Social aspects of low birth weight

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Dr. Harry Medovy, in whose honour these lectures are given, has long been interested in social aspects of low birth weight. With Drs. Briggs and DePape and others he carried out a 10-year study of perinatal mortality and morbidity in 1954–63, and with Dr. Briggs he summarized some of the findings in 1958.[1] Also, with Drs. Grewar and Wylie he published a paper on the prognosis of prematurity in 1962.[2] Two years later he chaired a panel discussion on the later history of the small-weight baby at the annual meeting of the Canadian Paediatric Society.[3]

Introduction

In the developed countries about 4% to 8% of all children weigh 2500 g or less at birth, and in the developing countries the proportion is considerably higher, ranging up to 28% in India.[4] While there has been a marked fall in both neonatal and infant mortality in most Western countries during the past 25 years, low birth weight has remained the single most important factor in infant mortality and morbidity. For instance, in England and Wales about 6% of singletons are born weighing 2500 g or less, and these account for 60% of infant deaths.[5] In British Columbia, as elsewhere, the mortality of infants of both full and low birth weight has diminished considerably, but infants weighing 2500 g or less now account for more than half of the infant deaths (Table I).

During this 25-year period the incidence of low birth weight has remained fairly constant, at about 6% to 7% of live births in England and Wales[5] and 7% to 8% in the United States.[6] A slight, transient increase in the incidence of low and very low birth weight in Canada and in the United States during the 1960s remains unexplained.[7] A reduction in the low-birth-weight ratio from 4.9% in 1960–69 to a record low of 4.1% in 1970–76 was reported in Sweden, and a fall in the ratio was also noted in some other areas, such as metropolitan counties in the United States[6] and the province of British Columbia (division of vital statistics, British Columbia Ministry of Health: personal communication, 1980).

The low-birth-weight ratio is influenced by many variables, including socioeconomic status and education. In fact, the causes of low birth weight may serve to illustrate the difficulties in analysing the significance of multiple interdependent factors.

Earlier investigators in the United Kingdom noted the association between low birth weight and low social class. Baird[8,9] took a wide view of the mother's reproductive efficiency as being greatly influenced by the quality of her environment from birth to maturity, and he attributed the high prevalence of stillbirths and premature labour in the low social classes to the poor health and nutrition of the mother. He considered that the high neonatal mortality in the lower social classes was largely due to the high proportion of infants of low birth weight. Drillien[10] found that the social class into which a woman marries has only a very minor influence on her chance of having a premature baby compared with the class in which she was born and brought up (i.e., that of her father). An association was even found between risk of prematurity and unemployment of the grandfather. On the other hand, Douglas,[11] from a national survey of

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Table I—Infant mortality in British Columbia by birth weight (data for weighed infants only)

Variable	Birth weight (g) ≤ 2000	2001–2500	> 2500	Total
1958				
No. of live births	802	1750	36 748	39 300
Total no. of deaths in first year of life	347	118	507	972
Infant mortality (%)	43.3	6.7	1.4	2.5
1966				
No. of live births	811	1506	30 512	32 829
Total no. of deaths in first year of life	324	90	335	749
Infant mortality (%)	40.0	6.0	1.1	2.3
1977				
No. of live births	732	1422	34 717	36 871
Total no. of deaths in first year of life	203	53	233	489
Infant mortality (%)	27.7	3.7	0.7	1.3

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more than 13 000 singleton births in Britain, considered that social class differences in the risk of premature delivery were present but relatively unimportant. He found abnormally high rates of premature births only in two well defined groups of working-class women, namely primiparas aged 20 years or less and multiparas with closely spaced pregnancies.

Categories of low-birth-weight infants

In 1948 the World Health Assembly designated children who were born weighing 2500 g or less as "immature" and further stated that a liveborn infant with a period of gestation of less than 37 weeks or specified as "premature" may be considered as the equivalent of an immature infant.[12] This almost synonymous use of the terms "immature" and "premature" led to considerable confusion. Drillien[10] was one of the first to note that one half of "premature" infants born to primiparous women and one third of those born to women in the high-parity group had a gestation period of 38 weeks or longer. She concluded that babies classed as premature on a weight basis were a mixture of two categories, early and small. The mothers of small babies were significantly shorter than those of early babies. Liability to early delivery was related to the social class of upbringing and not at all to stature, whereas liability to produce a small baby at term was affected about equally by social class and maternal stature. In general the proportion of underweight children born at term was found to be higher in the lower socioeconomic groups and in developing countries. Accordingly, in 1961 the expert committee on maternal and child health established by the World Health Organization[13] recommended that babies weighing 2500 g or less should no longer all be referred to as being "premature" and that the concept of "prematurity" in the definition should give way to that of "low birth weight". Lubchenco and her colleagues[14] and others[15,16] then devised intrauterine growth curves for liveborn males and females from data on birth weight and gestational age. As an example, we may simplify the curves drawn by Babson and his associates[16] in Portland, Oregon, where the social situation and altitude are similar to those in Vancouver (Fig. 1).

Infants born prior to 37 completed weeks of gestation whose weight lies between the 10th and 90th percentiles on such curves may be called preterm with a weight appropriate for gestational age (AGA), whereas infants born after any length of gestation whose birth weight is at or below the 10th percentile may be named hypotrophic or small for gestational age (SGA).

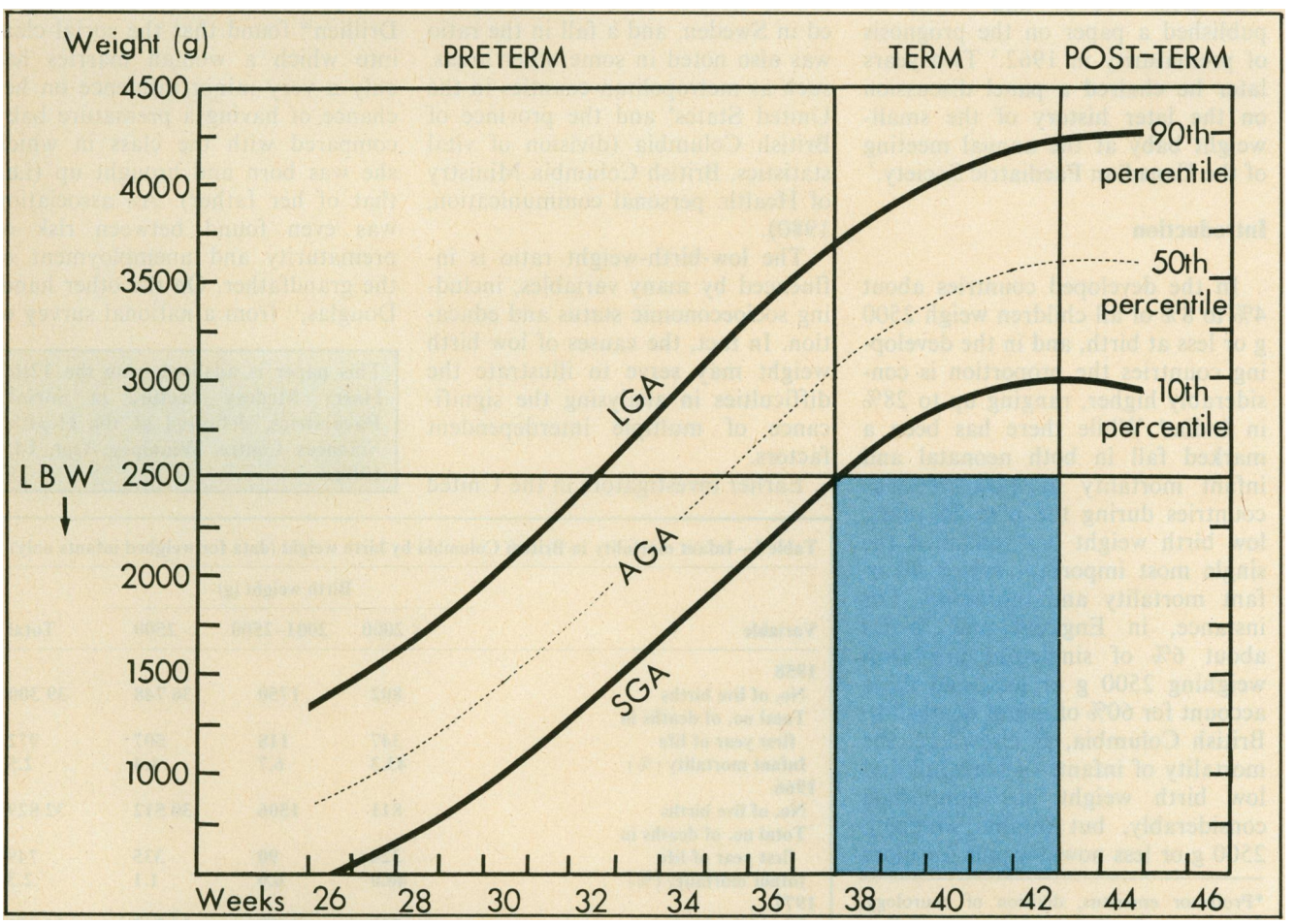

Fig. 1—Classification of newborn infants by birth weight and gestational age. Infants of low birth weight (LBW; ≤ 2500 g) may be born preterm with a weight appropriate for their gestational age (AGA) or at term and be small for their gestational age (SGA; screened area). There is also an overlap group of SGA infants born preterm. LGA = large for gestational age. Sex differences are omitted for clarity. Reproduced in modified form, with permission, from reference 16.

Thus, children of low birth weight include two major categories with somewhat different causation and handicaps — preterm AGA infants, who are "born too soon", and term SGA infants, who are "born too small".[17] SGA infants who are born preterm represent an overlap group, which is liable to have mixed handicaps. SGA infants are a heterogeneous group that may be divided into several etiologic categories, such as those of a multiple birth (twins, triplets etc.), those with congenital defects or hereditary "maternal constraint",[18] those with fetal intrauterine disease (e.g., rubella) and those whose growth was impaired by maternal malnutrition, disease, smoking or drug intake, or by placental insufficiency, as in preeclamptic toxemia. They all share the characteristic of having had slow intrauterine growth. On a worldwide scale it has been estimated that about 22 million low-birth-weight babies, representing roughly one sixth of all births, are born alive each year. Only about 1 million of them (mostly preterm) are born in developed countries; of the 21 million born in developing areas, roughly 16 million are SGA full-term and not preterm babies.[19]

Social versus racial factors

It has been widely assumed that the high incidence of low birth weight in developing countries is due to poor nutrition of mother and fetus. Even in the United States blacks have a higher mean low-birth-weight ratio than whites, and this has been attributed to socioeconomic rather than racial differences.[20,21] Further, members of the same racial group can have quite different low-birth-weight ratios in different areas. For example, the ratios for Chinese range from 7.2% in Hawaii to 16.6% in Malaya.[22] Gruenwald and his associates[23] noted that with the better nutrition in Japan after World War II there was a spectacular increase in birth weights. This appeared to have been caused by better fetal growth and not by any increase in the duration of pregnancy.

However, race by itself may also have some influence on birth weight. In a thorough study of the case material in the national Collaborative Perinatal Project in the United States, Naylor and Myrianthopoulos[24] investigated 11 selected socioeconomic factors to assess their contribution to the variation of birth weight. Multiple regression and covariance analyses of data on 20 000 births indicated that in all races birth weight was positively related to first-trimester household income and many other socioeconomic variables. None the less, very little of the variance in birth weight was accounted for by these variables. All attempts to account for racial differences in terms of regression on socioeconomic factors failed to remove the possibility that white babies were inherently about 130 g heavier than black babies. Similarly, recent studies by Garn and his colleagues[25] in the United States showed that although socioeconomic status was inversely related to the low-birth-weight ratio in whites, Puerto Ricans and blacks, independent of parity and smoking, race also had a major bearing on the incidence of low birth weight at each income, occupational and educational level. In Sweden Bjerre and Värendh[26] found that biologic factors, such as mother's age, parity, stature and weight, appeared to play the greatest role in low birth weight but that these variables were difficult to distinguish from socioeconomic factors, such as mother's civil status, parents' social group and family income.

Table II—Factors increasing the risk of low birth weight

Low maternal weight (and height) before pregnancy
Low maternal weight gain during pregnancy
Prior delivery of a low-birth-weight infant or prior abortion after first trimester
Maternal smoking, alcoholism or use of drugs during pregnancy
Low socioeconomic status
Maternal age (risk is greatest for infants of teenagers and of mothers more than 40 years old)
Complications of pregnancy and delivery (e.g., bleeding, toxemia, breech presentation)
Parity (risk is lowest in second pregnancy)
Antenatal factors, such as physical overwork, coitus and lack of medical care
Race (risk is greater for nonwhite infants)
Altitude (risk is greater at higher altitude)
Female gender of infant
Congenital malformation or infection of infant (e.g., chromosomal defects, rubella)
Multiple pregnancy

Factors increasing the risk of low birth weight

The many factors that may influence the risk of low birth weight are listed in Table II. In the list maternal height is enclosed in brackets because although it is significantly related to birth weight and social class the relationship often ceases to be significant when maternal weight before pregnancy is taken into consideration.[27] Like other investigators, we have found that maternal smoking reduces birth weight, and to a lesser extent gestational age, so that SGA infants commonly result.[28] The same applies to alcoholism and the use of nonmedical drugs.

With respect to maternal age and parity, the high incidence of low birth weight among the offspring of teenagers seems to be largely due to factors other than age and can be reduced to the expected rate by good antenatal care and nutrition.[29] However, girls aged 16 years and less do tend to have a slightly increased frequency of toxemia, pregnancy-induced hypertension and a small pelvic inlet.[30-32] Dowding[33] considers that the major part of the birth order effect can be attributed to social class differences.

Fedrick and Adelstein,[34] in their analysis of singleton births, found that delivery of a low-birth-weight infant *at term* was significantly associated with low maternal weight before pregnancy, low maternal height, maternal smoking, primiparity, maternal employment, low social class, previous delivery of an infant of low birth weight, threatened abortion and severe toxemia. This contrasted with the results of a similar investigation of spontaneous *preterm* births in which the risk of such an event was again found to be related to low maternal weight before pregnancy, maternal smoking, low social class, previous delivery of

an infant of low birth weight and threatened abortion but was also related to low maternal age, illegitimacy, and a previous history of antepartum hemorrhage and perinatal loss and was not significantly associated with maternal height (when weight was controlled for), primiparity or severe toxemia.[27]

Miller and his associates,[35] studying 1200 white mothers in Kansas, found that the incidence of low birth weight was highest in the lowest socioeconomic class and did not depend on medical problems of the mother during pregnancy but on four specific practices, largely of her own choosing, namely low weight gain during pregnancy, cigarette smoking, the use of certain addictive drugs and alcohol, and failure to obtain prenatal care.

Thus, we may conclude that socioeconomic status is significantly related to low birth weight but in direct correlation accounts for only a small portion of the variance and probably exerts most of its influence through intermediate variables, which may be biologic, like the mother's weight, parity, age and "reproductive efficiency", or may be environmental, like maternal smoking, physical overwork, coitus and inadequate prenatal care. The relative importance of these factors differs to some extent in the categories of AGA pre-term, SGA and large-for-gestational-age infants.[33,34,36]

Prevention of low birth weight

Recently Guyer and his coworkers[37] cited smoking, infections, nutrition and adequacy of prenatal care as the four critical influences on the incidence of low birth weight. They calculated that the weight-related neonatal mortality rates in Massachusetts from 1977 to 1979 were actually lower than those in Sweden and that if only the incidence of low birth weight in Massachusetts could be reduced to the Swedish level the neonatal mortality rate in that state would be greatly lessened. How could this be accomplished? Table III lists some measures for the prevention of low birth weight that could be incorporated in a public health program.[38]

Social factors in the development of low-birth-weight children

Two decades ago, Medovy and his colleagues[2] concluded that the premature infant who survived the hospital nursery period was 3 times as likely to die in the first year and almost 10 times as likely to be handicapped as a full-birth-weight baby. They found strong evidence that sociocultural deprivation was an important factor contributing to death in the first year "but not the only one". They made a plea that a number of these untimely deaths could be prevented by better sociologic, public health and clinical appreciation of the vulnerability of such infants. This plea needs to be repeated now as pediatricians are proposing to provincial governments that infants "at risk" — and particularly the alumni of intensive care nurseries who have had intracranial bleeding, seizures or a need for prolonged respiratory assistance — should be followed regularly in special clinics.

One of the first articles on the effects of environmental factors on the development of low-birth-weight infants and of term matched controls was published by Knobloch and Pasamanick.[39] They related these findings to their previously introduced concept of a continuum of reproductive casualty, with a lethal component of cerebral damage giving rise to fetal or neonatal death and a sublethal component resulting in various degrees of neuropsychiatric disability, ranging from the more obvious conditions of cerebral palsy and mental deficiency to lesser handicaps like behaviour disorders and reading disabilities. By analysing the effects of socioeconomic factors in pregnancy retrospectively and relating them to later neuropsychiatric functioning they demonstrated an increased prevalence of brain damage in the lower economic strata, where they found a higher incidence of complications of pregnancy and a greater proportion of babies of low birth weight. In 992 infants examined at 40 weeks of age by the Gesell developmental technique pregnancy experience, birth weight and physical status after birth were the only major factors that could explain group differences in developmental quotients between the low-birth-weight children and their controls. The relatively small amount of variability found in infancy could be explained largely by the presence of damage to the central nervous system. There was no significant difference between premature and control infants or between white and black infants when the developmental quotients were adjusted for birth weight, nor was there any significant difference between three economic groups of white infants. These findings supported the view that at this period of life social factors affect the psychologic level of integration primarily through biologic mechanisms. The direct influence of sociocultural forces on psychologic development was thought to become manifest during the preschool period.

Since then there has been considerable divergence of views in the literature concerning the effects of social factors on the development of low-birth-weight children. Thus, the relatively good outcome with respect to physical health and intelligence in 100 prematurely born children with a birth or minimum weight of 1000 g or less reported by Dann and her colleagues[40,41] was attributed largely to their good socioeconomic status. A significantly higher proportion of the children with intelligence quotients (IQs) above 100 was found

Table III—Measures for the prevention of low birth weight

Family planning
Avoidance of pregnancy before age 18 years and after age 35 years
Spacing of pregnancies
Adequate nutrition during pregnancy
Educational programs
Dietary supplements, especially in last trimester
Correction of anemia by improved intake of iron, folate and vitamins
Treatment of infections, especially urinary tract infection, hookworm and malaria
Avoidance of physical overwork and coitus in later stages of pregnancy
Antenatal obstetric supervision
Cessation of smoking and limitation of drinking and drug intake during pregnancy

among families of higher socioeconomic rating. An advantage of girls over boys and of white over nonwhite children was also noted, and the latter was thought to be secondary to socioeconomic factors. Similarly, Robinson and Robinson,[42] in a controlled follow-up study of low-birth-weight children aged between 8 and 10 years, concluded from analysis of covariance that, aside from physical size and major physical defects, social class assumed more importance than birth weight in a child's developmental prognosis. On the other hand, Wiener and his coworkers[43] concluded that the psychologic impairment of low-birth-weight children was not due to social class or to maternal practices. Although there were highly significant differences between white and black subjects, which tended to increase with age and were assumed to be influenced by environment, it appeared that black children were no more impaired than white children as a function of birth weight. Low-birth-weight children appeared to have a greater risk of impaired mental performance largely because of associated indications of neurologic defect.

With respect to intelligence Drillien[44] had already shown that it varies directly with both birth weight and social class. While mental retardation with a global IQ below 70 occurred particularly in children with a birth weight of 3.5 lb (1600 g) or less and in the lowest social class, it ensued most of all in those with a very low birth weight who were also in the lowest social class; in contrast, gifted children, with IQs of 120 or more, were most likely to be in one of the two highest social classes and to have had a normal birth weight — more than 5.5 lb (2500 g). In a study of child development on the island of Kauai in Hawaii, Werner and her associates[45] noted the cumulative risk of a depressed IQ in children with a low socioeconomic status or family instability who were exposed to severe perinatal stress.

Our own findings may be quoted in this connection.[46] We examined 501 low-birth-weight infants (most with a birth weight of 4.5 lb [2041 g] or less) in the newborn nurseries at the Vancouver General Hospital during the years 1959 through 1965 and managed to follow 335 of them, 80% of the survivors, to school age. We were also able to follow 139 out of 203 control children of full birth weight who were intentionally selected largely from nonpaying patients so that their mean social class was somewhat low and not significantly different from that of the low-birth-weight infants. When the developmental and intelligence quotients of these children are shown graphically at successive ages (Fig. 2) one can clearly see the association with birth weight, but it should also be noted that the scatter of scores diminishes from about 23 points for the developmental quotient (determined with Griffiths' technique[47]) at 3 months, uncorrected for gestational age, to about 13 points for the full-scale IQ on the Wechsler Intelligence Scale for Children (WISC) at 6½ years.[46] It appears, then, that the effect of birth weight diminishes somewhat as the children become older.

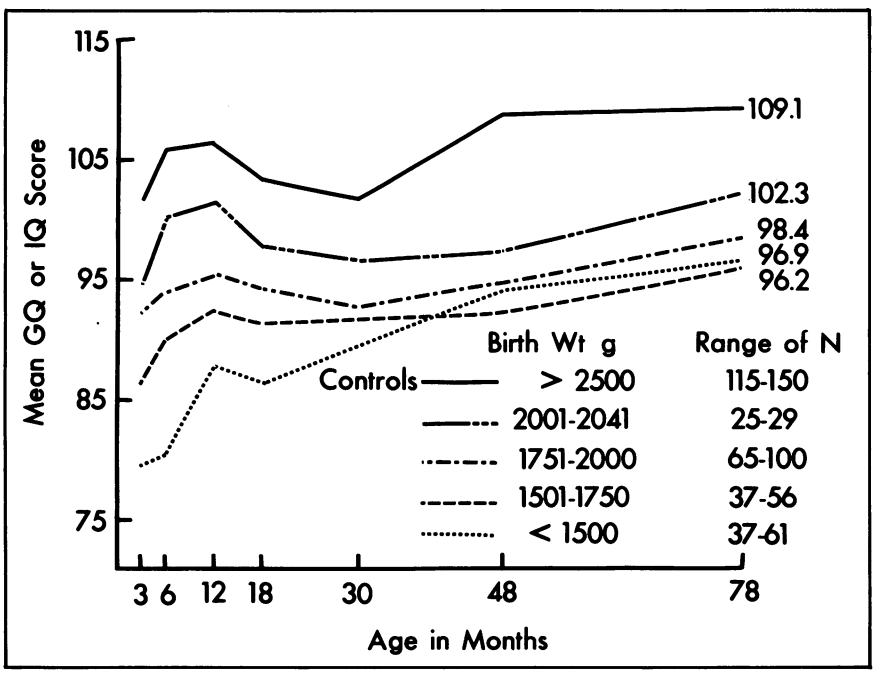

Fig. 2—Mean general developmental quotient (GQ) or intelligence quotient (IQ) scores according to birth weight of all low-birth-weight and full-birth-weight children in prospective study in Vancouver. GQ determined with Griffiths' technique,[47] IQ with Stanford–Binet Intelligence Scale before 78 months and Wechsler Intelligence Scale for Children at 78 months. N = number. Reproduced with permission from reference 46.

On the other hand, the association of developmental and intelligence quotients with socioeconomic status, measured by the Hollingshead two-factor index (derived from the father's education and profession), only became definite at 2½ to 4 years (Fig. 3).[48] The difference in IQ, as determined with the Stanford–Binet Intelligence Scale, between low-birth-weight children in social classes I to III as compared with those in classes IV and V was already significant ($p = 0.01$) at 2½ years of age, but by the age of 4 years the social classes had sorted themselves out more clearly. Among the full-birth-weight control children the correlation of developmental quotient with social class was already significant ($p = 0.02$) at 1½ years.

In this context one of our research assistants, Dr. Brian Warriner, calculated that there was a significant difference ($p = 0.01$) between the mean full-scale WISC IQ of children whose fathers were in different *educational* classes but that the difference was less marked between the mean IQs of children whose fathers were in different *occupational* classes on the Hollingshead scale. Further, there was a very significant difference ($p = 0.005$) in the mean full-scale WISC IQ at 6½ years between foster children and children from stable homes but not between adopted children and those from stable homes. The mean WISC IQs

at 6½ years in relation to social class in our low-birth-weight and full-birth-weight control children are shown in Table IV. It is evident that the adjusted mean IQ of the children with a birth weight of 2041 g or less is significantly lower than that of the full-birth-weight control children according to analysis of covariance, even when the significant effect of social class has been controlled for. In both categories of birth weight the mean IQ becomes progressively lower with lower socioeconomic status. We also noted that 80% of the children with a Stanford–Binet IQ below 70 at 4 years came from social class V, which accounted for about 36% of all the low-birth-weight children in our study, whereas 25% of the children with an IQ above 110 came from social classes I and II, which accounted for only about 13% of all the low-birth-weight children. Moreover, our educational psychologist, Dr. Ruth Grunau, found that the frequency of low placement in the third school year was significantly increased in the lower social classes and that children in social classes I to III obtained better mean IQ scores than those in class V. The school placement of SGA and preterm AGA white low-birth-weight children in the third year was also compared: within social classes I to IV combined, but not within social class V, the preterm AGA children had a significantly higher placement ($p < 0.02$). This suggests that in social classes I to IV the preterm AGA children have a considerable advantage over the SGA children, whereas in social class V both groups do poorly, with presumably any advantage the preterm AGA group might have had being outweighed by the drawbacks of being in the lowest social class.

For neurologic outcome a correlation with social class could also be demonstrated: the distribution of social classes among the neurologically normal and abnormal children in the seventh year of life differed significantly in favour of the former.[47]

With regard to the ill effects of maternal smoking during pregnancy we also noted that social class differences play a part. In our study parity, age, weight and height did not differ significantly between the smoking and nonsmoking mothers, but the mean social class was significantly lower for the smokers than for the nonsmokers.[27] Analysis of

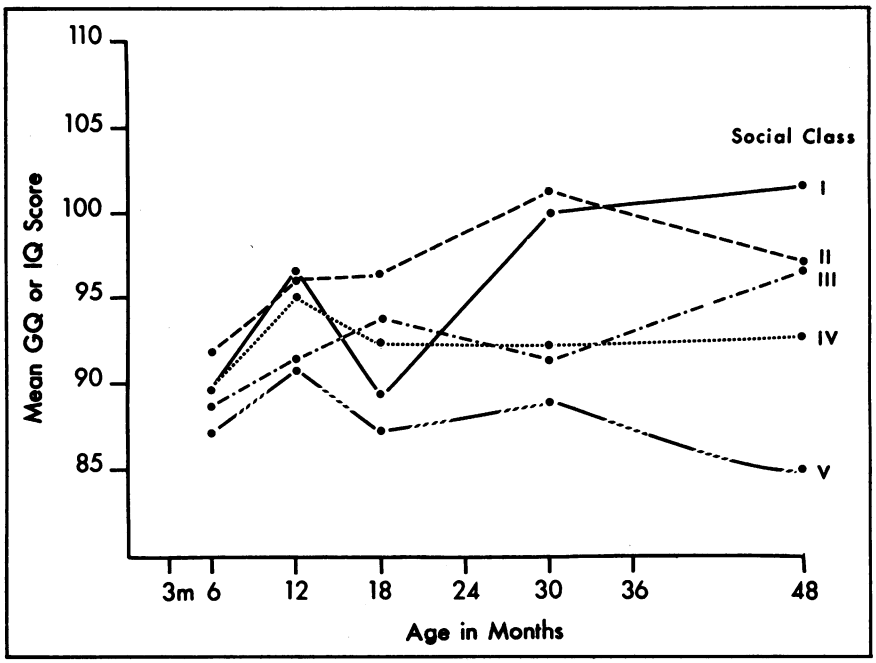

Fig. 3—Mean GQ or IQ scores of children with birth weights below 2000 g grouped by social class at various ages. IQ determined with Stanford–Binet Intelligence Scale at 30 and 48 months. Sample sizes for social classes: I, 20 to 21; II, 10 to 13; III, 23 to 24; IV, 82 to 104; V, 76 to 99. Reproduced in modified form, with permission, from reference 48.

Table IV—Comparison of adjusted mean full-scale intelligence quotients (IQs) determined with the Wechsler Intelligence Scale for Children at 6½ years of age in low-birth-weight children and full-birth-weight controls in Vancouver study (excluding those with an IQ less than 50) by analysis of covariance*

Birth weight and social class	n	Adjusted mean IQ†	Level of significance	Comparisons yielding significant differences
Low birth weight (≤ 2041 g)	311	96.0		
I	23	109.8	F = 12.32	I v. III
II	18	103.8	p = 0.000	I v. IV
III	38	99.5		II v. V
IV	117	96.8		III v. V
V	115	85.8		IV v. V
Full birth weight (> 2500 g)	139	108.7		
I	9	119.8	F = 6.969	I v. III
II	7	119.9	p = 0.000	I v. IV
III	11	106.7		I v. V
IV	61	109.4		II v. III
V	51	103.9		II v. IV
				II v. V
				IV v. V

*Age at testing and sex were included as covariates but were not found to be significant in this analysis. Social class, however, was a significant covariate ($p = 0.000$) in the comparison of mean IQs in the total groups of low-birth-weight and full-birth-weight infants.
†The means for the total groups of low-birth-weight and full-birth-weight infants were significantly different at $p = 0.000$ ($F = 87.17$).

variance of the verbal, performance and full-scale WISC IQ scores of their offspring showed that all three IQ measures were strongly correlated with social class and were not significantly linked with smoking. None the less, there were higher mean IQ scores in nearly all the birth weight and social class categories of children of nonsmokers than in the corresponding categories of children of smokers.[49] Thus, although the full-scale WISC IQ appears to correlate more highly with social class than with the smoking status of the mother, there does appear to be a trend for the children of nonsmoking mothers to have a slightly higher IQ than the children of smoking mothers, irrespective of social class. This was shown more definitively in a large-scale British study.[50]

In their book on disadvantaged children Birch and Gussow[51] discussed the association between low birth weight and subsequent handicap. They emphasized that studies in Scotland[52] and in Hawaii[50] showed how even severe perinatal stress could be compensated for by a good postnatal environment. They went on to discuss the greater prevalence among low-birth-weight children of behaviour disorders, learning disabilities and all the minor disorders of perception, cognition and behaviour that we might now include in the term minimal brain dysfunction. We found minimal brain dysfunction to be the commonest sequel of low birth weight, as shown in Table V.[47]

We have been interested to find that the behavioural component of minimal brain dysfunction, which used to be called the hyperkinetic syndrome and has recently been renamed "attention deficit disorder" by the American Psychiatric Association,[53] is actually most common in social class III, as was previously pointed out for hyperactivity by Werry.[54]

Table V—Neurologic or ophthalmic disorders in 140 (42%) of 335 Vancouver children of low birth weight followed to 6½ years of age

Disorder	No. of children* (and % of total cohort)
Minimal brain dysfunction (IQ ≥ 80)	61 (18)
Mental retardation (IQ < 70)	30 (9)
Cerebral palsy	27 (8)
Major visual defect (excluding strabismus)	16 (5)
Epilepsy	14 (4)
Sensorineural hearing defect	12 (4)†
Miscellaneous (e.g., borderline low-normal intelligence, more than minimal cerebral dysfunction)	21 (6)

*Some children had more than one disorder.
†Only 205 children had a detailed audiologic assessment at about 6½ years of age; thus, the 12 children discovered to have a sensorineural hearing defect represented 6% of those tested.

Influence of social factors versus other variables

The question arises how far either the lowness of birth weight or the social class of the parents affects the neurologic and intellectual outcome when we are obviously dealing with a host of other interdependent factors, such as maternal age, weight, smoking, race and intelligence, as well as perinatal brain damage and the subsequent health and education of the child. To define the role of all these factors quantitatively will ultimately require multiple analyses of covariance in very large samples. However, meanwhile we have some pointers to show the important role of socioeconomic status.

In our own study we endeavoured to determine which variables among those available in the neonatal period and during infancy had the greatest predictive value for neurologic, intellectual and educational outcome. First, by stepwise discriminant analysis our statistician, Dr. Michael Schulzer, reduced the 100 variables available in the neonatal period to the 5 that together were the most predictive; as shown in Table VI, birth weight and socioeconomic status are 2 of the 5.[47] With this combination of variables 71% of the low-birth-weight children would have been correctly classified as to their neurologic status at age 6½ years: namely normal for 76% and abnormal for 63%.

We then reduced the number of variables at 12 and 18 months similarly and by further discriminant analysis determined the five most predictive factors of the total available in the first 2 years for each sex separately. Birth weight range was among the five best predictors of neurologic outcome for low-birth-weight girls, whereas social class and weight percentile at 12 months were among the five best predictors for low-birth-weight boys. With these combinations of variables about 83% of the low-birth-weight girls would have been correctly classified by the age of 1 year as neurologically normal or abnormal at 6½ years, and about 74% of the low-birth-weight boys would have been correctly classified by the age of 1½ years. The fact that minimal brain dysfunction, which is commonest in boys, was the hardest to predict seems to account for the lower accuracy of prediction in the boys.

One can then calculate a weighted formula that would enable the physician to forecast neurologic status at age 6½ years from the findings in infancy. The five most predictive variables for boys are listed in Table VII; with appropriate scoring these can be multiplied with a coefficient and then added to a constant. A positive sum would mean a prediction

Table VI—The five best variables available in the neonatal period and during infancy, selected by discriminant analysis, for predicting neurologic status at age 6½ years

Variable	Probability of F value
Moro response on initial examination in nursery	0.000
Overall neurologic status on discharge from nursery	0.000
Birth weight	0.002
Sex	0.004
Socioeconomic status	0.003

Table VII—The five best variables available by age 18 months, selected by discriminant analysis, for predicting neurologic status of boys at age 6½ years

Variable	Coefficient
Neurologic status at 18 months	−1.87
Neonatal truncal tone	−1.34
Social class (Hollingshead index)	−0.43
Weight percentile at 12 months	+0.38
Landau reflex at 12 months	−1.31
Constant	+6.92

of neurologic normality, while a negative sum would mean a prediction of abnormal neurologic outcome. For instance, a boy with a birth weight of 1559 g has a normal neurologic status at 18 months (score 1) after having had truncal flaccidity in the neonatal nursery (score 4). His social class is 5 on the Hollingshead scale. At 12 months his weight was between the 50th and 74th percentiles (score 5) and his Landau reflex was normal (score 1). The calculation of the sum would be as follows:

$$\begin{aligned} 1 \times -1.87 &= -1.87 \\ 4 \times -1.34 &= -5.36 \\ 5 \times -0.43 &= -2.15 \\ 5 \times +0.38 &= +1.90 \\ 1 \times -1.31 &= -1.31 \\ \text{Constant} &= +6.92 \\ &= -1.86 \end{aligned}$$

Since the sum is negative, an abnormal neurologic outcome would be expected.

Thus, social class is clearly one of the most important variables in infancy determining the neurologic outcome in the early school years. Social class is also one of the most predictive variables with respect to the final IQ and educational achievement.

Implications for management

If it is, then, accepted that socioeconomic status represents one of the most important factors in the neurologic and intellectual prognosis of low-birth-weight children, the following seem important facets of the management of these children:

- Optimal obstetric and perinatal care.
- "Bonding" by parents visiting the intensive care nursery and handling the baby.
- "Anticipatory guidance", particularly for single mothers and those who lacked one parent in childhood.
- Regular pediatric follow-up for at-risk infants (perhaps at a special clinic).
- Infant stimulation, special day care and enrichment programs (e.g., Operation Head Start) from infancy to kindergarten, particularly in the lower social classes.
- Early correction of refractive errors, strabismus, other visual defects, hearing defects and orthopedic deformities; occupational and physiotherapy for cerebral palsy; speech stimulation and therapy; special education and social services as required.
- Developmental assessments and school readiness tests; detection and treatment of minimal brain dysfunctions, including learning disabilities and attention deficit disorder, and of secondary emotional disturbance.

A few further comments may be appropriate. Evidence has accumulated that optimal obstetric and perinatal care for low-birth-weight infants is best provided when facilities are regionalized and expert tertiary care centres are available for mother and baby.[55,56] With respect to the pediatric follow-up, criteria for a high-risk group and for predictive scoring should be established collaboratively. Service-based, multidisciplinary follow-up programs should be established for high-risk low-birth-weight infants, along with those suffering from severe malformations, congenital rubella syndrome, neonatal seizures and other serious conditions. Such selected infants should be placed on an at-risk register.[57]

Ideally one would like to provide a stimulating, affectionate environment at a high social level for all handicapped children, and particularly for those of low socioeconomic status. Detailed documentation from the United States concerning the benefits of Operation Head Start in comparison with more traditional methods of treatment for underprivileged children with mental or physical handicaps is still awaited. However, initial reports indicate that such programs are indeed particularly helpful to children of low socioeconomic status but must be started early in infancy and continued until the school years if they are to be of lasting benefit.[58-60] Infants with mild brain dysfunction may benefit from the provision of social stimulation and early learning experiences. Attempts at assessing the value of these programs face great methodologic difficulties,[61,62] but it seems that a poor, nonstimulating environment, and especially one with emotional deprivation, can reduce a child's cognitive development, whereas children with mild forms of brain dysfunction can benefit from enrichment programs based on sensory stimulation applied without undue pressure in an affectionate environment. Further long-term research is required to devise optimal methods for helping the handicapped to achieve their maximum potential.[63]

Conclusion

Socioeconomic status appears to be one of the most important determinants of the ultimate level of brain function in children of low birth weight, and this is true with respect to neurologic, psychologic and educational outcome. Social class also has an indirect effect through birth weight, frequency of perinatal brain injury and other biologic variables, as well as maternal habits, the quality of nutrition and health care for mother and child, and other "cultural" factors. To some extent it may be possible to compensate for social disadvantage by careful environmental, medical and educational assistance throughout early childhood.

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Prescribing Information

Lopresor® (metoprolol tartrate)

50 mg and 100 mg tablets
200 mg slow-release tablets

Therapeutic Classification
Antihypertensive and anti-anginal agent.

Actions
Metoprolol tartrate is a beta-adrenergic-receptor-blocking agent with predominant blocking effect on beta$_1$ receptors.

Indications
a) **Mild and Moderate Hypertension:**
Usually used in combination with other drugs, particularly a thiazide diuretic, however, may be tried alone as an initial agent in those patients whose treatment should be started with a beta-blocker rather than a diuretic. The combination of Lopresor with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than Lopresor alone. Incompatibility with other antihypertensive agents has not been found, experience is limited however.
Not recommended for the emergency treatment of hypertensive crises.
b) **Angina Pectoris**
Lopresor is indicated in patients with angina pectoris due to ischemic heart disease.

Contraindications
Sinus bradycardia, second and third degree A-V block, right ventricular failure secondary to pulmonary hypertension, congestive heart failure, cardiogenic shock, anesthesia with agents that produce myocardial depression, e.g. ether and chloroform.

Warnings
a) *Cardiac Failure:* Special caution should be exercised when administering Lopresor to patients with a history of heart failure, since inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients without a history of cardiac failure, continued depression of the myocardium can lead to cardiac failure. At the first sign of impending cardiac failure, patients should be digitalised and/or given a diuretic and observed closely.
Lopresor does not abolish the inotropic action of digitalis on the heart muscle, however, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of Lopresor when the two drugs are used concomitantly. The effects of beta-blockers and digitalis are additive in depressing A-V conduction. If cardiac failure continues, despite adequate digitalisation and diuretic therapy, discontinue Lopresor therapy.
b) *Abrupt Cessation of Therapy with Lopresor:* Warn patients against abrupt discontinuation. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias in patients with angina following abrupt discontinuation of beta-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris.
When discontinuation of Lopresor is planned in patients with angina, dosage should be gradually reduced over a period of about two weeks and the patient carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, Lopresor should be discontinued stepwise, under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with Lopresor be reinstituted promptly, at least temporarily.
c) Various skin rashes and conjunctival xerosis have been reported. A severe syndrome (oculo-muco-cutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic-blocking agent (practolol) but has not been observed with Lopresor or any other such agent. Physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.
d) Severe sinus bradycardia may occur, in such cases, dosage should be reduced.
e) Lopresor may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of Lopresor may be followed by an exacerbation of the symptoms of hyperthyroidism including thyroid storm.

Precautions
a) Careful monitoring of patients with diseases associated with bronchospasm is mandatory and a bronchodilator must be administered concomitantly.
b) Administer with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia.
c) Adjust dosage individually when used concomitantly with other anti-hypertensive agents.
d) Closely monitor patients also receiving catecholamine-depleting drugs, such as reserpine or guanethidine. Lopresor should not be combined with other beta-blockers.
e) Appropriate laboratory tests should be performed at regular intervals during long-term treatment.
f) Lopresor should not be given to patients receiving verapamil. In exceptional cases, when in the opinion of the physician concomitant use is considered essential, such use should be instituted gradually, in a hospital setting, under careful supervision.
g) *In patients undergoing elective or emergency surgery:* Lopresor should be withdrawn gradually following recommendation given under Abrupt Cessation of Therapy (see WARNINGS). Available evidence suggests that the clinical and pharmacological effects of beta-blockade induced by Lopresor are no longer present 48 hours after cessation of therapy.
In emergency surgery, effects of Lopresor may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or levarterenol.
h) *Usage in pregnancy and nursing mothers:* Lopresor crosses the placental barrier and appears in breast milk. It should not be given to pregnant women as it has not been studied in human pregnancy. If use of the drug is deemed essential in nursing mothers, the patient should stop nursing.
i) *Usage in children:* There is no experience with Lopresor in the pediatric age groups.

Adverse reactions
Cardiovascular: Congestive heart failure (see WARNINGS), secondary effects of decreased cardiac output which include: syncope, vertigo, lightheadedness and postural hypotension; severe bradycardia, lengthening of PR interval, second and third degree A-V block, sinus arrest, palpitations, chest pains, cold extremities, Raynaud's phenomenon, claudication, hot flushes.
Central Nervous System: headache, dizziness, insomnia, mental depression, lightheadedness, anxiety, tinnitus, weakness, sedation, vivid dreams, vertigo, paresthesia.
Gastrointestinal: diarrhea, constipation, flatulence, heartburn, nausea and vomiting, abdominal pain, dryness of mouth.
Respiratory: shortness of breath, wheezing, bronchospasm, status asthmaticus.
Allergic/Dermatological (see WARNINGS): exanthema, sweating, pruritus, psoriasiform rash.
EENT: blurred vision and non-specific visual disturbances, itching eyes.
Miscellaneous: tiredness, weight gain, decrease in libido.
Clinical Laboratory: The following laboratory parameters have been rarely elevated: transaminases, BUN, alkaline phosphatase and bilirubin. Thrombocytopenia and leucopenia have been reported rarely.

Symptoms and Treatment of Overdosage
Symptoms: bradycardia, congestive heart failure, hypotension, bronchospasm, hypoglycemia.
Treatment: Discontinue Lopresor and observe patient closely. In addition, if required, the following therapeutic meaures are suggested.
1. *Bradycardia, and hypotension:*
Initially 1-2 mg of atropine sulfate should be given intravenously. If a satisfactory effect is not achieved, a pressor agent such as norepinephrine may be administered after preceding treatment with atropine.
2. *Heart Block: (second or third degree)*
Isoproterenol or transvenous cardiac pacemaker.
3. *Congestive heart failure:*
Conventional therapy.
4. *Bronchospasm:*
Aminophylline or a beta$_2$-agonist.
5. *Hypoglycemia:*
Intravenous glucose.

Large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of Lopresor. However, the complications of excess isoproterenol, e.g. hypotension and tachycardia, should not be overlooked.

Dosage and Administration
a) *Hypertension:* Initial Dose: 50 mg b.i.d. If adequate response is not seen after one week, dosage should be increased to 100 mg b.i.d. In some cases the daily dosage may need to be increased by further 100 mg increments at intervals of not less than two weeks up to a maximum of 200 mg b.i.d., which should not be exceeded.
Usual Maintenance Dose: 150-300 mg daily.
When combined with another antihypertensive agent which is already being administered, Lopresor should be added initially at a dose of 50 mg b.i.d. After 1 or 2 weeks the daily dosage may be increased if required, in increments of 100 mg, at intervals of not less than 2 weeks, until adequate blood pressure control is obtained.
b) *Angina pectoris:* Initial Dosage: 50 mg b.i.d. for the first week. If response is not adequate, the daily dosage should be increased by 100 mg for the next week. The need for further increases should be closely monitored at weekly intervals and the dosage increased in 100 mg increments to a maximum of 400 mg/day in 2 or 3 divided doses.
Usual Maintenance Dosage: 200 mg/day.
Dosage Range: 100-400 mg per day in divided doses. A dose of 400 mg/day should not be exceeded.
c) *Slow-release Lopresor SR 200 mg:* Lopresor SR 200 mg is intended only for maintenance dosing in those patients requiring doses of 200 mg per day. Treatment must always be initiated and individual titration of dosage carried out using the regular tablets. Patients with hypertension or angina pectoris on a maintenance regimen of one 100 mg tablet twice daily may be changed to one Lopresor SR 200 mg tablet taken in the morning.
Lopresor SR 200 mg tablets should be swallowed whole.

Availability
Lopresor
Tablet: 50 mg:
Film coated, light red, capsule-shaped tablet, embossed 51 and scored on one side and GEIGY on the other.
Tablet: 100 mg:
Film coated, light blue, capsule-shaped tablet, embossed 71 and scored on one side and GEIGY on the other.
Lopresor SR
Slow-release Tablet: 200 mg:
Film-coated, light yellow, round tablet, embossed GEIGY on one side and CDC on the other.
Product monograph supplied on request.

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