Größen- und Formveränderung orientieren, deren Auffindung keine Schwierigkeiten bereitet und die vergleichbare Meßwerte liefern. Der in der früheren Arbeit angenommene Ausgangspunkt am Tuberculum sellae wurde mit einem anderen am Nasion ergänzt, um auch die Höhenzunahme direkt feststellen zu können. Die vom Tuberculum sellae zum Nasion ziehende Strecke wurde auch diesmal als Grundlinie betrachtet. Die erste Strecke läuft vom Tuberculum sellae zur Spina nasalis ant.: Strecke 10 (Strecken bis 9 beziehen sich auf das

Neurocranium). Die folgende Strecke zieht vom Tuberculum zur Spitze des ersten Schneidezahns: Strecke 11. Dieser Orientierungspunkt wurde auch vor dem Ausbruch der Zähne beibehalten. Die letzte Strecke vom Tuberculum sellae verläuft zur Kinnspitze, zum Prosthion: Strecke 12.

Vom Nasion gehen zwei Strecken nach unten: Strecke 13 zur Kinnspitze und Strecke 14 zur Spitze des ersten Schneidezahns. Es sind insgesamt fünf Strecken, von denen die ersten drei hauptsächlich die Längen-, die beiden letzteren die Höhenzunahme repräsentieren (Abb. 1).

Da zur Ausmessung aus einer Entfernung von 1 m angefertigte Röntgenbilder dienten, bei denen der Öffnungszustand des Mundes keine Rolle spielte, mußte eine Methode gefunden werden, um Aufnahmen mit unterschiedlicher Mund- bzw. Mandibulastellung verwenden zu können. Auf die Stellung des Unterkiefers muß besonders bei kleinen Säuglingen geachtet werden; ihre Stellung vor dem Ausbruch der Schneidezähne verrät sich lediglich durch den Weichteilschatten der Gingiva. Berühren sich die gesenseitigen Gingivae, ist die Aufnahme zur Auswertung geeignet (Abb. 2). Auch bei Säuglingen kann es aber vorkommen, daß sich bei geschlossenem Mund die Gingivae nicht berühren [2]. In solchen Fällen oder wenn die Aufnahme bei offenem Mund angefertigt wurde, mußte eine Korrektur stattfinden. Zu diesem Zweck wurde vom Unterkiefer eine Skizze gezeichnet und so an den Oberkiefer genähert, wie sich der Unterkiefer bei geschlossenem Zustand befindet, was sich bei durchgebrochenen Schneidezähnen ohne Schwierigkeiten ausführen läßt. Vor dem Ausbruch der Zähne muß es aber durch genaue Feststellung der Gingivakontur erfolgen (Abb. 3). Bei Fällen, wo sich Gelegenheit bot, Ausmessungen mit offenem und mit geschlossenem Mund zu machen, überzeugten wir uns von der Richtigkeit dieses Verfahrens.

Die Winkel wurden lediglich mit der Spitze am Tuberculum sellae angestellt und ausgemessen. Der Winkel zwischen

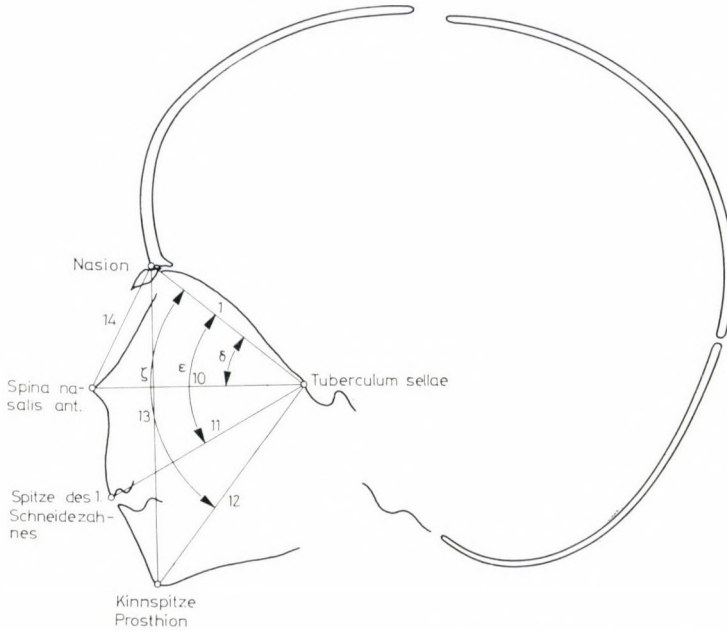


ABB. 1. Zeichnung einer seitlichen Schädelröntgenaufnahme, wie sie zur Ausmessung verwendet wurde. Darstellung der Orientierungspunkte der Strecken und Winkel. Die Strecke vom Tuberculum sellae wird als Grundlinie betrachtet: Strecke No. 1. Vom Tuberculum zieht die Strecke 10 zur Spina nasalis ant., die Strecke 11 zur Spitze des ersten Schneidezahnes, die Strecke 12 zur Kinnspitze, zum Prosthion. Mit dem Scheitel am Tuberculum sellae liegen 3 Winkel. Zwischen Strecke 1 und 10 befindet sich Winkel δ , zwischen Strecke 1 und 11 Winkel ϵ und zwischen Strecke 1 und 12 Winkel ζ . Vom Nasion wurden die Strecke 13 zur Kinnspitze und zur Spina nasalis ant. die Strecke 14 gezogen

FIGURE 1. Tracing of a frontal cephalogram with landmarks, distances and angles. The plane tuberculum sellae and nasion have been used as orientation planes. No. 1. From tuberculum to anterior nasal spine: distance No. 10. From tuberculum to the top of the first incisor: distance No. 11., and to prosthion: distance No. 12. Angles with the vertex on tuberculum sellae are: between lines 1 and 10 the angle δ , between 1 and 11 the angle ϵ and between 1 and 12 the angle ζ . From the nasion to the superior nasal spine the distance No. 14 and to the prosthion the distance No. 13. have been investigated.

Strecke 1 und 10 wurde mit δ bezeichnet (Winkel α , β , γ befinden sich am Neurocranium). Zwischen Linie 1 und 11 liegt der Winkel ϵ und zwischen 1 und 12 der Winkel ζ . Es schien überflüssig, auch Winkel mit dem Scheitel am Nasion liegend zu untersuchen. Die Längen- und Höhenzunahme des Unterkiefers kann durch die am Tuberculum liegenden Winkel und durch die von hier und vom Nasion ausgehenden Strecken ausreichend dargestellt werden.

Ausmessungen des Gesichtsschädels an in a—p Richtung gemachten Aufnahmen wurden nicht vorgenommen, da Messungen an seitlichen Aufnahmen den praktischen Forderungen hinsichtlich Größenzunahme und Formveränderung auszureichen schienen. Eine Korrektion der unrichtigen Unterkieferstellung, wie wir es an seitlichen Aufnahmen gemacht haben, läßt sich auch kaum ausführen, so daß wir, besonders in den früheren Lebensperioden, kein ausreichendes Material hatten. Messungen

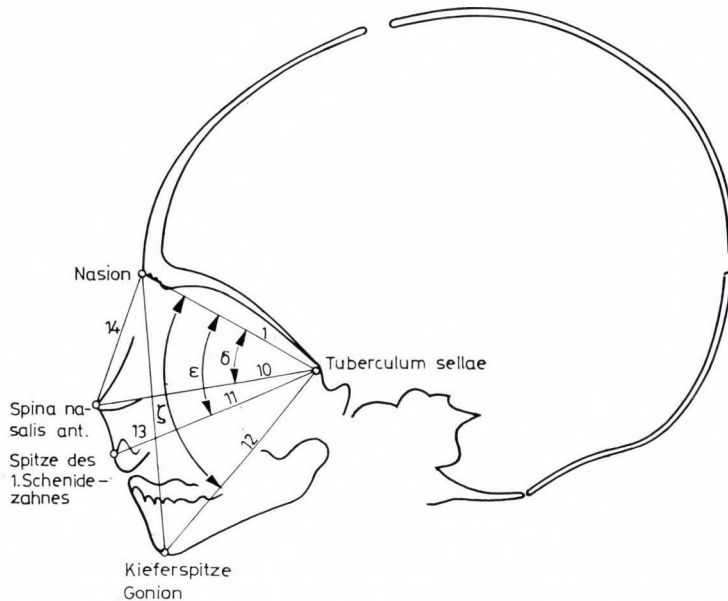
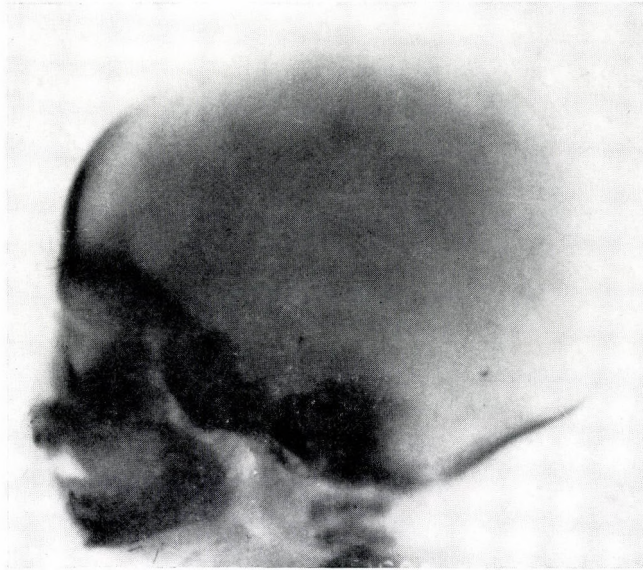


ABB. 2. Seitliche Schädelröntgenaufnahme eines 2 Tage alten Neugeborenen mit Skizze. Der Mund ist geschlossen. Gingivae beider Kiefer berühren sich. Die Zahnkeime befinden sich tief im Weichteilschatten der Gingivae, die unteren Keime, etwas hinter den oberen. Der zweite Markierungspunkt wurde bei solchen Fällen an der Spitze des oberen Schneidezahnkeimes festgelegt

FIG. 2. Lateral X-ray of a two days old baby and tracing. Mouth closed. The contours of the maxillary and mandibular gums in contact. The tooth germs are deep in the shadow of the gums. The inferior incisor is behind the superior incisor. The second mark of orientation is at the outmost corner of the germ of the superior incisor.

dieser Art wurden in jüngster Zeit von SCHMIDT und Mitarb. [9] vorgenommen.

BESPRECHUNG

Es hat sich herausgestellt, daß bei der Geburt Mädchen höhere Werte aufweisen als Knaben. Tabelle I zeigt unsere Meßergebnisse der fünf Strecken ausgedrückt in arithmetischen Mittelwerten und $\pm\sigma$ bei Knaben, und Tabelle II bei Mädchen. Der Nachteil wird von den Knaben bald eingeholt. Wenn man von den in Gruppe 2 gefundenen Werten absieht, wo die Knaben einen jähen Vorsprung machen, findet sich in Gruppe 3 ein gewisser Ausgleich, und im Alter von 6 Wochen haben die Knaben die Mädchen bereits überholt. Dieser Vorteil wird dann bis zum Ende der Beobachtungszeit beibehalten. Grob gerechnet findet eine Vergrößerung statt, die eine Verdoppelung der Anfangswerte oder mehr ausmacht und die bei Knaben ausgiebiger ist als bei Mädchen. Die größte Zunahme wurde in Übereinstimmung mit BRODIE [2] und SCHMID und FILTHUT [8] an den Strecken mit Endpunkt an der Unterkieferspitze, also an den Strecken Nr. 12 and 13 erreicht. Je weiter die Strecken von der Unterkieferspitze entfernt liegen, um so geringer ist die Zunahme. BRODIE [2] betonte, daß trotz des unterschiedlichen Wachstums die Form des Gesichts gleich bleibt. SCHMIDT und Mitarb. [9] konnten an a—p Aufnahmen ein stärkeres Wachstum bei Mädchen mit Ausnahme der Mandibularhöhe verzeichnen, kamen schließlich doch zu

dem Endergebnis, daß eine Gleichmäßigkeit in den Gesichtsschädelmaßen besteht. Diese Beobachtung kann aber nicht verallgemeinert werden. Die Mandibula scheint eine gewisse Selbständigkeit unter den Gesichtsknochen aufzuweisen. Im Gegensatz zu den Krankheitsbildern mit einer Hypoplasie des Unterkiefers, konnte bei an Vitamin D resistenter Rachitis leidenden Kindern ein verzögertes Wachstum der übrigen Gesichtsknochen, jedoch eine fast ungestörte Vergrößerung der Mandibula beobachtet werden [11].

Unsere Strecken Nr. 11, 12 und 13 sind mit den Strecken VIII, IX und X von SCHMID und FILTHUT [8] identisch angelegt, jedoch wurden Knaben und Mädchen nicht getrennt, sondern zusammen ausgewertet. Mit einem gewissen Vorbehalt dürfte ein Vergleich von Interesse sein. Als erstes läßt sich feststellen, daß unsere Neugeborenen kleinere Ausgangswerte aufweisen. Dieser Nachteil besteht auch dann, wenn man unsere 3—5 Wochen alten Säuglinge mit den 0 bis 1 Monate alten der ersten Gruppe von SCHMID und FILTHUT [8] vergleicht. Mit der Zeit ändert sich die Situation. Der Rückstand wird bei den Strecken 11 und 12 nicht nur eingeholt, sondern sogar überholt, so daß im Alter von 14 Jahren nicht nur die Knaben, sondern auch die Mädchen viel höhere Werte aufweisen. Die Strecke 13 bleibt jedoch auch im weiteren rückständig. Das würde somit bedeuten, daß die Mandibula stärker, die Gesichtshöhe weniger wächst als im Material von SCHMID

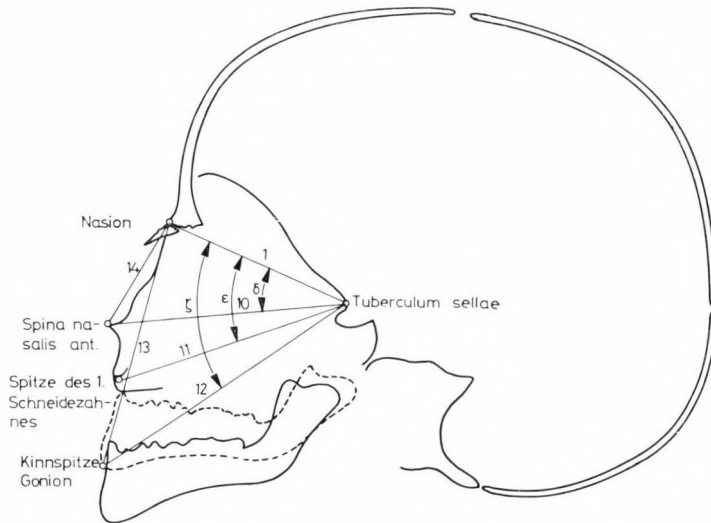
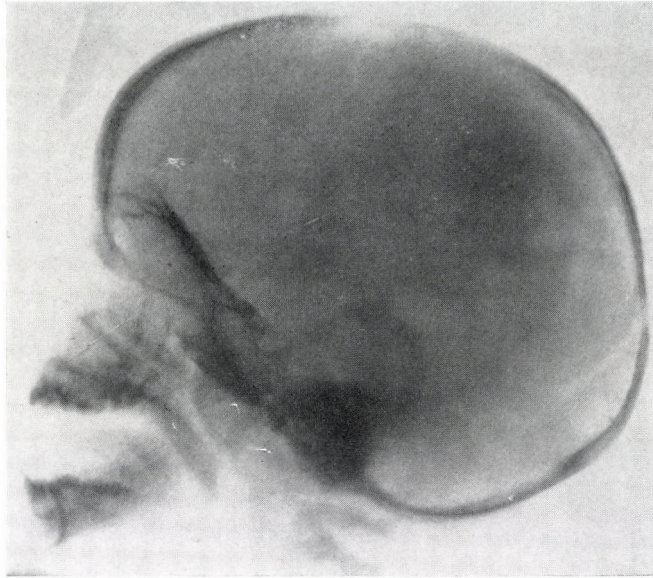


ABB. 3. Seitliche Schädelröntgenaufnahme eines 8 Monate alten Knabens, mit Skizze. Der Mund ist geöffnet, deshalb mußte vom Unterkiefer eine separate Skizze gezeichnet werden und so an die Maxilla genähert, wie sich der Unterkiefer bei geschlossenem Zustand des Mundes befindet. Zur Orientierung dienen die Zähne. Die oberen Schneidezähne stehen vor dem Ausbruch, die unteren sind bereits durchgebrochen. Diese sollten an die Gingiva der Maxillae genähert werden. Weil sich aber beim Mundöffnen die Mandibula nach vorne verschoben hat, mußte sie dementsprechend zurückgeschoben werden. Gerade Linie: Mund im offenem Zustand. Die gebrochene Linie repräsentiert die separate Skizze

FIG. 3. Lateral cephalogram and tracing of an 8 months old by. The mouth is open; it was therefore necessary to draw an extra tracing from the mandible. This was placed near the maxilla according to physiological posture. The teeth served for orientation. The upper incisors are before cutting out, the lowers are already out. The latter incisors are to be brought opposite to the contour of the gum of the Maxilla. As the mandible has moved forward on opening the mouth the tracing had to be moved something backward accordingly. — Straight line: mouth open. Broken line is representing the extra tracing from the mandible.

und FILTHUT [8], also war bei unseren Kindern das Wachstum des Gesichtschädels nach vorne und bei denen von SCHMID und FILTHUT ausgeprägt stärker in der Höhenrichtung.

Die Obergesichtshöhe repräsentierende Strecke 14 sollte noch mit den Werten von SINGH und SAVARA [10] verglichen werden. Diese Autoren haben 3 bis 16 Jahre alte Mädchen in jährlichen Abständen untersucht. Es ist merkwürdig, daß ihre Meßwerte bei allen Altersstufen geringer sind als unsere. Der Unterschied macht 5 mm im Alter von 3 Jahren und 6 mm mit 16 Jahren aus. Weil nun diese Meßstrecke einen Teil der ganzen Gesichtshöhe repräsentiert, haben diese Mädchen niedrigere Gesichter als die unseren, obwohl die Gesichtshöhe der letzteren geringer war als bei den Kindern von SCHMID und FILTHUT [8]. Wenn man bedenkt, daß bei den Messungen der genannten Autoren [8, 10] Kinder germanischer Abstammung zur Untersuchung gelangten, ist der Unterschied noch auffallender.

SINGH und SAVARA [10] machten longitudinale Untersuchungen, während SCHMID und FILTHUT [8] Klinikaufnahmen ohne Auswahl verwendeten. Es stellt sich die Frage, ob und wie weit eine relativ kleine, wenn auch ausgewählte Population als repräsentativ betrachtet werden darf. Unserer Meinung nach kann die horizontale Untersuchung der longitudinalen überlegen sein und man sollte jedesmal überlegen, welcher der Methoden der Vorzug gehört.

Die Größe der Winkel im Neugeborenenalter ist bei Knaben und Mäd-

chen etwa die selbe. Die größte Zunahme findet in den ersten $2-2\frac{1}{2}$ Jahren statt, wobei das Kauenerlernen auch einen Einfluß haben kann. Die Zunahme scheint zu dieser Zeit bei Mädchen bescheidener zu sein als bei Knaben (Tabelle III, IV).

Jeder der Winkel entwickelt sich charakteristisch. Der Winkel δ zeigt während der ganzen Beobachtungszeit eine ständige Zunahme, wobei die Mädchen den früheren Rückstand einholten. Dieser Winkel bildet insofern eine Ausnahme, daß die Zunahme nach dem zweiten Lebensjahr etwa mit der früheren Zunahme identisch war (Tabelle IV).

Der Winkel ε nimmt am meisten in den ersten zwei Jahren zu, kann aber auch bis zum fünften-sechsten Lebensjahr ein beträchtliches Wachstum aufweisen, wobei das Vordringen der Zähne eine Rolle spielen kann. Von dieser Zeit an weisen die Mädchen einen kleinen Vorsprung auf (Tabelle IV).

Den Höhepunkt erreicht der Winkel ζ bei beiden Geschlechtern etwa im Alter von $1\frac{1}{2}-2$ Jahren, mit einer Zunahme von 9° . Dann folgen Abwechslungen mit einer Tendenz zum Sinken, wobei die Mädchen schließlich etwas kleinere Werte aufweisen. Dieser Winkel ist mit dem Winkel ε von SCHMID und FILTHUT [7, 8] identisch. In diesem Material wurde bereits bei Neugeborenen ein größerer Öffnungswinkel gefunden, der die größten Werte im frühen Kindesalter mit einer Zunahme von 10° erreichte und 79° maß. Zu dieser Zeit hatten unsere Kinder Meßwerte

TABELLE I

Streckenmaße des Gesichtsschädels von Knaben von Geburt bis Nachpubertät,
Mittelwerte in mm und $\pm \sigma$
Mean distances of the face of boys from birth to late puberty; mean in mm and S. D.

Gruppe Nr. Group No.	Alter Age	Zahl der Fälle No. of cases	Mittelwert und $\pm \sigma$ Mean and S.D.				
			10	11	12	13	14
No. 1.	1-7 Tage Days	22	45.86 3.36	46.36 3.23	52.62 3.99	48.43 4.33	23.18 1.65
No. 2.	8-20 Tage Days	10	48.40 2.55	48.00 2.21	55.67 3.61	52.00 3.08	24.30 1.83
No. 3.	3-5 Wochen Weeks	16	47.75 1.88	48.06 1.48	55.73 3.59	52.00 3.61	25.00 2.03
No. 4.	5 Woch-21/2 Monate 5 Weeks-21/2 Months	23	51.46 2.93	51.14 2.36	59.74 3.31	57.64 3.71	27.30 2.51
No. 5.	2 1/2-3 1/2 Monate Months	17	52.35 2.89	51.35 2.91	62.00 3.12	56.88 3.24	27.47 2.03
No. 6.	3 1/2-5 Monate Months	18	53.44 4.07	53.61 4.00	64.00 5.57	61.89 4.59	29.59 3.18
No. 7.	5-7 Monate Months	21	56.15 2.83	56.57 2.56	69.05 3.64	66.58 4.67	31.30 1.98
No. 8.	7-10 Monate Months	25	57.56 2.80	60.54 4.39	73.20 5.27	70.62 5.84	32.32 2.54
No. 9.	10-15 Monate Months	30	59.76 2.90	65.33 3.89	77.48 4.60	75.62 4.66	34.47 6.25
No. 10.	15-21 Monate Months	20	62.45 4.07	70.75 5.10	83.61 7.69	82.39 6.72	35.90 3.26
No. 11.	1 3/4-2 1/4 Jahre/Years	22	66.48 4.33	76.38 5.62	90.14 5.14	88.77 5.60	38.48 4.25
No. 12.	2n1/4-2 3/4 Jahre/Years	15	69.00 4.11	78.07 3.59	95.77 4.44	95.31 3.40	41.00 2.73
No. 13.	2 3/4-3 1/4 Jahre/Years	22	70.45 3.47	81.04 3.61	96.86 4.86	92.62 8.07	41.19 2.77
No. 14.	3 1/4-3 3/4 Jahre/Years	15	73.80 5.73	82.64 6.39	99.08 4.46	96.17 4.65	42.47 3.68
No. 15.	3 3/4-4 1/2 Jahre/Years	14	73.71 5.24	84.86 8.28	103.18 6.38	101.18 6.05	44.15 4.08
No. 16.	4 1/2-5 1/2 Jahre/Years	19	76.84 5.97	86.42 4.78	104.94 4.60	103.41 5.02	45.16 3.02
No. 17.	5 1/2-6 1/2 Jahre/Years	21	77.38 5.28	88.08 7.07	111.15 8.07	107.10 7.64	46.62 4.13
No. 18.	6 1/2-7 1/2 Jahre/Years	22	80.86 5.04	93.04 5.31	114.57 5.57	110.95 4.42	50.00 3.95
No. 19.	7 1/2-8 1/2 Jahre/Years	20	81.45 4.29	95.50 4.47	114.10 5.64	109.84 5.12	50.25 3.23
No. 20.	8 1/2-9 1/2 Jahre/Years	20	83.35 4.07	99.65 4.96	120.00 8.15	113.68 7.47	51.75 4.77
No. 21.	9 1/2-10 1/2 Jahre/Years	23	84.14 3.58	101.17 3.61	121.55 5.42	115.35 6.02	52.64 3.06
No. 22.	10 1/2-11 1/2 Jahre/Years	23	83.54 5.04	101.00 4.98	124.50 7.53	120.38 6.27	54.40 3.78
No. 23.	11 1/2-12 1/2 Jahre/Years	20	83.45 5.61	102.05 6.26	124.63 7.76	119.15 7.44	53.75 2.57
No. 24.	12 1/2-13 1/2 Jahre/Years	31	85.77 4.76	105.70 4.71	129.26 6.60	122.65 6.64	54.48 3.72
No. 25.	13 1/2-14 1/2 Jahre/Years	24	88.62 7.17	107.67 7.55	132.04 11.49	124.96 9.47	56.87 3.54
No. 26.	14 1/2-17 1/2 Jahre/Years	27	91.69 6.88	111.62 6.84	139.54 9.69	130.96 7.96	58.50 4.41
	Insgesamt	540					

TABELLE II
 Streckenmaße des Gesichtsschädels von Mädchen von Geburt bis Nachpubertät
 Mittelwert in mm und $\pm \sigma$
 Mean distances of the face of girls from birth to late puberty, in mm and S. D.

Gruppe Nr. Group No.	Alter Age	Zahl der Fälle No. of cases	Mittelwert in mm und $\pm \sigma$ Mean in mm and $\pm \sigma$ Strecken Nr./No. of distances				
			10	11	12	13	14
No. 1.	1—7 Tage Days	14	46.43 3.03	46.64 2.06	53.93 3.25	50.14 4.61	23.36 2.24
No. 2.	8—20 Tage Days	14	46.14 1.99	46.93 2.78	54.54 3.78	50.38 3.71	23.50 1.79
No. 3.	3—5 Wochen Weeks	10	47.80 2.44	47.00 2.58	55.11 3.02	53.89 3.37	28.00 2.11
No. 4.	5 Wochen/Weeks	13	47.62 1.50	47.15 1.95	56.33 2.84	53.08 2.81	24.85 1.68
No. 5.	2 1/2 Monate/Months	15	50.93 2.81	50.33 2.69	59.53 4.27	56.40 4.34	26.93 2.89
No. 6.	3 1/2—5 Monate, Months	13	52.00 2.56	51.31 2.87	62.45 2.84	58.45 2.71	27.92 1.78
No. 7.	5—7 Monate, Months	21	53.57 3.19	54.19 3.03	66.86 4.07	64.48 4.00	29.57 2.06
No. 8.	7—10 Monate, Months	16	56.12 2.19	59.12 4.06	70.73 4.88	68.80 3.88	30.56 2.34
No. 9.	10—15 Monate, Months	24	56.87 2.89	62.26 3.26	75.19 4.39	72.57 4.66	31.83 3.12
No. 10.	15—21 Monate, Months	16	61.19 3.54	69.44 3.71	82.87 4.93	79.27 5.57	33.31 3.61
No. 11.	1 3/4—2 1/4 Jahre, Years	15	65.67 3.20	74.40 4.14	89.58 4.80	88.50 4.78	37.53 2.45
No. 12.	2 1/4—2 3/4 Jahre, Years	15	67.93 3.28	77.20 4.00	93.14 6.26	90.36 6.39	38.93 2.46
No. 13.	2 3/4—3 1/4 Jahre, Years	17	70.23 4.60	80.59 5.11	97.94 6.66	95.06 6.20	39.41 3.99
No. 14.	3 1/4—3 3/4 Jahre, Years	11	89.45 5.07	79.00 4.41	95.58 6.07	93.09 4.59	40.70 2.71
No. 15.	3 1/4—4 1/2 Jahre, Years	19	72.94 3.98	81.72 6.52	101.05 7.91	99.94 6.95	43.28 4.06
No. 16.	4 1/2—5 1/2 Jahre, Years	16	74.37 4.24	83.94 4.11	100.73 5.13	98.47 4.03	44.94 2.61
No. 17.	5 1/2—6 1/2 Jahre, Years	20	76.30 4.64	86.80 5.75	109.12 6.04	105.23 6.18	46.75 4.38
No. 18.	6 1/2—7 1/2 Jahre, Years	18	76.11 5.21	88.11 5.63	108.55 5.26	105.83 5.18	47.94 3.24
No. 19.	7 1/2—8 1/2 Jahre, Years	19	76.89 3.57	90.00 4.26	109.89 5.49	104.78 7.07	48.74 5.23
No. 20.	8 1/2—9 1/2 Jahre, Years	26	79.63 3.44	95.52 4.89	116.50 5.51	111.08 6.18	51.58 5.24
No. 21.	9 1/2—10 1/2 Jahre, Years	25	80.79 5.15	98.00 5.18	120.42 6.40	114.25 6.65	51.12 3.10
No. 22.	10 1/2—11 1/2 Jahre, Years	25	80.52 4.95	97.87 5.21	119.04 7.40	114.92 7.57	51.00 4.02
No. 23.	11 1/2—12 1/2 Jahre, Years	35	83.57 5.38	101.20 4.81	125.11 6.57	117.67 7.51	53.67 4.03
No. 24.	12 1/2—13 1/2 Jahre, Years	29	84.43 3.97	102.75 5.23	127.20 7.39	119.52 8.06	54.00 3.33
No. 25.	13 1/2—14 1/2 Jahre, Years	15	85.06 5.50	104.46 5.62	129.93 6.83	121.26 5.32	54.93 3.43
No. 26.	14 1/2—19 Jahre, Years	43	85.98 5.17	104.14 5.70	128.22 9.94	120.17 10.76	54.14 5.71
	Insgesamt	504					

TABELLE III

Winkelmaße des Gesichtsschädels von Knaben von Geburt bis Nachpubertät;
Mittelwerte in mm und $\pm \sigma$
Mean angles of the face of boys from birth to late puberty; mm and S. D.

Gruppe Nr. Group No.	Alter Age	Zahl der Fälle No. of cases	Mittelwert und $\pm \sigma$ Mean and $\pm \sigma$		
			δ	ϵ	
No. 1.	1-7 Tage/Days	22	29.86	40.09	62.29
			1.70	2.16	5.03
No. 2.	8-20 Tage/Days	10	29.80	41.10	64.56
			1.55	2.64	4.03
No. 3.	3-5 Wochen, Weeks	16	30.25	41.19	64.53
			2.54	2.51	3.94
No. 4.	5 Wochen - 2 1/2 Monate Weeks Months	23	31.56	44.39	65.90
			1.90	3.19	4.46
No. 5.	2 1/2-3 1/2 Monate, Months	17	32.41	44.82	62.00
			2.62	2.88	2.24
No. 6.	3 1/2-5 Monate, Months	18	33.37	46.11	66.50
			2.31	2.70	4.44
No. 7.	5-7 Monate, Months	21	33.50	47.19	66.95
			2.12	2.61	4.60
No. 8.	7-10 Monate, Months	25	34.12	48.16	66.62
			3.24	3.33	3.61
No. 9.	10-15 Monate, Months	30	34.27	50.23	68.41
			2.46	3.06	3.49
No. 10.	15-21 Monate, Months	20	34.25	49.90	69.33
			1.86	3.28	3.77
No. 11.	n1 3/4-2 1/4 Jahre, Years	22	34.33	50.76	70.27
			3.45	3.92	3.72
No. 12.	2 1/4-2 3/4 Jahre, Years	15	36.00	52.33	71.69
			2.78	2.32	3.43
No. 13.	2 3/4-3 1/3 Jahre, Years	22	35.50	51.59	69.76
			2.77	3.86	4.77
No. 14.	3 1/4-3 3/4 Jahre, Years	15	35.00	51.50	68.75
			2,20	3.82	3.98
No. 15.	3 3/4-4 1/2 Jahre, Years	14	36.86	53.21	71.09
			2.11	3.33	2.39
No. 16.	4 1/2-5 1/2 Jahre, Years	19	35.68	53.10	71.00
			3.42	4.12	4.24
No. 17.	5 1/2-6 1/2 Jahre, Years	21	35.95	52.60	69.05
			2.07	3.71	3.95
No. 18.	6 1/2-7 1/2 Jahre, Years	22	37.54	52.91	69.67
			3.36	3.25	4.00
No. 19.	7 1/2-8 1/2 Jahre, Years	20	37.75	52.80	68.89
			2.90	3.40	3.67
No. 20.	8 1/2-9 1/2 Jahre, Years	20	37.79	52.84	68.00
			2.70	2.61	2.57
No. 21.	9 1/2-10 1/2 Jahre, Years	23	38.23	52.48	68.00
			2.99	2.76	3.51
No. 22.	10 1/2-11 1/2 Jahre, Years	23	39.45	53.72	70.27
			2.91	3.34	4.25
No. 23.	11 1/2-12 1/2 Jahre, Years	20	39.50	53.40	68.57
			2.93	3.50	3.02
No. 24.	12 1/2-13 1/2 Jahre, Years	31	38.77	52.83	68.61
			3.17	4.09	4.52
No. 25.	13 1/2-14 1/2 Jahre, Years	24	39.25	52.62	67.96
			3.78	4.04	5.36
No. 26.	14 1/2-17 1/2 Jahre, Years	27	40.69	52.92	76.75
			7.18	3.37	3.47
	Insgesamt	540			

K. Gefferth: *The growing skull*

TABELLE IV

Winkelmaße des Gesichtsschädels von Mädchen von Geburt bis Nachpubertät,
mm und $\pm \sigma$

Mean angles of the face of girls from birth to late puberty; mm \pm S.D

Gruppe Nr. Group No.	Alter Age	Zahl der Fälle No. of cases	Mittelwert und $\pm \sigma$ Mean and $\pm \sigma$		
			δ	ϵ	ζ
No. 1.	1-7 Tage/Days	14	29.57 2.56	40.93 2.92	62.57 4.22
No. 2.	8-20 Tage/Days	14	29.43 2.34	40.93 2.37	62.54 4.67
No. 3.	3-5 Wochen/Weeks	10	30.70 3.95	43.70 1.77	66.33 3.74
No. 4.	5 Wochen/Weeks	13	30.85 3.16	43.62 2.18	64.00 3.98
No. 5.	2 1/2 Monate/Months	15	31.78 4.53	45.13 3.11	64.20 5.20
No. 6.	2 1/2-3 1/2 Monate/Months		32.17 2.04	44.54 2.79	64.09 3.88
No. 7.	5-7 Monate/Months	21	32.95 3.12	46.86 2.73	66.55 2.87
No. 8.	7-10 Monate/Months	16	32.12 3.14	47.37 3.56	67.00 3.53
No. 9.	10-15 Monate/Months	24	33.67 3.32	49.22 3.04	67.95 3.19
No. 10.	15-21 Monate/Months	16	32.75 2.86	48.19 3.69	67.80 3.99
No. 11.	1 3/4-2 1/4 Jahre/Years	15	34.60 2.43	50.80 3.19	70.33 3.54
No. 12.	2 1/4-2 3/4 Jahre/Years	15	34.80 1.82	50.80 3.19	69.57 2.41
No. 13.	2 3/4-3 1/4 Jahre/Years	17	34.12 2.18	50.53 3.37	70.59 4.72
No. 14.	3 1/4-3 3/4 Jahre/Years	11	35.18 1.84	51.75 1.86	68.92 3.12
No. 15.	3 1/4-4 1/2 Jahre/Years	19	36.61 2.00	51.61 3.27	70.28 2.59
No. 16.	4 1/2-5 1/2 Jahre/Years	16	36.75 2.18	52.69 3.52	69.87 3.62
No. 17.	4 1/2-5 1/2 Jahre/Years	20	37.40 3.03	53.05 4.32	69.53 3.56
No. 18.	6 1/2-7 1/2 Jahre/Years	18	38.67 2.45	53.83 2.96	70.50 2.41
No. 19.	7 1/2-8 1/2 Jahre/Years	19	38.10 3.11	52.63 4.06	67.39 4.27
No. 20.	8 1/2-9 1/2 Jahre/Years	26	38.52 3.10	53.28 3.59	68.50 3.68
No. 21.	9 1/2-10 1/2 Jahre/Years	25	39.00 3.55	52.13 4.31	60.87 4.08
No. 22.	10 1/2-11 1/2 Jahre/Years	25	38.91 3.44	53.04 3.38	70.16 3.60
No. 23.	11 1/2-12 1/2 Jahre/Years	35	39.00 3.14	52.54 3.98	68.20 4.19
No. 24.	12 1/2-13 1/2 Jahre/Years	29	39.20 2.72	52.20 3.08	68.00 3.54
No. 25.	13 1/2-14 1/2 Jahre/Years	15	39.26 3.37	51.86 4.00	67.60 4.76
No. 26.	14 1/2-19 Jahre/Years	43	38.38 3.99	51.59 4.30	66.73 4.99
	Insgesamt	504			

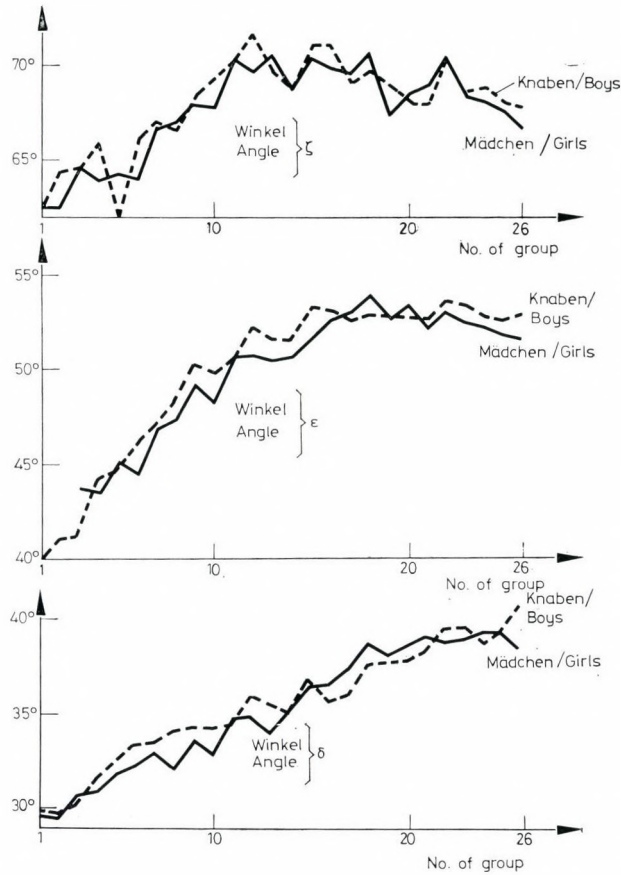


ABB. 4. Meßergebnisse der drei mit Scheitel am Tuberculum liegenden Winkel des Gesichtsschädels bei Knaben und Mädchen von Geburt bis Nachpubertät.

FIG. 4. The three mean maxillary angles having their vertex at the tuberculum sellae, in boys and in girls from birth to late puberty.

von etwa 70° . Trotz späteren Schwankungen blieb die Differenz unverändert, hat sich sogar auf 10° erhöht und war bei Mädchen vielleicht noch ausgeprägter. Diese Differenz bestand auch bei den die Gesichtshöhe repräsentierenden Streckmaßen, bei denen die Meßwerte ständig niedriger waren. Obwohl diese Strecke bei unseren Knaben von 48.83 mm auf 130.83 mm gewachsen ist, und so den Meßwert

13.1 cm von SCHMID und FILTHUT praktisch erreicht hat, blieben die Mädchen mit 120.17 mm immer noch zurück. Somit scheinen die ungarischen Kinder einen niedrigeren Gesichtsschädel zu haben, als die in Südwestdeutschland.

Die eigenen Winkel- und Streckenmaßen scheinen einander zu widersprechen. Die Winkel δ und ϵ erfahren nämlich eine deutlichere Zunahme als

der Winkel ζ , obwohl die beiden oberen Strecken eine mäßigere Zunahme aufweisen als die untere Strecke 12. Diese scheinbare Dysharmonie kann so erklärt werden, daß die Mandibula ihr longitudinales Wachstum nach vorne auch ohne eine stärkere Zunahme des Winkels ζ zu entfalten imstande ist. Das stärkere Wachstum nach vorne wurde auch von BRODIE [2] nachgewiesen.

*

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Dr. K. GEFFERTH
Bókay J. u. 53
H-1083 Budapest

Pathogenesis of angiodysplasias

By

G. TASNÁDI and Magda OSZTOVICS

Heim Pál Children's Hospital, Budapest

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The pathogenesis of angiodysplasias was studied in 382 patients. Of the primary and secondary morphogenetic factors importance is attached to fetal diseases, intrauterine reparation, hormonal effects in neonatal age and early walking. It is concluded that angiodysplasias develop under the joint effect of genetic and environmental factors. They are evolutionary anomalies undergoing changes in the course of life.

Genetic anomalies of the vessels are met with in every period of life. In infancy they occur in the form of naevi, haemangiomas, angiomatosis and as hypertrophic or hypoplastic extremities due to angiodysplasia. In childhood the anomaly manifests itself as a gradually developing varicosity, phlebectasia, arterio-venous shunt or lymphangioma, while in adults primary varicosities may appear. Successful attempts have been made in the last few years to present a satisfactory classification of angiogenetic malformations [17, 31, 37, 48].

In the first ten weeks of embryonic life, three stages can be distinguished in the development of the vascular system [15, 31, 41, 42, 44, 46, 50]: (1) the capillary network; (2) the retiform; and (3) the truncular stages. Some authors [17, 31] attribute the angiodysplasias to dysontogenetic processes. Disorders in the first stage may lead to capillary malformations (naevi, capillary haemangiomas); those

in the retiform stage may cause phlebangiomas, arterio-venous angiomas and arterio-venous fistulae; disturbances in the truncular stage may lead to arterial and venous deformities such as agenesis, hypoplasia, anomalous vascular topography, etc.

Considering that the development of vessels, particularly that of the veins, proceeds during the whole course of fetal life and even after birth, the primary morphogenetic factor exerts its effect not only in the first phase of embryonic life but also in the fetal and postnatal periods. These malformations may significantly be modified by vascular function, blood circulation, and other secondary morphogenetic factors.

PRIMARY MORPHOGENETIC FACTORS

Followers of the genetic theory [5, 13] explain the changes by gene mutation. Some authors [27, 28]

reported the familial occurrence of congenital absence of valves in the deep veins, while others [2, 49] described the familial occurrence and heredity of cavernous haemangioma, and phlebangiomas has been suggested to represent a hereditary condition [32]. The familial nature of primary varicosity has been confirmed by many authors [38]. Angiodysplasias are often attributed to some endogenous and/or exogenous factors acting in different stages of ontogenesis [1, 8, 9, 10, 18, 21, 25, 35, 39, 47]. Some authors observed angiodysplasias developing in connection with embryonic lesions of the nervous system [7, 10, 16, 22, 25, 40].

In the present study including 382 patients with angiodysplasia, attempts have been made to reveal the aetiology of these alterations.

OBSERVATIONS

(1) The role of certain genetic information is unquestionable.

(a) The familial occurrence of the lesion could be verified in two cases.

N.N., a 4 months old male infant from the mother's first pregnancy, had cavernous haemangiomas on the tip of the nose and upper lip. The mother displayed dysplasia of the hip and haemangiomas, a maternal aunt and the grandmother also had haemangiomas.

F.G., a 1-month-old female infant, the first child from a first pregnancy, had a vascular naevus and varicosity on her moderately hypertrophic left

upper extremity. Her father, paternal aunt and grandmother also had varicosities.

(b) Considering that certain hereditary diseases are associated with angiodysplasia, the role of genetic factors cannot be excluded. Teleangiectasias occur in Osler disease, one of dominant hereditary character, and in ataxia teleangiectasia, an autosomal recessive condition. Haemangiomas is characteristic of the autosomal dominant syndrome of Hippel—Lindau and agenesis of the lymph vessels in the equally autosomal dominant disease, Milroy lymphoedema.

(c) Chromosome analysis was performed in 21 patients with angiodysplasia. An aberrant chromosome was found in one case of complex angiodysplasia with lymphoedema. It is, however, well known that some conditions due to chromosomal anomalies, like Turner syndrome, are frequently associated with angiodysplasias. Aortic isthmus stenosis occurs in one fifth of these cases and lymphoedema in an even higher proportion. In a Hungarian material of 48 cases of Turner syndrome angiodysplasias occurred in 22 patients: 9 had lymphoedema, 8 coarctation of the aorta, 3 lymphoedema with coarctation of the aorta, 1 patient a congenital heart defect and 1 intestinal angiomatosis. Of our own 6 patients with verified Turner syndrome 3 had lymphoedema and 1 intestinal angiomatosis.

(2) To study the role of environmental factors we examined 7 pairs of twins of whom 2 were monozygotic.

Angiodysplasia occurred in one of them and cavernous haemangiomas were observed in one, and arteriovenous angiomas of the left hand in the other. This suggests the role of environmental factors in the development of angiodysplasias.

(a) The significance of teratogenic compounds has also been stressed [12] as haemangioendothelioma was observed in patients working with vinyl chloride, thorium dioxide and organic arsenicals. Liver angiomas and cutaneous haemangiomas were observed also in subjects residing in the vicinity of polyvinyl chloride plants.

(b) Drug-induced lesions have not been observed. Forty-four of the 382 mothers took some drugs, mostly phenothiazine derivatives, in the 1st to 3rd months and 23 in the 4th to 8th months of pregnancy. Mothers of the other 315 children with angiodysplasia did not take any drugs throughout pregnancy apart from iron preparations; these were regularly taken by close to 90% of the pregnant. One mother reported on taking anticoncepient pills in the 1st month of pregnancy; her child was born with venous trunk anomalies.

(c) No correlation was found between maternal diseases during pregnancy and angiodysplasia in the

offspring. Four mothers were ill in the 1st to 3rd months and 9 in the 4th to 8th months; they delivered normal children. There was one exception, a mother who had contracted rubella in the 2nd month of gestation; the infection was confirmed serologically. The baby was born with a giant haemangioma on the left leg associated with thrombocytopenia (Kasabach—Merritt syndrome).

(d) Age distribution of the mothers of the patients was comparable to that of the normal population Table I.

(e) No correlation was found between induced abortion and angiodysplasias.

Fifty per cent of the patients were first children, half of them were born from first pregnancies, the others from first deliveries after some abortions. Half of the second to fourth children were also born after abortions.

(f) The conditions of delivery were studied in 324 instances. In 281 cases the delivery was uncomplicated, in 18 complicated, and in 25 instances by Caesarean section.

(g) Effect of fetal diseases. It was remarkable that patients with the same truncular angiodysplasia may have different syndromes.

F. I. and *S. T.*, male newborns, were born with congenital absence of

TABLE I
Age of mothers at birth of children with angiodysplasia

Age, year	<16	17—20	21—24	25—29	30—34	35—39	>40
No. of mothers	2	52	101	82	36	14	0

the femoral vein as confirmed by angiography. Nevertheless, one had a complete Klippel—Trenaunay syndrome, while the only symptom of the other baby was a slight swelling of the extremities. It was assumed that in the first patient the aetiological factor had acted in the early embryonic period, while in the other patient the noxa occurred much later, in the prenatal period (intrauterine thrombosis?).

Such cases can only be explained by fetal diseases, in other words certain congenital anomalies of the vessels point to intrauterine vascular diseases. Among these, intrauterine thrombosis seems to have special importance. Benirschke and Driscoll [3] found in 11 of 1718 placentas (0.64%) allantoic vessel thrombosis,

once in a stillborn baby. Kless and Vogel [24] attribute importance to several missed abortions. Klippel and Trenaunay [23] ascribed the syndrome named after them to embryonic infection. Mottled skin was observed in connatal toxoplasmosis, obliterating endangiitis in connatal syphilis and granulomatous lesions of the hepatic vessels in cytomegalic inclusion disease [24].

SECONDARY MORPHOGENETIC FACTORS, HAEMODYNAMIC EFFECTS

Blood circulation and haemodynamic conditions play an important role in shaping the vessels. Accordingly, angiodysplasias react sensitively to the physiological haemodynamic changes occurring at a given age.



FIG. 1. Congenital arterio-venous angioma

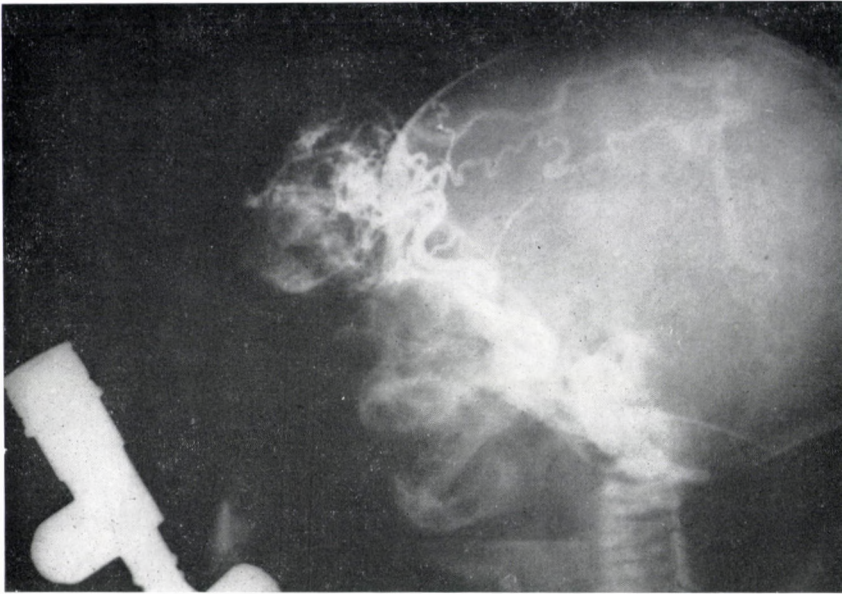


FIG. 2. Angiogram of an arterio-venous angioma



FIG. 3. Quickly proliferating arterio-venous angioma

(1) The influence of haemodynamic changes may manifest during fetal life.

K. A., a female newborn, was delivered with a giant arterio-venous haemangioma, while in *V. T.*, another female infant, the angioma developed some weeks after birth (Figs 1, 2, 3).

M. F., a male infant, exhibited congenital hypoplasia of the femoral vein. Compensatory venous dilatation could be detected at birth already: a dilated vein transported the blood from the femoral vein in front of the symphysis to the external iliac vein (Figs 4, 5).

It seems as if the defective venous flow could have been repaired before birth. Thus, similarly to intrauterine regeneration [4] a process of intra-uterine reparation may also exist.

(2) Haemodynamic changes may have more importance in extrauterine

life. In 165 of our 334 patients no lesion could be observed at birth (Fig. 6).

(a) Haemodynamic changes due to trauma, local infection, physical and hormonal effects may induce the growth of congenital arterio-venous angiomas and accentuate the effect of shunts [20, 36].

Hormonal effects may play a role in the development of arterio-venous angiomas indiscernible at birth but identifiable in 1 to 2 months old infants. They grow rapidly thereafter. The high serum oestradiol level of 11 400 $\mu\text{g}/\text{ml}$ 2 weeks after birth, then its sudden fall to 22 $\mu\text{g}/\text{ml}$ may elicit haemodynamic changes similar to those induced by hormonal activity in puberty and during the menopause. In these periods of life haemangiomas grow in number and size,

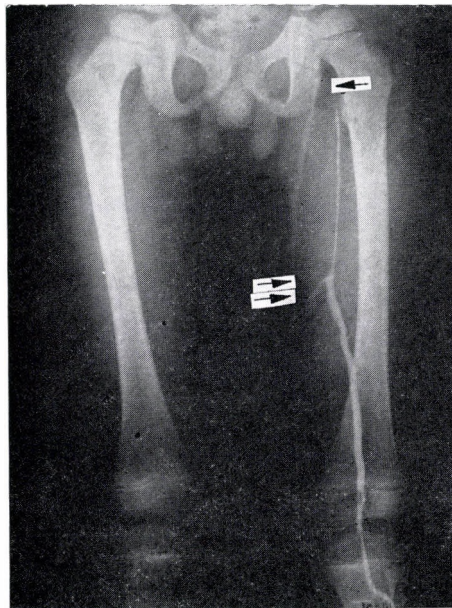


FIG. 4. Hypoplastic femoral vein. The great saphenous vein is filling from the deep vein

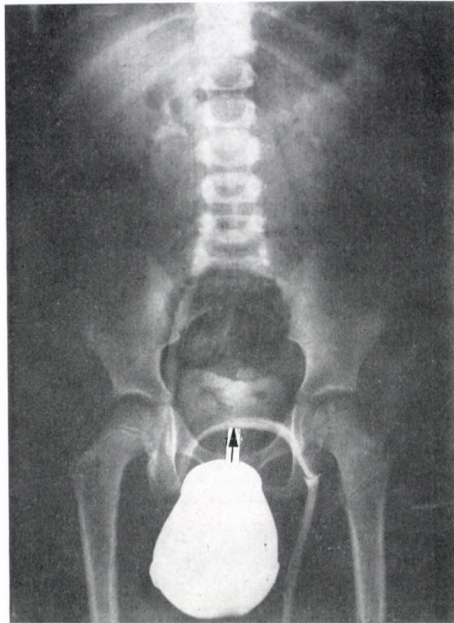


FIG. 5. From the great saphenous vein the blood is transported via a congenital compensatory vessel to the contralateral external iliac vein

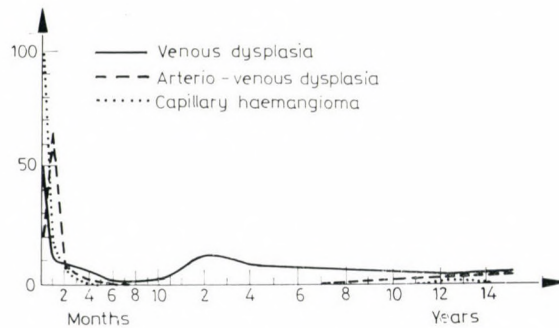


FIG. 6. Age at appearance of angiodysplasia

latent shunts may open up and in this way varicosities appear. This seems to be supported by our observation that the occurrence and quick proliferation of arterio-venous angiomas cannot be observed in preterm and small for date newborns. In such babies the oestradiol level is low and

the hormonal reactions of gestation are hardly demonstrable.

(b) Prolonged haemodynamic effects may considerably contribute to the appearance of venous dysplasias [11, 19, 33]. This would follow from our observation that standing and walking increase the incidence of

venous dysplasias, assumedly by overcharging the veins of the legs. In cases of aplasia of the venous valves or after congenital venous lesions the symptoms manifest in the later periods of life under the effect of physical and hydrostatic loads [14, 29, 30, 45].

(c) The role of trauma is clearly indicated by lympho-venous angiomas. They are usually observed between 6 and 10 years of age. In such cases some trauma is regularly mentioned in the history.

In our own material there were 22 lymphatic and 4 lympho-venous angiodysplasias. Diagnosis in the latter 4 cases was confirmed by needle biopsy and angiography.

Thus, both genetic and environmental factors contribute to the development of angiodysplasias which are evolutionary anomalies changing in the course of life. They are usually considered to represent minor anomalies but in view of their frequently severe consequences in later life they deserve special attention.

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G. TASNÁDI, M. D.

Üllői út 86

H-1089 Budapest

Effective thyroxine ratio in newborn infants during exchange transfusion

By

F. PÉTER, I. ILYÉS and J. KECSKÉS

Department of Paediatrics, University Medical School, Debrecen, Hungary

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The effect of blood exchange transfusion on the thyroid has been studied by serially establishing the effective thyroxine ratio (ETR). The ETR value is slightly increased in the newborn infant and the level is further augmented by blood exchange. Since the ETR level is lower in the transfused blood than in the blood of the newborn, the finding points to the good thyroid hormone producing capacity of the neonate.

It has been known for long that the serum protein-bound iodine (SPBI) and the butanol-extractable iodine (BEI) levels are increased in the first days of life [2, 5]. The cause of the finding was then shown to be the increased thyroid hormone binding capacity (TBC) of the serum proteins [7, 12, 13], though the thyroid gland of the newborn shows hyperfunction by the iodine uptake test [8] as well as histologically [14, 16]. The slight neonatal hyperthyroidism was finally corroborated by determining the serum free T_4 and T_3 contents [3, 6].

In view of its considerable influence on homeostasis, it seemed interesting to study the influence on the thyroid household of an exchange transfusion. This the more so as after the only investigation into the subject [17] it has been recognized that the effective thyroxine ratio (ETR) [9, 10, 15] was especially suited for studying the function of the thyroid gland in the perinatal period [1, 4, 11].

MATERIAL AND METHOD

The material consisted of 10 infants, 6 males and 4 females ranging in age from 1 to 5 days and in weight from 1100 to 2700 g. Three of the babies were full-term and 7 preterm. The babies received a total of 12 exchange transfusions indicated by severe hyperbilirubinaemia. The dose of preserved blood was 200 ml/kg.

Blood samples were obtained from the neonates at the beginning of each 200 ml and at the end of the exchange transfusion and from each 200 ml bottle of blood. Thus, a total of 31 neonate blood samples and 19 bottle samples were tested.

ETR was determined with the Res-O-Mat ETR kit (Mallinckrodt). The basis of the method is to establish the serum total T_4 level by competitive protein binding and to determine the free capacity of thyroid binding globulin (TBG) by labelled hormone.

For statistical evaluation, Student's *t*-test was used.

RESULTS

Mean values \pm S.D. are shown in Table I.

TABLE I
Mean ETR values \pm S.D. in newborn and preserved blood

Blood sample	No.	ETR level Mean \pm S.D.
Neonatal		
Pre-exchange	12	1.05 \pm 0.1
After first 200 ml	12	1.12 \pm 0.08
After second 200 ml	7	1.14 \pm 0.28
Preserved		
First 200 ml	12	0.96 \pm 0.09
Second 200 ml	7	0.99 \pm 0.11

In the samples obtained prior to exchange transfusion, in two cases the ETR proved to be higher than the normal upper limit (Fig. 1) but the mean ETR did not reach the hyperthyroid level, although it exceeded the cord blood value (Table II). After infusing the first bottle, the mean approached the normal upper limit, while half of the individual cases attained the hyperthyroid level. In two-thirds of the individual cases an increase, while in one third a very

slight decrease occurred. After transfusing the second bottle the mean value was still somewhat higher but the scatter was wider and in the majority of the cases a decrease was observed (Fig. 2). It was remarkable that the mean ETR was low in the samples of preserved blood.

When analysing the individual values for age, body weight, maturity and body temperature, no close connection could be observed.

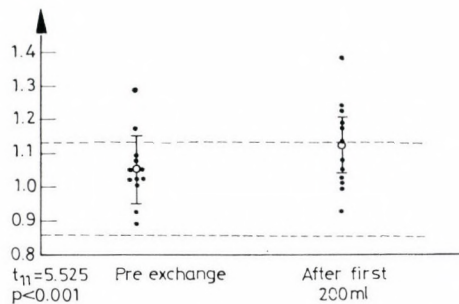


FIG. 1. ETR after transfusion of first 200 ml of blood

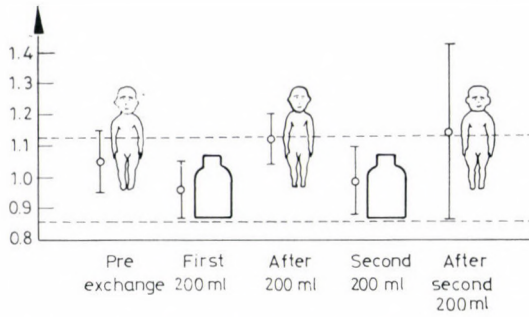


FIG. 2. Mean ETR \pm S. D. in blood of the newborns and in preserved blood during exchange transfusion

DISCUSSION

As described in our earlier study [11], on the first days of life the ETR was somewhat higher than in cord blood. The mean remained below the normal upper limit and, even in individual cases, it seldom reached the hyperthyroid zone. Recently, similar results have been reported by other authors [1, 4].

Some 15 years ago it was found [17] that the low BEI values of neonates at the end of the exchange transfusion increased shortly after it and stabilized at the high pre-exchange level. This was ascribed to the low BEI content of the blood used for exchange and by the increased thyroid function of neonates.

Determination of ETR is particularly suitable for studying the effect of blood exchange on the thyroid household, since the value is not affected by changes of the binding proteins. Such changes must namely be expected from the use of blood from adult donors.

In our material, the mean ETR increased during the blood exchange transfusion and in half of the cases the value attained the hyperthyroid level in spite of the fact that in the transfused blood the ETR was low almost without exception. Thus, the T_4 produced by the baby must have been responsible for the increase. This is an additional proof of the fact that the newborn baby has an independent and well-reacting thyroid household

TABLE II

ETR values in cord and newborn blood

Blood sample	No.	ETR level Mean \pm S.D.	Range
Cord	10	0.99 \pm 0.08	0.86 — 1.2
Newborn	12	1.05 \pm 0.1	0.89 — 1.28

and its capacity to secrete hormones can be related to this weight category as well.

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F. PÉTER, M. D.

Buda Regional Children's Hospital

H-1277 Budapest, Pf. 14

Recensiones

H. SCHOEPPNER: *Anästhesie und Reanimation in der Kinderneurologie*. 316 Seiten mit 59 Abbildungen und 26 Tabellen. Georg Thieme Verlag, Leipzig 1975. M 59,—

Die sprunghafte Entwicklung der Kinderneurologie hat die rasche Erkennung der akuten neurologischen Katastrophen ermöglicht. Bei der Therapie dieser Zustände bieten die modernen Verfahren der Anästhesie und Reanimation eine unentbehrliche Hilfe. Das Buch behandelt die Probleme der Anästhesie im Säuglings- und Kindesalter, und die Fragen der Lokal- und Allgemeinanästhesie anhand einer gründlichen Erörterung der anatomischen, physiologischen und metabolischen Besonderheiten des Organismus dieser Altersgruppen. Den kinderneurologischen diagnostischen Methoden ist ein gesondertes Kapitel gewidmet, und es werden auch die Formen der Prämedikation, deren Formen und klinischer Effekt ausführlich besprochen.

Besonders wertvoll erscheint die Schilderung der Pathogenese und Therapie der vitalen Gefährdungen, u. a. die des Schocksyndroms, der zerebralen Anfälle, des apalischen Syndroms. Hier wird auch die Radiotherapie der Hirntumoren erläutert. Die Anführung der dringlichen Laboratoriumsuntersuchungen und der Normalwerte des Kindesalters, ferner eine Liste der in Frage kommenden Narkotika und anderer Präparate stellen einen sehr nützlichen Teil des Buches dar. Das jedem Kapitel zugefügte Schrifttum bietet die Möglichkeit zum weiteren Studium der Themen.

O. KOHLHÉB

W. WENZ und D. BEDUHN: *Extremitätenarteriographie*. VIII + 158 Seiten mit 162 Abbildungen in 277 Einzeldarstellungen. Springer-Verlag, Berlin—Heidelberg—New York 1976. DM 148,—

Mit der Entwicklung der modernen funktionellen Angiologie wurde es offenbar, daß sich die sog. peripheren Gefäßkrankheiten nicht nur auf die Extremitäten beschränken; oft wird das ganze Gefäßsystem oder ein beträchtlicher Teil miteinbezogen. Die veraltete Anschauung der vaskulären Krankheitsbilder, die den pathophysiologischen Geschehnissen sehr wenig Aufmerksamkeit schenkte, hat zu einseitigen diagnostischen und therapeutischen Schemen geführt, deren Revision im Spiegel der modernen Angiologie schon lange unerläßlich schien.

Das vorliegende Buch stellt ein hervorragendes Beispiel der zeitgemäßen Konzeption der dynamischen Angiologie dar. Es widerspiegelt die vieljährige ausgezeichnete Arbeit der Autoren, auf deren Grundlage sie für den sich mit Angiologie befassenden Kliniker und praktizierenden Arzt die Indikationen und die optimale technische Durchführung der Kontrastangiographie beschreiben und die Auswertung der erhaltenen Aufnahmen gründlich schildern.

Nach einer ausführlichen Besprechung der klinischen funktionellen Tests, der verschiedenen röntgentechnischen Apparaturen und der angiologischen Meßgeräte werden die radiologischen Interpretationen der einzelnen Vaskulaturen erörtert: dies geschieht nicht aufgrund der statischen deskriptiven Röntgenmorphologie, sondern

es werden alle einzelnen Erkrankungen und Syndrome in ihren pathophysiologischen und klinischen Zusammenhängen behandelt.

Die Methoden der Wahl zur Darstellung der Gefäßkrankheiten verschiedener Lokalisation und Natur werden eingehend angegeben und erörtert, und danach werden die bei den einzelnen organischen oder funktionellen, degenerativen oder entzündlichen, chirurgischen, internistischen und pädiatrischen arteriellen, venösen und Lymphgefäßkrankheiten ermittelten Kontrastbilder im Zusammenhang mit den klinischen Symptomen ausgewertet.

Die Monographie bedeutet eine lückenfüllende Hilfe für alle sich mit der Angiographie befassenden Ärzte.

L. URAI

The Genetics of Diabetes Mellitus. Edited by W. CREUTZFELDT, J. KÖBERLING, J. V. NEEL. IX + 248 pages with 64 figures and 74 tables. Springer-Verlag, Berlin—Heidelberg—New York 1976. DM 38.—

In this book outstanding experts of the question treat the problem of heredity, essentially supporting the multifactorial origin and emphasizing the heterogeneity of the disease. Data which seem to prove the recessive or dominant inheritance of diabetes are also mentioned. Beside the genetic factors, the environmental ones are discussed in detail. A separate chapter (Genetic Syndromes Associated with Glucose Intolerance) deals with diseases which may be connected with diabetes. From the paediatric aspect the chapter A Possible Virus Aetiology for Juvenile Diabetes is of particular interest. It stresses the seasonal variations in the manifestation of diabetes; the fluctuation might be associated with the seasonal changes of virus diseases. It is an important observation that in children who start school in their fifth year of life the manifestation of diabetes before the age of eight is much more frequent than in those who start school

education after the age of five. In the chapter HLA Autoimmunity and Insulin-Dependent Diabetes Mellitus the authors point out that the occurrence of HLA-B₈ and HLA-BW₁₅ antigens is significantly more frequent than in maturity onset diabetes, or in diabetes not requiring insulin treatment. It is emphasized that hyperlipidaemia too might be associated with hereditary characteristics, and in juvenile hyperlipidaemia anomalies of lipid metabolism can be demonstrated in the parents. In the majority of cases hyperlipidaemia is, however, connected with some disturbance of sugar metabolism, which can favourably be influenced by due treatment. In the chapter Diabetes Mellitus in Identical Twins reference is again made to the heterogeneity of the process and to the marked differences in hereditary factors in diabetic conditions below and over the age of 40. From the point of view of complications the inherited conditions are of high importance, but the significance of metabolic disorders will undoubtedly come in the foreground together with the development of vascular complications. The genetical problems have not yet been clarified and their importance is increasing in marriage and genetic counselling. The book offers considerable help to all those who deal with diabetes.

L. BARTA

R. S. JONES: *Asthma in Children.* 270 pages with illustrations. Edward Arnold, London 1976. Price £ 10.—

During the last two decades numerous new results were added to the physiology and immunopharmacology of asthma and the arsenal of asthma therapy has been completed by new drugs. In spite of this, there are a number of difficulties in the course of treatment and mistakes are common.

The frequency of asthma varies from 1 to 14%, the incidence being higher in males. About 5 to 10% of the patients belong into the severe group. The mortality of

asthma amounts to about 1 in 100,000. Within this number there was a transitory elevation in the nineteen-sixties, particularly in England. Asthma is more frequent in the higher social groups, whereas the incidence of its severe form is higher in the lower social groups. The probability of multifactorial heredity is emphasized.

In the chapters on pathology and immunopharmacology the now commonly accepted allergic mechanism is discussed. The antigen-antibody reaction occurring on the surface of mast cells induces the release of chemical mediators (histamine, Slow Reacting Substance of Anaphylaxis, Eosinophil Chemotactic Factor of Anaphylaxis), then these mediators elicit bronchial spasm, increased capillary permeability, etc. In this series of reactions IgE, Ca ion as well as cAMP participate.

C. B. S. Wood describes in the chapter on immunological relations the definition of "allergy" by Gell and Coombs, and stresses the importance of immunoglobulins, together with the role of T and B lymphocytes. In asthma, beside IgE, other antibodies can also be demonstrated. In the induction of bronchial spasm, the role of prostaglandins has been shown. Clarification of the immunological status (allergen demonstration, IgE level, radioallergosorbens: RAST test, bronchial provocation) is of high importance from prognostic and therapeutic aspects.

The chapter on respiratory function discusses in detail the characteristic alterations. The expiratory flow-volume curve is the most sensitive test of the obstruction of small airways. Among the loading examinations, free running up to a pulse frequency of 180–190/min is considered the most appropriate test.

In therapy, epinephrine is recommended, as well as theophylline, and of the newer preparations, terbutaline. The toxic effect of the misuse of aerosol preparations is emphasized. Disodium chromoglycate is mentioned as adjuvant in prevention of the attack. Steroid therapy should be applied with caution.

As to the psychological relations, the adequate relations between child and physician and between physician and parents is of high importance; the cooperation of a psychologist is frequently required.

The last three chapters describes the program of asthma therapy. For the severe asthmatic, short hospital treatment is important and education in a special sanitarium school may be necessary. The appendix contains a number of useful tables, dosage of drugs, nomograms.

The book supplies useful help and directives, particularly for the paediatric pulmonologist.

G. PÓDER

Recent Advances in Paediatrics, No. 5. Edited by DAVID HULL. Churchill Livingstone, Edinburgh, London and New York 1976. IX + 367 pages. Price £ 10.—

This is the fifth volume of a series, edited earlier by Douglas Gairdner and now by David Hull. In the preface a "help to busy doctors to keep abreast of developments" is promised. This seems to be an understatement as the thirteen papers, all masterpieces in their field, are useful refreshers even for the more orientated specialist. The topics cover nearly all aspects of a child's life and death. The prevailing importance and fast development of perinatal medicine is represented by half of the reviews.

The first chapter by E. M. Symonds deals with intrauterine diagnostics, a growing field of interest and information also for the paediatrician. Closely related are the next two papers by J. K. Brown treating perinatal brain damage. Pathology, clinical picture, sequelae are discussed with a well-balanced evaluation of the role of hypoxia, trauma and haemorrhage in all these processes. A logical sequence is the fine review of Pamela Davies on the care and prognosis of very low birth weight infants. Most recent papers herald a breakthrough in this field, which would have

been impossible without all the practices (especially respiratory support) surveyed in the chapter.

The next three papers are similar in their preventive tendency. J. A. Dudgeon lays out the up to date strategy of immunization programs: "the best and most effective investments which any government can make towards its citizens" (CIE Seminar, Kampala, 1971). Barbara D. Clayton considers the possibilities of the early detection and later care of inborn amino acid disorders, not losing out of sight the cost/benefit ratio. An important part of preventive medicine and human(e) physiology is the early parent-infant relation, decisive for the future psychosomatic status of the newborn (M. H. Klaus and J. H. Kennell).

Two epidemiologic papers follow: on respiratory diseases (J. R. T. Colley) and on sudden infant death (J. L. Emery). While the first is a well-known problem in Great Britain and countries of similar climate, the second shows an unexpectedly high importance of sudden death in the lethality of infants from two weeks to one year.

The rich volume is completed by two monographs of June L. Lloyd and O. H. Wolff, both building a bridge to the pathologic events of older age. The first is on obesity and the second on hyperlipoproteinaemias.

The text of all these papers is well constructed, informative, clear and concise. Rich references, many of them from the seventies, are listed at the end of each chapter.

J. ROSTA

J. PEDERSEN: *The Pregnant Diabetic and Her Newborn*. 280 pages with 49 figures. Munksgaard, Copenhagen 1977. D. Kr. 140.—

Before the use of insulin the mortality of babies born to diabetic women amounted to 40–60%. By now this figure has decreased dramatically but the number of diabetic pregnancies has increased con-

siderably. After an introductory chapter quoting the data for this change, Chapter II discusses the characteristics of carbohydrate metabolism during pregnancy, the hormonal interrelations and the tendency of the insulin/glucagon ratio to increase. Chapter III deals with the different forms of diabetes and the importance of the baby's birth weight, Chapter IV with the classical and oral treatment of mild gestational diabetes, and Chapter V with screening for diabetes in pregnancy. Chapter VI reviews subsequent diabetes in women with abnormalities of the carbohydrate metabolism in the pregnant and non-pregnant state, and Chapter VII the influence of pregnancy on the diabetic woman. Special emphasis is laid here on the vascular complications and it is recommended to discourage the diabetic woman with proliferative retinopathy or nephropathy from becoming pregnant. Chapter VIII discusses the complications and stresses the severity of toxæmia, hydramnios and urinary infections in the diabetic pregnant. Chapter IX is devoted to the placenta, its hormones and transplacental passage. Chapter X, the longest of the book, reviews modern knowledge concerning the fetus, its growth relations, its pancreas, comparing the changes observed in this organ with those seen in the hypertrophic pancreas associated with erythroblastosis. The half-life in the fetus of maternal insulin-antibodies is estimated at 25 days and it is shown that the changes in the insulin and glucose levels under a glucose load are uninfluenced by the presence of antibodies. The type and frequency of congenital malformations are discussed in detail, emphasizing their increased incidence in association with severe vascular disease and with insulin coma occurring in the first trimester. Important are Chapters XIII and XIV; they deal with the management of diabetic pregnancy and the newborn infant including the timing and method of delivery, and with the future years of the surviving baby. It is mentioned here that the postnatal mortality of diabetic mothers has decreased

to 4% which is still tenfold of the overall figure in Denmark. Manifest diabetes may be expected to occur in 1% of such children before 18 years of age, a frequency 25-fold of the one for the whole population. The final chapter discusses the planning of pregnancy; it is stressed that diabetic women must not have more than two children.

This excellent monograph is a reliable source of knowledge concerning the diabetic pregnant and her fetus and child and offers a well-selected large list of papers and monographs on the subject. The book is a must for all obstetricians and paediatricians, and also internists, who have to treat diabetic pregnant or their babies.

L. BARTA

C. E. KOOP: *Visible and Palpable Lesions in Children*. 123 pages with 62 figures. Grune and Stratton, New York, San Francisco, London 1976. Price \$ 13.75

From the preface we understand that the author's aim was to give in the hands of the practising paediatrician a manual that will supply him due information about all the visible and palpable changes developing in children and also enable him to give adequate answers to the parents' questions which they may pose concerning the changes at issue. Most of them require some surgical solution and they seldom cause any difficulty to the paediatric surgeon, but it is not this specialist but the paediatrician or the G. P. to whom the questions are addressed. The questions raised mostly concern three problems, *viz.* whether the change is benign or malignant in nature; whether it calls for surgery and, if so, when must the intervention be performed; and lastly, what is the prognostic aspect. On the basis of his vast experience, the author, one of the world's leading authorities in paediatric surgery, gives clear and concise answers, often in a single sentence, to every question that may arise. In seven chapters he discusses the single parts of the organism, *viz.* 1. head and

face; 2. neck; 3. chest; 4. abdomen; 5. inguinal area, scrotum and penis; 6. rectum; 7. extremities and skin. Chapters 8-9 deal in some more detail with the haemangiomas and lymphangiomas. The last chapter deserves special attention although it extends to two pages in all. It discusses neonatal screening for inborn conditions incompatible with life. In this chapter there is a 20-line paragraph on two-minute examination. Both the chapter and especially this paragraph should be learnt by heart by every obstetrician and paediatrician who has to deal with neonates.

E. KONTOR

H. F. R. PRECHTL und D. J. BEINTEMA: *Die neurologische Untersuchung des reifen Neugeborenen*. 2. überarbeitete Auflage. VIII + 104 Seiten mit 54 Abbildungen in 89 Einzeldarstellungen. G. Thieme Verlag Stuttgart 1976. DM 13,80

Mit der Entwicklung der Kinderneuro-psychiatrie ist die Beherrschung der neurologischen Untersuchungsmethoden bei Neugeborenen eine Notwendigkeit geworden. Hierzu bietet die vorliegende ausgezeichnete Monographie eine unentbehrliche Hilfe. Sie schildert auf wenigen Seiten äußerst gedrungen und klar diese Untersuchungsverfahren.

In der Einleitung wird die Strategie der Untersuchungen und der Begriff Risikokind erörtert. Sodann werden die Magnusreflexe und vegetativen Symptome in den verschiedenen Körperlagen besprochen und schließlich die Ergebnisse und diagnostischen Möglichkeiten der neurologischen Untersuchungen zusammengefaßt.

Der Umstand, daß die Methodik jeder Untersuchungsart auch mit zahlreichen gut verständlichen und plastischen Abbildungen demonstriert wird, gestaltet das hervorragende kleine Taschenbuch zu einem unentbehrlichen Wegweiser in der täglichen diagnostischen Arbeit des Neonatologen.

O. KOHLHÉB

A. WINDORFER und H. TRUCKENBRODT: *Kinderärztliche Notfälle*. X + 378 Seiten mit Abbildungen und 24 Tabellen. G. Thieme Verlag, Stuttgart 1976. Preis: DM 26,80

Das Buch ist die neunte neubearbeitete und erweiterte Auflage der von B. de RUDDER vor 28 Jahren konzipierten und herausgegebenen »Kinderärztliche Notfallfiel«. Es ist ein ausgesprochen der Praxis dienendes Werk, das die Autoren für den akute Zustände behandelnden Arzt als einen praktischen Wegweiser verfaßt haben. Die theoretischen Erläuterungen der verschiedenen Krankheitszustände werden sozusagen ganz unterlassen, um nach ihrer Definition die charakteristischen Symptome der einzelnen akuten Zustände zu besprechen und sodann eine entschiedene Stellungnahme und Anweisung hinsichtlich der therapeutischen Maßnahmen zu geben. (Diese kategorische Bestimmtheit kann zu der Ansicht führen, daß ein davon abweichender Therapieplan stets unrichtig sei; das ist aber sogar bei der Versorgung akuter Zustände nicht immer eindeutig der Fall. *Rez.*) Bei der diagnostischen und therapeutischen Arbeit dürften die vielfältigen nützlichen Tabellen, und für den sich mit diesen Themen eingehender befassenden Pädiater das ausgezeichnete zusammenfassende Literaturverzeichnis eine große Hilfe bedeuten.

D. BÉKEFI

W. FRÖSCHER: *Therapie des Status epilepticus*. X + 104 Seiten. Schattauer Verlag, Stuttgart—New York 1976. Preis: DM 18,—

Der Verfasser hat die Probleme der Behandlung des Status epilepticus aufgrund von zahlreichen (314) Literaturangaben und eigenen Erfahrungen zusammengefaßt. Obwohl sich die Häufigkeit des Krankheitsbildes vielleicht vermindert hat, muß man auch bei den heutigen therapeutischen Möglichkeiten mit einem lebensgefährdenden Zustand rechnen, dessen

Letalität etwa 20% beträgt. Unter den Todesursachen sind vor allem Herz- und Kreislaufinsuffizienz, Depression des Atemzentrums und Hirnödeme zu verzeichnen. Unbehandelt kommt ein Status nur selten zum Stillstand, so daß die adequate Behandlung eine Notwendigkeit ist.

Das Buch bespricht die verschiedenen Status-Formen, die antikonvulsiven Medikamente und deren Wirkungsmechanismus. Es wird betont, daß nicht jeder Fall unbedingt mit Bewußtseinsverlust einhergehen muß und es Formen gibt, bei denen die motorischen Komponenten fehlen. Unter Berücksichtigung des Schrifttums und der eigenen Erfahrungen hält der Autor nach wie vor Diazepam als das Mittel der Wahl. Die Anwendung von Diphenylhydantoin oder Phenobarbital ist etwas in den Hintergrund getreten, und in bezug auf das vielversprechende Clonazepam sind die Erfahrungen ziemlich widersprechend.

Es wird ferner hervorgehoben, daß die antikonvulsiven Substanzen immer intravenös und in entsprechender Dosis verabfolgt werden sollen. Ausführlich werden Dosierung, die Vor- und Nachteile und schließlich die Nebenwirkungen der einzelnen Medikamente erörtert. Die Monographie bietet eine gründliche Besprechung der heutigen Auffassung über die zeitgemäße Therapie des Status epilepticus.

O. KOHLHÉB

P. OTTO und K. EWE: *Atlas der Rectoskopie und Coloskopie*. XI + 96 Seiten mit 31 Textabbildungen, 115 vierfarbigen Abbildungen und 11 Tafeln. Springer-Verlag, Berlin—Heidelberg—New York 1976. DM 98,—

Die Rectoskopie und Coloskopie, diese wichtigen und notwendigen endoskopischen Untersuchungsverfahren, werden nicht nur von Chirurgen, sondern gelegentlich auch von den Vertretern verschiedener Fachdisziplinen, wie Internisten, Gynäkologen, Urologen, Pädiatern usw. durchgeführt. Die Bedeutung des vorliegenden

aus 26 Kapiteln bestehenden Atlases soll ohne auf die Beschreibung der Einzelheiten einzugehen, im folgenden zusammengefaßt werden.

Es wird die Wichtigkeit der die Grundlage der endoskopischen Untersuchung bildenden Anamnese und der in erster Reihe vorzunehmenden und schon gewisse Orientierung bietenden digital-rectalen Tastuntersuchung betont. In zahlreichen ausgezeichneten Abbildungen werden die verschiedenen optimalen Lagerungsarten und das benötigte Instrumentarium ausführlich dargestellt. Die vorzüglichen farbigen Schleimhautaufnahmen sind von einem kurzen, doch klaren, die Diagnosen unterstützenden erklärenden Text begleitet. Zur weiteren Information enthält jedes Kapitel entsprechende Literaturhinweise.

Der Atlas wird jedem Arzt, der die Rectoskopie und Coloskopie erlernen möchte, ein wertvoller Ratgeber sein und auch für jene manche Anregung und Bereicherung bieten, die diese Methoden schon beherrschen.

I. HITNER

H. HARBAUER, R. LEMPP, G. NISSEN, P. STRUNK: *Lehrbuch der speziellen Kinder- und Jugendpsychiatrie*. 3., überarbeitete Auflage. XIV + 475 Seiten mit 43 Abbildungen. Springer-Verlag, Berlin—Heidelberg—New York 1976. DM 98,—

Das vorzüglich verfaßte Lehrbuch hat binnen fünf Jahren seine dritte Auflage erreicht. Es ist auch ganz verständlich, da die Kinderpsychiatrie, diese neue Disziplin, bis dahin ein die vielen Richtungen in Betracht ziehendes, dennoch eine einheitliche Auffassung aufweisendes Lehrbuch vermissen mußte.

Die gute Orientierung ist durch die klare Einteilung gesichert: die Krankheitsbilder und Syndrome werden stets im Spiegel der Symptome, Ätiologie, sozialen Bedeutung, Diagnostik, Differentialdiagnostik Fehldiagnosemöglichkeiten, Therapie und Prognose behandelt.

Die Rahmen einiger in der Uraufgabe lediglich berührten Krankheitsbilder (z. B. Verwahrlosung, Schulprobleme) wurden mit den wissenschaftlichen Forschungen der vergangenen Jahre entsprechendem Inhalt, von plurilateralen-plurikausalen Aspekten bearbeitet, bereichert. In der vorliegenden Auflage wurden der Enurese ein größerer Raum gewidmet und hinsichtlich der Oligophrenie und des Dementationszustandes die Maße eines Handbuchs erreicht. Für den sich mit den Sprachstörungen und der neuerdings häufiger vorkommenden Legasthenie befassenden Spezialisten bietet das Buch in bezug auf deren Entwicklung und Korrektur viel Hilfe. Den neuen gesellschaftlichen Erscheinungen angepaßt werden auch die Probleme der jugendlichen Rauschmittel-Halluzinogensucht mit ihren asozialen und organischen Zusammenhängen und jene der dis- und antisozialen Haltung eingehend besprochen. Das Buch informiert ferner über die sich auf die kriminellen Jugendlichen in der Bundesrepublik beziehenden präventiven, protektiven und Strafmaßnahmen.

Allen, die sich mit der Jugend befassen: dem praktizierenden Arzt, Kinderarzt, Kinderpsychiater, Pädagogen, Erzieher, Vertreter von Justiz oder Vormundschaftsbehörde vermittelt das Werk zeitgemäße Anschauungen, guten Rat und erste Hilfe.

L. CSÉPÁNYI

Kardiotokographie. Herausgegeben von W. M. FISCHER. 2. überarbeitete und erweiterte Auflage. XVIII + 508 Seiten mit 216 Abbildungen in 565 Einzeldarstellungen. Georg Thieme Verlag, Stuttgart 1976. DM 98,—

Das von W. M. FISCHER, E. HALBERSTADT, H. RÜTTGERS, D. BERG unter Mitwirkung von H. BRANDT, J. HEEP, A. HUCH, R. HUCH, H. D. JUNGE und I. STUDE bearbeitete Lehrbuch (Atlas) ist von höchstem Range. Es gliedert sich in 7 Kapitel. Einleitend werden von FISCHER die Methoden zur Erfassung und Betrennung

der Risikofälle und dann im 2. Kapitel von BERG die Kontrolle von Risikoschwangerschaften erörtert: Ultraschall- und hormonelle Diagnostik (Oeß, HPL, AFP), Fruchtwasseruntersuchung (Mekonium, Bilirubin, Phospholipide, Kreatinin, Zelltypen), abdominales EKG, Plazentaperfusionsmessung (STUDE und FISCHER), uteroplazentare Durchblutung (mit Isotopen), Kardiotokographie, Fetalblutanalyse (HEEP), transcutane pO_2 -Messung beim Feten (R. und A. HUCH). Das 3. Kapitel faßt die Grundlagen und klinische Wertigkeit der Kardiotokographie (CTG) vorzüglich zusammen (FISCHER). Die kontinuierliche kardiotokographische Überwachung ist heute die einzige zuverlässliche ante- und intrapartale fetale Kontrollmaßnahme. Dieses Kapitel ist ein Leitfaden zur Analyse und Interpretation des Kardiotokogramms. Auch erhält man einen guten Überblick über die Physiologie und Pathologie der Uterusmotilität, die Stimulation oder Hemmung der Wehentätigkeit und über das

physiologische und pathologische fetale Herzkreislaufsystem. Hierzu tragen die ausgezeichneten Abbildungen und Tabellen bei. In dem 4. Kapitel — ein Atlasteil — werden die Tokogramme der ante- und intrapartalen, in der Praxis für den Feten gefährlichsten Herzfrequenzalterationen demonstriert (HALBERSTADT). Das 5. Kapitel ist der Technik, den Registrierprinzipien und typischen Fehlinterpretationen von Kardiotokogrammen gewidmet (RÜTTGERS). Hervorzuheben sei noch das letzte Kapitel, das sich mit der modernen Neugeborenenüberwachung (verschiedene biochemische und biophysikalische Untersuchungsmethoden) befaßt, und die Variationen des Kardiorespirogramms und die praktische Bedeutung der transcutanen pO_2 -Messung erläutert.

Das Bildmaterial ist musterhaft. Das Werk ist bei der geburtshilflichen und perinatologischen Arbeit unentbehrlich und sollte in jedem sich mit diesem Gebiet befassenden Institut anzutreffen sein.

B. ZSOLNAI

Jena Symposium of Perinatologists of Socialist Countries

Subjects:

1. Perinatal mortality and morbidity
2. Risk pregnancy
3. Immediate care of the newborn at risk in the delivery room.
4. Organization of neonatal intensive care
5. Diagnostic and therapeutic problems of neonatal intensive care

Congress Hall: Gera, Haus der DSE, Am Markt

Date: 21 — 24. 11. 1978

Organizing Committee: Abt. Neonatologie Universitäts-Kinderklinik
Kochstraße 2. DDR-69 Jena

Printed in Hungary

A kiadásért felel az Akadémiai Kiadó igazgatója

Műszaki szerkesztő: Zacsik Annamária

A kézirat nyomdába érkezett: 1977. VIII. 29. – Terjedelem: 13,30 (A/5) ív, 73 ábra

78.4870 Akadémiai Nyomda, Budapest – Felelős vezető: Bernát György

KÉZIRATOK KÖVETELMÉNYEI

A cikkek két példányban adandók be, ugyanígy a táblázatok és ábrák is. Minden szöveget kérünk dupla sorokba legalább 4 cm-es margóval gépelni (szabvány oldal 25 sor×50 betű). Máshogy gépelt kéziratokat csak akkor fogadunk el, ha azokat mi fordítatjuk idegen nyelvre. Minden oldal (táblázatok és irodalom is) folyamatosan megszámozandó.

Az irodalmi hivatkozások ábécé sorrendben megszámozandók. A szövegben csak a számokat kell feltüntetni. Az irodalomjegyzékben szerepelni kell a hivatkozott cikk minden szerzője vezetéknevének és keresztnéve(i) rövidítésének, a cikk címének, a folyóirat rövidített nevének, a kötetszámnak, az oldalszámnak és a megjelenési évnek. Szerzők neve helyett nem szerepelhet et al. A folyóiratok nevének rövidítése a WHO World Medical Periodicals szerint történjék. Könyvekre való hivatkozásnál szerepelni kell a szerző(k) vezetéknevének és keresztnéve(i) rövidítésének, a könyv címének, kötetének, kiadási sorszámának, a kiadó nevének, a városnak, a kiadás évének és a hivatkozott rész oldalszámának. Például:

Kerpel-Fronius, E., Gács, G.: Serum insulin values. Acta paediat. Acad. Sci. hung. **16**, 197 (1975).

Crosse, V. M.: The Preterm Baby. 7th ed. Churchill Livingstone. Edinburgh and London 1971, P. 165.

Detter, J. C.: Biochemical Variation. In: Textbook of Human Genetics, ed. G. Fraser, O. Mayo. Blackwell Scientific Publications, Oxford 1975, P. 115.

A cikkben csak kongresszusnyelven megjelent munkákra lehet hivatkozni.

A cikknek rövid kivonattal kell kezdődnie. Ennek tartalmaznia kell azt, hogy mit vizsgáltak, milyen módon, valamint a vizsgálat eredményét és az esetleges következtetést egy mondatban. E kivonatból beadandó egy magyar verzió is két példányban; ennek tartalmaznia kell a cikk címét és összes szerzőjét.

A mellékelt képek (ábrák) hátlapjára ráírandó az első szerző neve, a kép száma és megjelölendő, hogy melyik része legyen felül.

A táblázatok ugyanígy jelölendők, és olyan címmel kell ellátni őket, amely a szöveg olvasása nélkül is érthetővé teszi az adatokat.

A táblázatok és képalírások külön oldalon adandók be.

A cikkben említett gyógyszerek a WHO kód nevükön kell hogy szerepeljenek (Recommended International Nonproprietary Names); gyári nevek nem szerepelhetnek.

Acta paediatrica Academiae Scientiarum hungaricae

PREPARATION OF MANUSCRIPTS

A current issue of the Acta should be consulted for general style.

Two complete copies of the manuscript including tables and illustrations must be supplied. All material should be double-spaced with margins at least 4 cm wide. Material typed otherwise will be returned for retyping. Pages should be numbered consecutively.

References must be numbered in alphabetical order and only the numbers should appear in the text. References to papers should contain every author's name, initials, title of paper, title of journal, volume, first page of paper, and year of publication. Use of et al. instead of authors' names is not accepted. Abbreviations of journals should be those listed in World Medical Periodicals. References to books should contain the authors' names, title of book, volume, edition, name of publisher, city, year of publication, and page number of reference. E.g.

Kerpel-Fronius, E., Gacs, G.: Serum insulin values. Acta paediat. Acad. Sci. hung. **16**, 197 (1975).

Crosse, V. M.: The Preterm Baby. 7th ed. Churchill Livingstone, Edinburgh and London 1971. P. 165.

Detter, J. C.: Biochemical Variation. In: Textbook of Human Genetics, ed. G. Fraser, O. Mayo. Blackwell Scientific Publications, Oxford 1975. P. 115.

Authors are requested to begin their paper with an abstract and to add an alphabetical list of any unusual abbreviations used, with meanings.

Illustrations must be identified by number and author's name, and the top should be marked. Their place should be indicated in the text. Legends for figures should be written on a separate sheet.

Tables must be comprehensible to the reader without reference to the text and accompanied by headings.

Drugs must be referred to by their WHO code designation (Recommended International Nonproprietary Name); use of proprietary names is unacceptable.

Papers are accepted subject to editorial revision.

**БАКТЕРИАЛЬНЫЕ ЗАРАЖЕНИЯ
НОВОРОЖДЕННЫХ В 1970-Х ГОДАХ**

З. Е. ШПЕЕР, Л. Х. ТАБЕР, А. Й. РУДОЛЬФ
и Й. УРТЕАГА

Для установления частоты заболеваний сепсисом и менингитом, определения смертности и выявления патогенных возбудителей был обработан материал отделения новорожденных одной большой больницы за 1973—74 гг. Из 18465 новорожденных только у 100 был обнаружен сепсис и у 20 сопутствующий ему менингит (5,1 или 1/1000), летальность в группе с сепсисом достигла 38%, в группе с менингитом 60%. Самым частым возбудителем был стрептококк В, вызвавший 28% заболеваний сепсисом и 65% менингитом. Грамположительные кокки в этиологии этих заболеваний принимали участие в 47% и, соответственно, в 42% случаев. В 20% случаев менингит был вызван грамотрицательными энтеробациллами. Результаты настоящего исследования указывают на все возрастающую роль грамположительных кокков — особенно В стрептококков — в летальности у новорожденных.

**ВЛИЯНИЕ МАТЕРИНСКОГО ДКАБЕТА
НА РАЗВИТИЕ ЗУБОВ У ДЕТЕЙ, НЕ
СТРАДАЮЩИХ ДИАБЕТОМ,
В ПЕРИОД СМЕНЫ ЗУБОВ**

П. АДЛЕР, К. Д. ФЕТТ и Л. БОХАТКА

Мы изучали развитие зубов у 150—170 детей 6—15-летнего возраста, достоверно не имевших нарушений углеводного обмена, матери которых страдали диабетом. При сравнении этой группы, обследованной в Диабетическом институте в Карлсбурге, с венгерскими стандартами и с стандартами ГДР, мы не обнаружили ни у мальчиков, ни у девочек заслуживающих внимания отклонений ни как в отношении выпадения отдельных молочных зубов и в среднем

сроке прорезывания отдельных постоянных зубов, так и ни в отношении среднего числа по годам прорезавшихся постоянных зубов. Опираясь на накопленные в Хагерстоуне (США) данные, мы оценивали развитие зубов также отдельно у каждого обследуемого и выражали его единственным числом (т. н. «характерное» число). Мы исследовали влияние на средние значения или распределение характерных чисел, — частично на всем материале, частично в отдельных подгруппах, — нескольких параметров ребенка или связанных с диабетом материнских параметров, определенных либо при рождении, либо во время данного обследования (натальные или актуальные параметры). К числу этих параметров относились: вес и длина тела ребенка при рождении, вес тела в период стоматологического обследования, классификация матери по *Уайти*, наличие и степень ретинопатии, состояние обмена веществ на всем протяжении беременности, а также хронологический возраст ребенка. Имеется некоторая зависимость между диабетом матери и развитием зубов у ребенка: диабет — параллельно его тяжести, выраженной тремя параметрами, — задерживает развитие, хотя в группах, выделенных согласно вышеизложенным точкам зрения, мы не выявили статистически достоверной разницы в развитии зубов. Статистически достоверное запаздывание мы наблюдали в развитии зубов у 8,5—11,5-летних по сравнению с 12,5—14,5-летними, у которых отмечалось небольшая акцелерация. Замеченная у 6,5—7,5-летних акцелерация не была статистически достоверной. Актуальный вес тела обследуемых детей тоже обнаружил определенную взаимосвязь с развитием зубов: у детей с большим весом наблюдалась небольшая акцелерация. Вес и длина тела при рождении сами по себе не влияли на развитие зубов у этой популяции. Вес тела, определенный во время зубо-врачебного осмотра, а также вес и длина тела при рождении, у данной популяций статистически достоверно отличались от международных стандартов.

СЛУЧАЙ 22-ТРИСОМНОЙ МОЗАИКИ

М. ОСТОВИЧ и Г. ИВАДИ

В 60% разводимых в культуре кровяных клеток, взятых от соматически и умственно отсталой девочки с врожденным пороком сердца и разными признаками дисморфии, нашли маленькую, лишнюю акроцентрическую хромосому. Эта добавочная хромосома оказалась 22-й.

10q25—qter ТРИСОМИЯ ИЗ СЕМЕЙНОЙ ТРАНСЛОКАЦИИ, С t(4;10) (q33;q24) ТРАНСЛОКАЦИЕЙ У РОДИТЕЛЕЙ ОТЦА

М. ОСТОВИЧ и Т. КАСАШ

У грудного ребенка мужского пола обнаружили 10q24—qter трисомию. Симптомы соответствовали таковым, описанным другими авторами. Дедушка и бабушка ребенка были близкими родственниками, и у обоих имелась одинаковая сбалансированная t(4;10) (q33;q24) транслокация. В анамнезе тяжелая генетическая неуравновешенность: 4 детей из пяти умерли в младенческом возрасте. Единственный составившийся в живых — отец пробанда, обнаруживший ту же сбалансированную транслокацию.

ЛЕЧЕНИЕ ПЕНТАМИДИНОМ ВРОЖДЕННОГО ГЕНЕРАЛИЗОВАННОГО КАНДИДИАЗА

Г. ТОТ, Г. МИКЛОШ, А. КЕРЕКЕШ
М. КАТОНА и Д. САРВАШ

Авторы настоящей статьи сообщают о лечении пентамидином новорожденных детей, 7 из которых страдали конгенитальным генерализованным кандидиазом и один — сепсисом кандидного происхождения. Пентамидин вводился в течение 6 дней, в дозе 4 мг/кг в день внутримышечно. При лечении пентамидином быстро исчезли кожные проявления заболевания, не подававшиеся предшествующему местному лечению. После 7—8-дневного лечения все больные поправились и были выписаны из больницы.

ЭЛЕКТРОЭНЦЕФАЛОГРАФИЯ И ТЕРМОЖЕНИЕ МИГРАЦИИ ЛЕЙКОЦИТОВ АЛКАЛИЧЕСКИМ МИЭЛИНОВЫМ ПРОТЕИНОМ ПРИ МЕНИНГИТЕ НА ПОЧВЕ ЭПИДЕМИЧЕСКОГО ПАРОТИТА

Г. КАЛИ, О. УЙХЕЙИ и Г. НЕРГЕШ

У 20 больных с менингитом, возникшим на почве эпидемического паротита, проводились электроэнцефалографические исследования и выполнялся тест торможения миграции лейкоцитов щелочным миэлиновым протенном. В 14 случаях были обнаружены слабые или умеренные отклонения на электроэнцефалограммах, указывающие на одновременное наличие энцефалита. Клеточную реактивность на алкалический миэлиновый протеин, однако, удалось показать только в 4-х случаях. Это наблюдение подтверждает предположение, согласно которому менинго-энцефалит, возникший на почве эпидемического паротита, развивается путем прямого действия вируса на нервную ткань, то есть, нейроллергические механизмы не играют роли в его возникновении.

СРАВНЕНИЕ ДВУХ МЕТОДИК (НИТРИТНОЙ И ДИПСЛАЙДНОЙ), ПРИМЕНЯЕМЫХ ДЛЯ ВЫЯВЛЕНИЯ БАКТЕРИУРИИ

Г. ЙОЯРТ и И. ЭДЕР

Авторы сравнивают результаты выборочных анализов мочи, выполненных на основе реакции с нитритом и сосчитывания бактерий на дипслайдах. Специфичность реакции с нитритом равнялась 99,8%, чувствительность 93,10% и воспроизводимость — 100%. Специфичность dipslide-анализа равнялась 94,5%.

Авторы считают, что для выборочных обследований целесообразно выполнять реакцию с нитритом, поскольку она специфична, достаточно чувствительна, быстро выполняемая и дешевая. dipslide-методика — вследствие своей высокой стоимости и частоты ложноположительных реакций — не годится для выборочных обследований, но вполне пригодна для подсчета количества бактерий в нитритноположительной моче.

АКТИВНОСТЬ LDH-ИЗОЭНЗИМА ПЕРИФЕРИЧЕСКИХ КЛЕТОК ТИПА Т И В У НОВОРОЖДЕННЫХ РАЗНОГО GESTАЦИОННОГО ВОЗРАСТА

Л. КАРМАЖИН, Х. ЧЕРНЯНСКИЙ,
А. МАКАИ и М. СЕВЕТЕШ

Авторы производили выделение лимфоцитов типа Т и В у здоровых зрелых новорожденных и у недоношенных детей, родившихся на 28—33 неделе беременности, на основании активности клеточного изоэнзима LDH. Авторы считают, что эта методика пригодна для дополнения и замещения техники, в основе которой лежит поверхностная маркировка. В ходе экспериментов была обнаружена разница между активностью энзимов у доношенных и недоношенных новорожденных. Оказалось, что у недоношенных детей активность фракции LDH-1 в клетках В-типа, а также активность LDH-5 фракции в клетках обоего типа, но, в первую очередь, в клетках типа В, была более высокой. Авторы считают эту методику подходящей для выявления дифференцирующихся клеток в фетальном периоде.

ЦИРКУЛИРУЮЩИЕ АНТИТЕЛА ПРИ ЦЕЛИАКИИ

М. КАВАИ, М. САБОЛЬЧ, Ш. ЧОРБА, Б. САБО
и Л. ФЕЙШНОШ

В крови больных с целиакией, а также в крови иммунизированных кроликов и крыс были обнаружены антитела, направленные против глиадина. Специфические антитела в крови больных относились к типу IgG. IgE, повидимому, участвует в сенсибилизации против глиадина, только связываясь с клетками.

УТИЛИЗАЦИЯ ГЛЮКОЗЫ И ЭКСКРЕЦИЯ ИНСУЛИНА У НОВОРОЖДЕННЫХ

П. АМЕНДТ, М. ЗИГЛЕР и П. ВУЛЬФЕРТ

Авторы определяли выделение глюкозы, глицерина, инсулина и проинсулина в обычных условиях и в условиях нагрузки глюкозой у новорожденных детей, матери которых страдали диабетом, токсикозом беременных или имели нормальный обмен веществ. Значения инсулина оказались значительно выше у детей, матери которых

страдали диабетом или токсикозом беременных. У новорожденных, матери которых болели диабетом, требующим приема инсулина, или имели моносимптомный токсикоз беременных, отмечалось выделение гораздо большего количества инсулина в ответ на нагрузку глюкозой, чем у контрольных новорожденных. Утилизация же глюкозы, напротив, была ниже, чем у нормальных новорожденных. Можно заключить, что гиперинсулинемия не является единственной причиной гипогликемии, наблюдаемой у новорожденных детей, родившихся от матерей с диабетом.

На основании полученных результатов авторы приходят к выводу, что чувствительность панкреатических В-клеток к глюкозе развивается только после рождения. В патологической внутриматочной среде активность этих клеток может быть повышенной уже перед рождением, результатом чего является базальная или проявляющаяся в ответ на раздражение гиперинсулинемия.

ЭФФЕКТИВНЫЙ ТИРОКСИНОВЫЙ КОЭФФИЦИЕНТ ПРИ ОБМЕННОМ ПЕРЕЛОВАНИИ КРОВИ У НОВОРОЖДЕННЫХ ДЕТЕЙ

Ф. ПЕТЕР, И. ИЙЕШ и Я. КЕЧКЕШ

Авторы исследовали влияние обменного переливания крови на функцию щитовидной железы у новорожденных, выполняя серийные определения эффективного тироксинного коэффициента (ETR — Effective Thyroxin Ratio). У новорожденных детей ETR слегка повышен, и его уровень продолжает повышаться во время переливания крови. Это наблюдение указывает на превосходную способность щитовидной железы новорожденных к экскреции гормона, поскольку значение ETR меньше в переливаемой крови, чем в крови реципиента.

ПОПЕРЕЧНЫЙ ДИАМЕТР ГРУДНОЙ КЛЕТКИ И СЕРДЦА У НОВОРОЖДЕННЫХ ДЕТЕЙ С ФИЗИОЛОГИЧЕСКОЙ СЕРДЕЧНОЛЕГОЧНОЙ АДАПТАЦИЕЙ

Я. ВАЙЗЕНБАХ, А. ХАЙПАЛ, Ш. ВАРАДИ,
В. ЯСАИ, М. ШМЕЛЬЦЕР, К. ШУЛЬЦ, Л. ПАП
и И. РИППЛ

На материале 824 новорожденных детей с нормальной сердечно-легочной адаптацией авторы делают анализ рентгенологической морфологии легких и сердца. Они

показали, что в нормальных условиях в пределах 6—12 часов после рождения наполнение легких воздухом удовлетворительное, и через 24 часа во всех случаях легкие содержат нормальное количество воздуха.

Кроме морфологического анализа легких и сердца авторы выполнили также количественные исследования: определяли поперечный диаметр грудной клетки и сердца. Полученные значения были скоррелированы с весом и длиной тела при рождении, а также с продолжительностью беременности.

Выделили отдельные подгруппы в зависимости от момента, в который производилось исследование (через 6—12, 24, 48, 72 часа и 5 дней после рождения).

Оказалось, что величина поперечного диаметра грудной клетки и сердца не изменяется в ранний постнатальный период (между 6—12 часами и 5-м днем).

Величина обоих диаметров находится в тесной связи с весом при рождении (эта взаимосвязь теснее всего в подгруппе детей с весом ниже 1550 г, снова переменчива в подгруппе с весом 1500—2000 г и снова тесная в категории с весом больше 2001 г). Взаимосвязь носит экспоненциальный характер.

Взаимосвязь обоих диаметров с длиной тела является линейной и очень тесной. Разницы в связи с ранними моментами обследования не обнаруживается. Между гестационным возрастом и размерами поперечного диаметра грудной клетки и сердца взаимосвязь очень слабая.

Авторы разработали для практического применения процентный стандарт поперечного диаметра грудной клетки и сердца как по отношению к весу, так и к длине тела при рождении.

СИНДРОМ ПОЛАНДА: КЛИНИЧЕСКИЕ И ЦИТОГЕНЕТИЧЕСКИЕ ИССЛЕДОВАНИЯ В СЕМИ СЛУЧАЯХ

Л. БОРБОЛЛА, Б. ВАЗКВЕЗ и А. ЛАНТИГУА

Были обследованы семь больных с синдромом Поланда: шесть мальчиков и одна девочка. В четырех случаях была затронута правая сторона и в трех случаях — левая. У всех обследованных детей наблюдалась асимметрия сосков грудной железы, которая была пропорциональна тяжести мышечного дефекта. У одного из больных была колобома радужной оболочки. Дефект верхней конечности — особенно кисти — был тяжелее, чем мышечная аномалия. В трех случаях кисть была почти нормальной, эти случаи рассматриваются как ва-

рианты уродства. В четырех случаях отмечались осложнения при родах, близнец одного из больных родился с миеломенингоцеле.

СИНДРОМ ПОЛАНДА: ДЕРМАТО-ГЛИФНЫЕ ИССЛЕДОВАНИЯ В СЕМИ СЛУЧАЯХ

Л. БОРБОЛЛА, Б. ВАЗКВЕЗ и А. ЛАНТИГУА

Были выполнены дерматоглифные исследования у семи детей с синдромом Поланда. В изменениях рук наблюдались большие варианты, результат был типичным для синбрахидактилии. Если рука была только короткопалой, то и тогда отмечались характерные конфигурации, а если рука на стороне дефекта была нормальной, то на ней, а также на нормальной руке другой стороны, изредка обнаруживались изменения.

РАСТУЩИЙ ЧЕРЕП

К. ГЕФФЕРТ

Автор данного сообщения пытался определять размеры лицевого черепа по рентгеновским снимкам, выполненным в рентгенологическом отделении 1-й педиатрической клиники Будапештского медицинского университета им. Семмельвейса. Подходящими для этой цели оказались снимки черепа 540 мальчиков и 504 девочек. Обработке подвергались исключительно снимки в боковой проекции. Возраст детей колебался от новорожденного до позднего пубертатного: у мальчиков до 17,5 лет, у девочек до 19 лет. По возрасту дети были подразделены на 26 групп. От первой отправной точки — бугорка турецкого седла — измерялись три расстояния и три угла, от середины лобно-носового шва — второй отправной точки — измерялись два расстояния. Увеличение в расстоянии было примерно 2-х или 2,5-кратным, у мальчиков несколько в большей степени, чем у девочек. Наиболее выраженным было увеличение расстояние по направлению к верхушке нижней челюсти, особенно у мальчиков. Увеличение углов было умеренным, у мальчиков несколько более выраженным. В увеличении углов у обоих полов наблюдались половые различия, а в расстоянии, повидимому, некоторое расовоеобразие. Результаты данного исследования указывают на то, что используемый автором горизонтальный метод исследования имеет преимущества перед продольным способом исследования, когда оценке подвергается такая же, но относительно замкнутая группа.

ЭТИОПАТОГЕНЕЗ АНГИОДИСПЛАЗИЙ

Г. ТАШНАДИ и М. ОСТОВИЧ

Основываясь на результатах обследования 382 больных с ангиодисплазией и данных литературы, мы даем анализ этиопатогенеза этого заболевания. Среди первичных и вторичных факторов морфогенеза мы

выделяем значение фетальных заболеваний, внутриматочной репарации, кроме того, роль гормональных воздействий в новорожденном возрасте, вставания на ноги и хождения. Мы пришли к выводу, что ангиодисциплиазии формируются под совместным воздействием генетических факторов и факторов окружающей среды и являются эволюционными нарушениями развития, изменяющимися в ходе жизни.



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