Late Sequelae of Prematurity

By

GERTRUD WOHLMUTH and RÓZSA FRÁTER

Department of Premature Infants of the Schöpf-Merei Hospital,
and Department of Psychiatry, University Medical School, Budapest
(Received January 11, 1965)

According to literary data, 70 to 80 per cent of prematurely born babies survive in adequate institutes. At least as important as the problem of survival is, however, the question as to what will become of the survivors, in other words, the problem concerning the effect of premature birth on later life.

In order to approach the problem we have subjected to a detailed examination 6 to 7-year old prematurely born children who — as immature and in many cases perinatally traumatized infants — had been in our care during the first postnatal weeks. The reason for our examining these children at the beginning of the school age was that in this period of life numerous up to then latent somatic phenomena and hidden behavioural disorders become manifest [17].

The questions to be elucidated were as follows.

(i) The incidence of
   (a) somatic anomalies;
   (b) neurological disorders and psychomotor retardation;
   (c) damage to the sense organs.
(ii) The mental development, i.e.
   (a) are these children mentally deficient or intellectually retarded?
   (b) how do those with normal intelligence behave and how far are they socially balanced?
(iii) What is the prognostic and diagnostic value of electroencephalographic examinations?

MATERIAL

Of the babies admitted to the Department of Premature Infants in 1957, 60 per cent had come from the provinces and 40 per cent from the capital; 21.7 per cent died during neonatal age and 11.5 per cent in the subsequent years.

All the 284 survivors were invited to report at a follow-up examination; and a total of 193 appeared and could be studied.

METHODS

I. Perinatal period. We studied the family history, the conditions of pregnancy and delivery, as well as the original case record. Apart from the clinical data, the results of repeated and detailed neurological examinations were of special catamnestic interest in these records. The infants were examined neurologically as described in an earlier paper [20] and, if necessary, the examination was supplemented by that of the cerebrospinal fluid, the eyegrounds, as also by an EEG.

Birth weight (g)	Examined	Not examined
Less than 1000	2	1
1000—1250	11	10
1250—1500	55	21
1501—1750	47	10
1750—2000	56	30
2001—2250	16	9
2251—2500	6	10
Total	193	91

On the evidence of the history and the said examinations, the children were divided into two categories.

(i) *Practically normal prematures,* i.e. those with uneventful family and obstetric history and normal clinical picture, whose examinations made in the neonatal period and during infancy had given normal results.

(ii) *Perinatally traumatized prematures.* This category included

a) children with probable foetal anoxia on the strength of the history (e.g. on account of a maternal disease such as toxaemia, asthma, etc.); postnatal apnoea; irregular delivery;

b) children who in the first 28 days of extrauterine life had suffered from some disease which may have damaged the nervous system either directly or by causing cerebral anoxia (e.g. icterus gravis, pneumonia, meningitis, etc.);

c) children who during early infancy had suffered a neurological disorder attributable to some injury sustained before, during or after birth (i.e. between the 28th week of intrauterine and the 28th day of extrauterine life).

Perinatal injuries will be discussed summarily; details are dealt with in a separate paper.

Hundred and eleven of the 193 examined prematures and 23 of the 91 not re-examined children had suffered some perinatal injury.

II. All prematures were kept under observation until the 3rd year of age; they were examined once every 6 month, then yearly, and later at suitable intervals.

III. The follow-up examination at the age of 6 to 7 years, the subject of this paper, involved a survey of the aforementioned antecedents and a detailed history covering the last 3 years, with especial attention to family and social conditions as well as to pathologic episodes. This was completed by paediatric, neurologic, psychiatric, electroencephalographic and other necessary examinations (cardiology, ophthalmology, otology, audiometry, orthopaedics, etc.).

RESULTS

Most of the children were slender in build and of low stature. Results of the somatic examinations are assembled in Tables I and II.

Gross changes (e.g. caput quadratum, beading of costochondral junctions, Harrison's sulcus) were regarded as criteria of rickets. They were found in 15 children (8 per cent).

A stooping carriage with hanging shoulders was seen in 13 children (7 per cent).

Congenital heart defect (patent ductus arteriosus) was observed in a single case.

Retrolental fibroplasia, blindness or other serious visual defects, did not occur, whereas refractive errors or strabism were found in 46 cases (24 per cent). Since none of these irregularities had led to mental retardation or abnormal behaviour, they are classified under the somatic findings.

Table III shows the graver damages to the nervous system and the sense organs as also their mental and behavioural consequences.

Grave nervous disturbances (e.g. cerebral palsy, extrapyramidal motor

TABLE I

Longitudinal growth

Age	Sex	Total	Percentile							Mean per cent
			5	3	10	25	50	75	90	
6	female	42	5	5	8	11	13	—	—	22 (112.7)
6½	,,	48	—	2	13	18	11	3	1	32 (117.1)
7	,,	19	—	5	4	5	5	—	—	22 (118.7)
6	male	38	1	5	8	12	10	2	—	27 (114.4)
6½	,,	37	5	5	7	12	6	2	—	20 (116.3)
7	,,	19	6	3	6	1	2	1	—	10 (116.6)

TABLE II

Disorder	Number	%
Rickets, bone deformity	15	7.77
Stooping carriage	13	6.73
Congenital heart defect ..	1	0.51
Visual defect	46	23.83

Standard: The tables of V. Meredith, Iowa Child Welfare Research Station, The State University of Iowa.

disturbances, etc.) were observed in 6 cases (3 per cent).

Slight psychomotor and/or intellectual retardation was found in 91 children (47 per cent). This group includes children with retarded motor or mental development, further those who had some slight locomotor defect or exhibited motor immaturity, e.g. disturbances of co-ordination.

Grave defects of the sense organs were encountered in 6 cases (3 per cent) (2 children were deaf-mute, 4 were hard of hearing).

Behavioural disorders, i.e. failure of adaptation to the environment or to school life, were observed in 114 cases (59 per cent).

TABLE III

Nervous system, sense organs	Number (%)	Mental			Behav- ioural dis- order	Ripe	Unripe	Unsuited
		in agree- ment with chrono- logical age	Retarded	Deficient		for normal schooling		
Normal	90 (46.9)	90	—	—	34	90	—	—
Slight motor and/or mental retardation	91 (47.1)	47	24	20	68	47	24	10
Serious impairment of sense organs	6 (3.1)	—	3	3	6	—	—	6
Serious impairment of nervous apparatus	6 (3.1)	—	—	6	6	—	—	6
Total	193 (100)	137	27	29	114	137	24	22
Per cent		71.0	13.5	15.0	59.0	71.0	12.5	11.5

4*

TABLE IV

Results of Binet—Simon tests

I. Q.	Number of children
> 90 (90—110)	137
> 75 (75—90)	27
> 50 (50—75)	16
< 50	9
Not accessible to examination	4
Total	193

Binet-Simon I. Q.-values are shown in Table IV.

Mental age was in harmony with chronological age in 137 cases (71 per cent), and the same number was ripe for school attendance, but only 56 (29 per cent) were faultlessly adapted from a social point of view.

The problem of behavioural disorders owes its importance to the fact that so many of intellectually normal prematures display lack of attention and diminished adaptability [2, 5, 6 10].

Two of the examined children were suffering from epilepsy; one of them was neurally damaged, the other was normal in other respects.

DISCUSSION

Six to seven-year old prematurely born children have been studied as to their somatic and mental condition. The results have been compared with data reported by other authors as also with data for full-term children of the same age.

Retarded longitudinal growth was a conspicuous feature; there was a high incidence of bone deformities due to rickets.

According to orthopaedic examinations, the slooping carriage observed in 7 per cent was in no case due to some anatomical irregularity. Its comparatively high incidence must have been due to muscular hypertonicity and a debility of the ligaments, and also to the fact that many parents, worrying too much about their premature offspring, prevent them from sufficiently engaging in physical exercise and sports.

The considerable proportion of neural damage and impaired sense organs in comparison to full-term children is only natural. It is, however, the great number of children with a slight psychomotor or intellectual retardation and of those having troubles of psychic maturation and social adaptation which has a decisive importance for education, schooling and society.

Disorders of behaviour were observed in 59 per cent of the examined subjects, of whom more than 71 per cent were not ripe for normal schooling. Against this, only 48 per cent of 204 children in the first grade of elementary school in a Budapest district were intellectually unsuited for the school; of these, 23 per cent were borderline cases [16]. Even if it is borne in mind that these figures refer to nursery-school children, i.e. to socially more or less adapted individuals and not to children selected at random, the difference between the prematures and the general population is remarkably high.

Literature contains several reports [3, 5, 6, 14] on the retarded development and especially on the retarded longitudinal growth of premature children. DANN [3] has shown that the second phase of the prematures' growth curve ascends more steeply than the standard curve. Our findings tend to support this concept.

As regards impairment of the sense organs, the present findings were in contrast with those reported in the literature. While numerous authors [3, 5, 6, 12, 13, 14, 15] registered a high percentage of blindness or retrolental fibroplasia, there was no such defect in our material, a phenomenon presumably explained by the fact that we are administering oxygen only if needed, and even then sparingly and at concentrations of 25 to 30 per cent. On the other hand, we have no explanation for the great number of hearing defects. (Only one of the 6 children received prolonged streptomycin treatment on account of meningo-encephalitis.)

Diseases of the respiratory tract were the most frequent intercurrent diseases, and they occurred chiefly in the first two years of life, just as in the material of other authors [4, 6, 11].

LUBCHENKO et al. [14] followed the development of 63 children with less than 1500 g birth weight until their 10th year of age. They observed neurological disorders in 30 cases of which 22 were spastic diplegia. The intellectual level was normal in 35 children; 20 of them had, however, to wrestle with problems of learning and adaptation. Among 50 children

of school age with birth weights under 1300 g, DRILLIEN [5] found only 25 who were ripe for the elementary school, and 78 per cent displayed an abnormal behaviour pattern.

DRILLIEN [6], HARPER et al. [9], WIENER et al [19], FISCHER et al. [8] and KNOBLOCH et al. [12, 13] compared the development of several hundred prematures with that of children born at term. They all agree in that prematures are inferior to full-term children not only in respect of somatic growth and the functioning of the sense organs but also as regards neuromotor functions, intellectual potential and especially in social behaviour. It is still a matter of debate whether

premature birth in itself,

socio-economic factors,

the intellectual status of the parents,

genetic factors, or

prenatal events and possible perinatal trauma are responsible for these disorders. The problem is not easy because — as has been stated by DUNHAM [7] and ALM [1] — there exists no standard of reference; the categories become, moreover, too limited if the criteria are exactly defined. Besides, most authors employed the retrospective method. In the study of HARPER et al. [9] the examiners did not know which of the children were premature so that preconceived ideas could not contaminate the results.

DRILLIEN [6] and WIENER et al. [19] attribute so much importance to socio-economic factors that they classified their material according to social position and the quality of the

household in which the children were living. In addition DANN et al. [3] regard the mother's intellectual faculties and DRILLIEN her "suitability" as further criteria.

For the examination of environmental, and partly for that of genetic influences, full-term siblings of the premature children were chosen by DANN et al. [3] and DRILLIEN [6] as standards of reference. Some full-term siblings of mentally deficient or retarded prematures brought up in unfavourable surroundings or born of intellectually inferior parents were mentally behind their chronological age. Our findings were in full agreement with the above.

Psycho-social development is particularly influenced by environmental factors. This was borne out by a pair of twins both of whom displayed behavioural disorders and raised educational problems at school. No perinatal trauma had been suffered by either twin, and the mental, motor and somatic development of both of them was adequate until the 3rd year of age. The twins were separated at the age of 3 1/2 years; one was henceforth living with the mother, the other with the paternal grandfather. Being neighbours, frequent meetings were unavoidable, and the mother and the grandfather would start heated disputes and verbal strifes on such occasions in the presence of the children.

It has been suggested by several authors [2, 10, 17] that diminished efficiency and adaptability originate from slight organic cerebral damage and that it is possible to prevent or mitigate them by early diagnosis and timely treatment. On the other hand, children with slight cerebral damage become increasingly susceptible to various disorders if kept in unfavourable surroundings. Electroencephalography is of great diagnostic and prognostic value in this respect, a subject to be treated in detail in another paper.

While our results are, essentially, in agreement with literary data, no detailed and objective comparison is possible on account of the heterogeneity of the weight groups. The existence of an inverse relation between birth weight and subsequent deficiencies has been claimed by several authors [3, 5, 6, 9, 12, 13, 14], whereas the causal correlation of low birth weight with the number and degree of neural defects is unclear. The problem requires further investigations.

We are in full agreement with the view [3, 5, 6, 18] that the development of prematurely born children is determined less by birth weight and more by the causes of premature delivery, such as familial and hereditary factors, conditions of pregnancy and labour, and the general course of the perinatal period. DANN et al. followed 100 premature children until their 10th year of age; the mothers of 45 mentally backward children had had grave complications during pregnancy. For example, 9 out of 13 children born of toxaemic pregnancy had an I. Q. below 99.

In our material there was for instance a premature baby born with 1300 g. Although no perinatal trauma had been

registered, the baby had fits at the age of one year. The child's school registration at the age of 6 years had to be postponed on account of its lack of attention and low efficiency. The mother was delivered of a second child of 2900 g after an apparently normal pregnancy 3 years later. This second child had multiple congenital anomalies. The same factor was presumably responsible for the premature birth of the first child and the defect of the second.

None of the various categories (formed according to birth weight or other characteristics) containing surviving prematures selected from the material of a given year has a sufficient number of members to warrant objective comparisons or definite conclusions. We have, therefore, started investigations in which prematures are divided into different categories according to certain characteristics (e.g. cases of placenta previa, birth weight, etc.) but irrespective of the year of birth. It will thus be possible to determine on the evidence of an adequately large material

(a) whether immaturity is a direct consequence of premature birth, in other words, whether a causal connection exists between premature birth and the subsequent disturbances;

(b) whether premature birth and the subsequent disturbances are connected not directly but through perinatal traumatization;

(c) whether irregularities observed in surviving prematures are not due to delivery before term but some subsequent trauma, environmental influence or disease.

The results are expected to be instructive by showing how the observed damages could have been prevented, how far prenatal care facilitates prevention, and also by revealing the usefulness of precise paediatric and neurological data recorded from the first moment of life, further the advantages of early diagnosis and adequate therapy.

SUMMARY

The late effect of premature birth have been studied in 193 prematurely born children of school age.

Most of the children were of low stature and slender. Grave nervous disturbances were observed in 6 cases, slight psychomotor retardation in 91; hearing defects in 6, behavioural disorders in 114 cases. Significance and the interpretation of the findings has been discussed.

REFERENCES

1. ALM, I.: The long term prognosis for prematurely born children: A follow-up study of 999 premature boys born in wedlock and 100 controls. Acta paediat. (Uppsala) **42**, Suppl. **94**, 116 (1963)
2. CLEMENTS, S. D., PETERS, J. E.: Minimal brain dysfunction in the school-age child. Arch. gen. Psych. **6**, 185 (1962)
3. DANN, M., LEVINE, S., NEW, E.: A long-term follow-up study of small premature infants. Pediatrics **33**, 945 (1964)
4. DOUGLAS, J. W. B.: Mental Ability and School Achievements of Premature Children at Eight Years of Age. Brit. med. J. **1**, 1210 (1956)
5. DRILLIEN, C. M.: The incidence of mental and physical handicaps in school-age children of very low birth weight. Pediatrics **7**, 452 (1961)
6. DRILLIEN, C. M.: The growth and development of the prematurely born infant. Livingstone, Edinburgh 1964
7. DUNHAM, E. C.: Premature infants: Manual for Physicians. Publication 325, Federal Security Agency, Children's Bureau, Washington 1948. p. 400
8. FISCHER, L. K., OPPEL, W., KNOBLOCH, H., RIDER, R., HARPER, P.: Longitudinal study of premature and full-term infants: Neurological and intellectual status at 3 to 5 years. Amer. J. Dis. Child. **96**, 617 (1958)
9. HARPER, P. A., FISCHER, L. K., RIDER, R. V.: Neurological and intellectual status of prematures at three to five years of age. J. Pediat. **55**, 679 (1959)
10. INGRAM, T. S.: A characteristic form of observative behaviour in brain damaged children. J. nerv. ment. Dis. **102**, 550 (1956)
11. JAMES, J. A.: The later health of premature infants: a field for further study. Pediatrics **22**, 154 (1958)
12. KNOBLOCH, H., RIDER, R., HARPER, P., PASAMENICK, B.: Neuropsychiatric sequelae of prematurity. J. Amer. med. Ass. **161**, 581 (1956)
13. KNOBLOCH, H.: The effect of prematurity on health and growth. Amer. J. Publ. Hlth **49**, 1164 (1959)
14. LUBCHENKO, L. O., HONER, F. A., REED, L. H., HIX, I., METCALF, D., COHIG, R., ELLIOTT, H. C., DENVER, M. B.: Sequelae of premature birth. Amer. J. Dis. Child. **106**, 101 (1963)
15. McDONALD, A. D.: Neurological and Ophthalmic disorders in children of very low birth weight. Brit. med. J. **1**, 895 (1962)
16. PALIK, I. Personal communication
17. POPELLA, E., WERNER, R.: Zur Psychopathologie der Reifungsstörungen im ersten Gestaltwandel, unter Berücksichtigung elektroencephalographischer Befunde. Verhandlungen des 2. internationalen Kongresses für psychische und Entwicklungsstörungen des Kinddesalters, Wien 1961. Karger, Basel 1963. Part I, pp 255—258.
18. THURSTON, D., GRAHAM, F. K., ERNHART, CL. B., EICHMANN, P. L., CRAFT, M.: Neurologic status of 3-year old children originally studied at birth. Neurology **10**, 680 (1960)
19. WIENER, G., RIDER, R., OPPEL, W.: Some correlates of I/ Q. changes in children. Child. Develop. **34**, 61 (1963)
20. WOHLMUTH, G., PERTORINI, R.: Beiträge zur Neurologie der Frühgeborenen. Mschr. Kinderheilk. **106**, 334 (1958)

Dr. G. WOHLMUTH
Salgótarjáni út 47—49
Budapest X. Hungary