Clin.Pediat. 8, 516-525 (1969).

The High-risk Infant

Implications in Adoption

FELIX F. DE LA CRUZ, M.D., M.P.H., F.A.A.P.

DURING 1967 some 158,000 children were adopted in the U. S. A., and nearly 100,000 of these were born out of wedlock.[1] About 72,800 of the latter were adopted by nonrelatives; 26,700 by relatives.

In July, 1968, a survey in the State of Maryland showed that 12.7 per cent of children in adoption service were retarded mentally.[2] This prevalence is at least four times that for mental retardation in the nation as a whole. A significant number of additional children had physical, neurologic or emotional problems.

Since such health hazards prevent a child from achieving his optimum potential, every health official should be alert to identify these conditions early. Otherwise, intervention designed to minimize their deleterious effects may not be maximally effective.

This communication discusses conditions which may exert harmful effects on a child's physical and intellectual growth, and identifies some of the research activities which hold special promise in preventing the occurrence or alleviating the effects of these harmful conditions.

The traits of a child, both physical and mental, are produced by the interplay of both intrinsic and extrinsic factors. The intrinsic elements are determined, to a large extent, by the genetic factors in the ovum and sperm of the parents, transmitted to the offspring during fertilization. The extrinsic factors may be subdivided into: (1) Those which may affect the child *in utero;* and (2) those which exert their impact during and after birth. In the former category are such matters as placental

TABLE 1. *Conditions which Could Place an Infant at Risk to Develop Neurosensory Handicaps*

Preconceptual factors
Low socioeconomic level
Nutrition
Metabolic disease in the mother
Endocrine
Amino acid
Carbohydrate
Lipid
Mucopolysaccharidoses
History of reproductive failures
Prenatal
Maternal infection
Toxemia of pregnancy
Drug ingestion
Radiation
Maternal age <16 or >38
Fetal-Maternal blood group incompatibility
Natal
Hemorrhage
Dystocia
Anesthesia
Trauma
Cesarean section
Prematurity, Postmaturity/Dysmaturity
Low Apgar score
Placental infarction
Postnatal factors
Trauma
Infection
Parental deprivation
Culturally-disadvantaged child
Single umbilical artery
Disproportion between weight or length and gestational age

From the National Institutes of Health, Bethesda, Md.

Correspondence: Felix F. de la Cruz, M.D., Chief, Children's Diagnostic and Study Branch, National Institute of Child Health and Human Development, National Institutes of Health, NNMC Building 125, Room 1, Bethesda, Md. 20014.

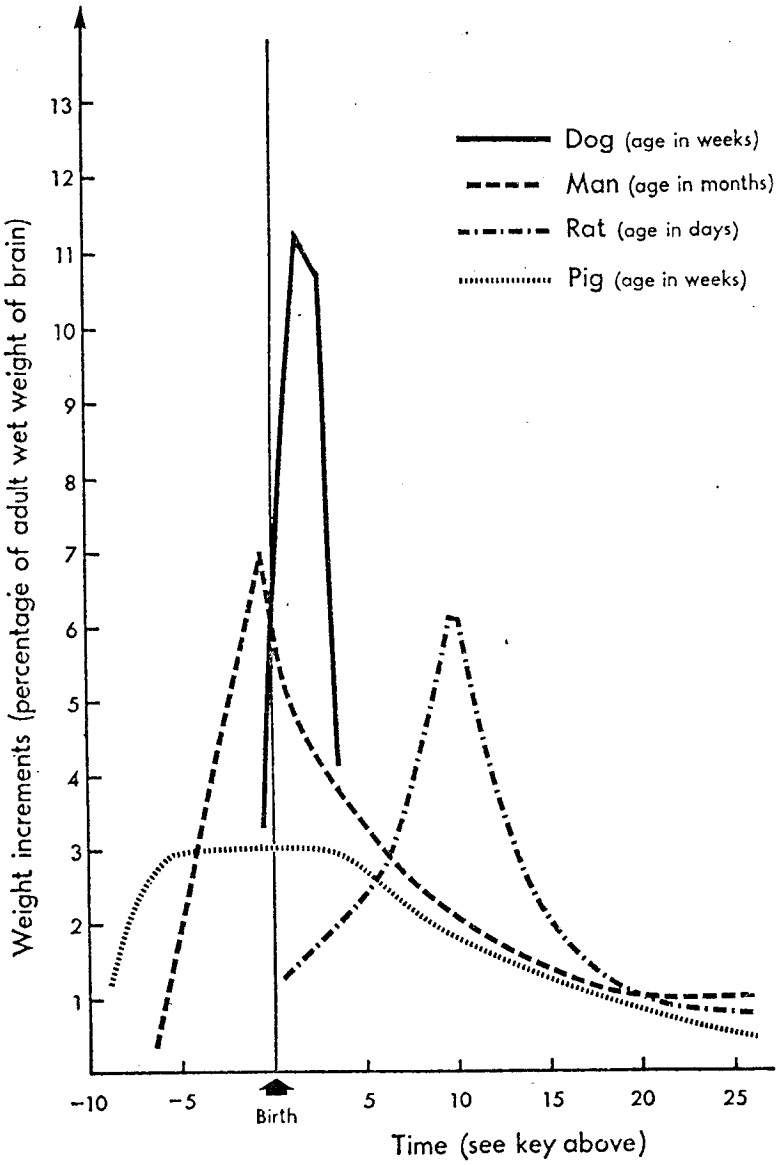

FIG. 1. The timing of brain growth in different species in relation to birth. Source: Davison and Dobbing. Brit. Med. Bull. 22: 1, 1966.

dysfunction, drugs ingested by the mother during pregnancy, maternal infections, physical agents such as x-ray, and others. In Table 1 are summarized some of the conditions which could make a fetus or an infant, because of his vulnerability, susceptible to various handicapping conditions such as mental retardation, congenital malformations and sensory, learning or motor defects. Some of these factors are hereditary; others are not.

Hereditary trait may not be recognized until some time after infancy. Cystic fibrosis and muscular dystrophy, for example, may not become evident until the affected child is over a year old. Other hereditary conditions do not typically become manifest until age four to seven years. Still others, such as diabetes mellitus, may not show themselves until much later in life.

Some hereditary conditions never become detectable unless the individual is exposed to an extrinsic agent, as occurs with G6PD (glucose-6-phosphate dehydrogenase) deficiency after ingestion of certain drugs.

Postnatal events, such as physical injury to the head, infections and especially those in-

volving the brain or meninges, and environmental deprivation can play an important role in determining a child's development.

Although early adoption is, in general, accepted as a desirable practice, it should always be remembered that some conditions do not become manifest early in life and hence may not be recognized at the initial physical evaluation of a newborn.

Nutrition and Intellectual Development

Recent studies have demonstrated the harmful physical and behavioral effects of malnutrition in both animals and humans.[3] The effects of dietary deficiencies on intellectual development are being studied by a host of scientists, both here and abroad.

In many parts of the world, and to a lesser extent in this country, many children fail to receive adequate calories and protein to support normal physical development. Severely malnourished children may be physically stunted, apathetic, lethargic and more susceptible to some infections. Compared to well nourished children their height and bone age may be retarded, even after the malnutrition has been corrected.

Protein-calorie malnutrition can lead to gross or microscopic tissue changes which, depending on the structures involved, may impair physiologic function. The brains of children who die of malnutrition during the first year of life may show a marked reduction in level of nucleic acid and protein.[4]

Figure 1 shows the rate of brain growth in different species in relation to birth. In man the peak of brain growth representing both cell division and increase of cell size, has already occurred prior to birth. This period overlaps with one of subsequent lipid accumulation representing myelination. It is not surprising, therefore, that various harmful agents, including metabolic disturbances which accompany maternal malnutrition, may harm the developing fetal nervous system prior to birth.

Interference with the learning process at specific times during its course may result in disturbances in function which are both profound and long-term, according to a considerable body of evidence already at hand. For example, during recovery from kwashiorkor, infants under six months old, as contrasted with older patients, did not regain their mental-age deficit during the recovery period (Cravioto and Robles[5]). Recovery from the initial deficit in these children, 15 to 41 months old, varied in direct relation to chronologic age at time of admission.

Studies in Mexico and in Africa suggest similarly that gross malnutrition in very young children may retard mental development. If this is so, is it always irreversible? At what age does it become irreversible? Unfortunately, there are as yet no adequately controlled studies which clearly define the importance of this effect of malnutrition. Children living in deprived environments, where nutrition is qualitatively or quantitatively inadequate, tend to be subjected to other concomitant influences such as educational deprivation, lack of maternal psychologic stimulation, high prevalence of illnesses including parasitism, and an inadequate hygienic environment.

Malnutrition is more a matter of politics, economics and distribution than of medicine and biochemistry. All concerned members of the community should endeavor to get food to the hungry. Pediatricians must impress upon parents and prospective parents the importance of proper nutrition.

Availability of food, of itself, is no guarantee of proper nutrition. We must be alert for imbalances and deficiencies set up by improper, and sometimes bizarre, dietary practices.

Congenital Malformations

Congenital malformations, defined also as morphologic anomalies or birth defects, are expressions of disturbances which may have taken place at any stage of ontogeny—from the fertilized ovum to near the end of the gestational period. The deformities run the gamut from total breakdown of the organism to minimal local distortions of a portion of one organ, in all sorts of intermediate variations and combinations. Sometimes the anatomic, structural or biochemical abnormalities do not become obvious until long after birth.

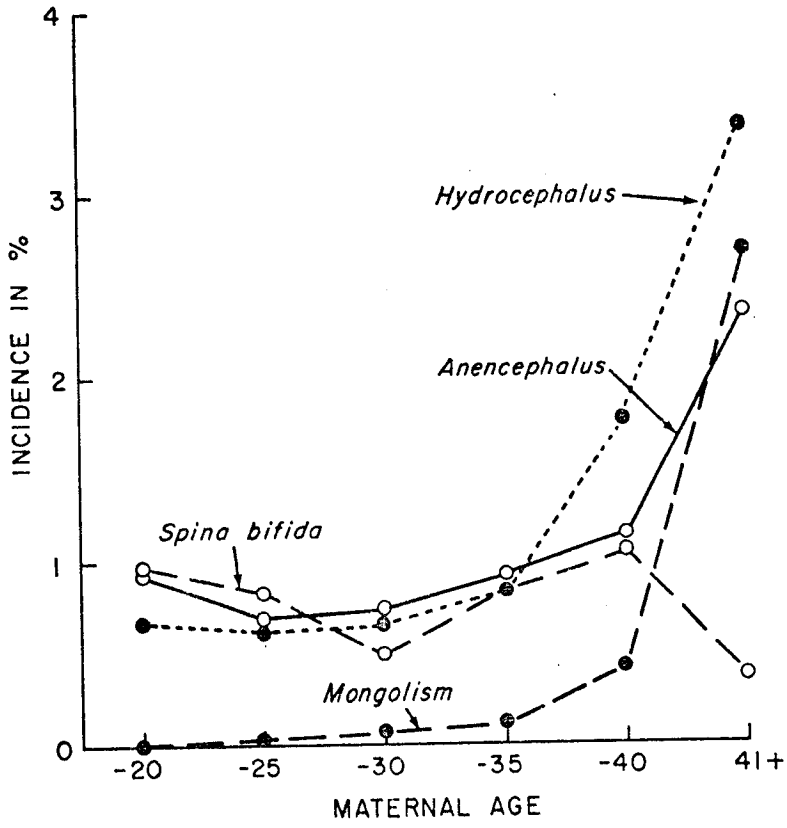

FIG. 2. Incidence of congenital malformations in relation to maternal age at birth. Source: H. Hegnauer. Geburtsh. u. Frauenh., 1951.

The causes of congenital malformations are many and complex, and in most instances not well understood. An estimated 20 per cent of known birth defects can be blamed primarily on heredity, and an equal proportion on prenatal environmental conditions. In many children, a combination of both hereditary and environmental factors seem to have been responsible.

In congenital rubella the frequency of congenital malformations is approximately 50 per cent when rubella occurs during the first month of pregnancy, 22 per cent in the second month, and 6 to 8 per cent in the third month. Major clinical findings are cataracts, congenital heart lesions, deafness, microcephaly and mental retardation.

Congenital malformations of the central nervous system often bear a positive relation to the mother's age (Fig. 2). The incidence of mongolism, hydrocephalus and anencephalus is higher with increasing maternal age, whereas spina bifida is not. The incidence of congenital malformations is not dependent upon parity, or number of pregnancies, when corrected for maternal age.[6]

In 1954, McIntosh[7] published the results of a longitudinal survey of 5,964 women who were admitted to the Sloan Hospital Antepartum Clinic, New York City. The incidence of congenital malformations among 5,739 products of conception weighing over 500 Gm. was 7.5 per cent. The rate was 7.0 per cent among infants born alive and surviving the neonatal period, 13.6 per cent among antepartum deaths, 23.3 per cent among intrapartum deaths, and 29.6 per cent among neonatal deaths. The rate among males (8.4 per cent) was higher than among females (5.5 per cent). Nonwhite infants had a higher rate (7.8 per cent) than did white infants (6.3 per cent). Infants weighing 2,500 Gm. or less had a higher proportion with defects (9.7 per cent) than did those weighing over 2,500 Gm. (6.7 per cent), although this difference occurred entirely among females. Of the malformed live-born infants 14.8 per cent had more than one malformation and in 9.1 per cent more than one system was involved.

In the above series, fewer than half of the malformations in the liveborn infants were suspected or noted at birth. This observation

TABLE 2. *Effects of Medication on Intrauterine and Newborn Patient*

Maternal Medication	Fetal or Neonatal Effect
Oral progestins, Androgens, Estrogens	Masculinization & advanced bone age
Potassium iodide, Propylthiouracil, Methimazole	Goiter
Iophenoxic acid	Elevation of serum protein-bound iodine
Aminopterin, Amethopterin, Chlorambucil	Anomalies & abortions
Bishydroxycoumarin, Ethyl bicoumacetate	Fetal death, Hemorrhage
Salicylates (large amounts)	Neonatal bleeding
Tetracyclines	Deposition in bone, Inhibition of bone growth in premature infants, Discoloration of teeth
Sulfonamides	Kernicterus
Chloramphenicol	Death ("gray syndrome")
Novobiocin	Hyperbilirubinemia
Erythromycin*	Liver damage (?)**
Nitrofurantoin	Hemolysis
Vitamin K analogues (excessive amounts)	Hyperbilirubinemia
Ammonium chloride	Acidosis
Reserpine	Nasal congestion & drowsiness
Hexamethonium bromide	Neonatal ileus
Intravenously administered fluids (excessive amounts)	Fluid & electrolyte abnormalities
Heroin & morphine	Neonatal death, convulsions & tremors
Phenobarbital (excessive amounts)	Neonatal bleeding
Smoking	Premature births
Orally administered hypoglycemic agents:	
Sulfonylurea derivatives	Anomalies (?)
Phenformin	Lactic acidosis (?)
Phenothiazines	Hyperbilirubinemia (?)
Meprobamate	Retarded development (?)
Chloroquine	Retinal damage or death (?)
Quinine	Thrombocytopenia
Thalidomide	Phocomelia & fetal death; hearing loss
Vaccination	Fetal vaccinia
Influenza vaccination	Increased anti-A & Anti-B blood-group titers in mother (?)
Antihistamines	Anomalies (?), Prevention of pregnancy (?)
Insulin shock	Fetal loss
Polio vaccine (live)	Fetal loss (?)

*Ed. note: Confined to the estolate salt.

** Question marks (?) indicate that the effect "can only be *suspected* on the basis of animal evidence, and has *not* been proved to occur in human beings."

Source: McKay, R. J., Jr. and Lucey, J. F.: New Eng. J. Med. 270: 1231, 1964.

underscores the importance of repeated examinations of infants prior to adoption.

Drugs

The noxious effects of therapeutic drugs taken during pregnancy range from fetal death to various types of malformations involving different organ systems with varying degrees of severity (Table 2). Many of these drugs may influence profoundly the developmental processes in fetus and newborn. Hence one must weigh carefully the potentials of a drug before giving it to a pregnant woman. But conversely, one must be cautious in blaming a fetal disturbance on a drug taken during pregnancy when the history of such ingestion is poorly documented, or the condition for which the drug was taken may have been the causative agent, or where impurities in an illicit drug may have been responsible.

No drug has stimulated greater public concern and debate than LSD (lysergic acid diethylamide). LSD is a remarkable drug capable of an enormous number of physiologic, behavioral and biochemical actions. It is a powerful antagonist of serotonin, a normally occurring neurohumor thought to be important for normal nervous-system function. The medical literature, as well as the lay press, is currently being flooded with conflicting reports concerning the effect of LSD on animal and human subjects. Ingestion of LSD by rats reportedly produces teratogenic effects persisting through four generations.[8] A number of investigators have reported a high percentage of chromosomal breaks *in vivo* in LSD users,[9-11] whereas others have found no significant difference between LSD users and controls.[12-15]

A group of investigators from Iowa [16] described a girl with a malformed right leg who was born to a 19-year-old woman who had taken LSD on the 25th day of her last menstrual period and three times between the 45th and 98th days. Her husband also had taken the drug. Chromatid breaks were found in the peripheral leukocytes of the father (two breaks), mother (five) and child (three).

Although LSD taken by expectant mothers can produce chromosomal breaks in the cells of the conceptus, it is not yet known whether these chromosomal breaks will actually lead

TABLE 3. *Signs of CNS Abnormality During the First Days of Life (rate per thousand)*

	Whites			Negroes		
	≤1,500	1,501–2,500	≥2,501	≤1,500	1,501–2,500	≥2,501
Seizures	14	8	2	19	5	2
Myoclonus	7	1	2	19	4	2
One or more neurologic signs	252	86	32	309	63	40

Source: Personal communication with Dr. Heinz Berendes, Chief, Perinatal Research Branch, National Institute of Neurological Diseases and Stroke, National Institutes of Health. Paper presented at the First International Meeting on Prematurity, Fort Lauderdale, Fla., January, 1968.

to malformations or other disturbances. It is not known how many pregnant women have taken these drugs with no effect on their infants.

As Dr. Apgar [17] stated five years ago, "There is no count of babies who have survived because of drugs administered during pregnancy, infants who escaped birth defects because their mothers were given certain drugs, or full-term babies who might have been born prematurely without drugs."

Prematurity

For purposes of classification, the World Health Organization defines a premature infant as a liveborn infant whose gestational period has been less than 37 weeks. Since the exact duration of pregnancy is not always easy to determine, the concept of immaturity has been introduced. An immature infant is one weighing 5-1/2 lb. (2,500 Gm.) or less.

Immature births are higher among:

Nonwhite than white; (In 1965 the immaturity rate for the U. S. as a whole was 8.3 per cent; 7.2 per cent of these were among the white population while 13.8 per cent were among the nonwhite.)

Plural born than single born;

First and fifth (and over) born infants than second, third, or fourth born infants;

Women under 19 and over 30 than in women between 25 and 29;

Women with poor diets than women with good diets;

Women who smoke than women who don't smoke;

Lower social class families than women in the higher social class;

Families in which pregnancies occur before two or after six years of previous births than in families in which pregnancies occur within two to six years of previous births;

Unmarried women than married women.

Prematurity and low birth weight have an increased tendency to be followed by neuropsychiatric disorders, overt neurologic impairment and specific learning difficulties. Intensive research efforts are underway to determine the causes of prematurity—and thus find means of prevention—and to develop measures to mitigate the adverse effects of premature birth. Paradoxically, the first fruits of this effort, the rising salvage rate of low-birth-weight children, has resulted in an initial proportional increase in children with neurologic or learning difficulties.

The Perinatal Research Branch of the National Institute of Neurological Diseases and Stroke at the National Institutes of Health in Bethesda, Maryland, in collaboration with 13 medical centers across the country, is conducting a prospective study involving approximately 50,000 mothers and their children. The goal of this collaborative project is to gain new knowledge about the relationship between events of pregnancy, labor and delivery and the first month of life, and the occurrence of neurologic and sensory disorders of infancy and childhood. The hope is that this new knowledge will make it possible to prevent these disorders and thereby enable every child to lead a full and useful life.

This collaborative study has already demonstrated an inverse correlation between central-nervous-system disturbances and birth weight. The frequency of seizures and other motor disorders increases as birth weight decreases (Tables 3, 4). Intelligence scores, measured at the age of four years, correlate inversely with birth weight. When I.Q. scores were broken down by the educational attainment of the mother within the same birth-weight group a direct correlation was obtained (Table 5).

TABLE 4. *Neurologic Abnormalities at One Year of Age (Rate per Thousand)*

	Whites			Negroes		
	≤1,500	1,501-2,500	≥2,501	≤1,500	1,501–2,500	≥2,501
Spastic diplegia	70	4	1	27	11	1
Hypotonia with deep tendon reflexes	70	24	8	27	6	3
Other motor disorders	70	16	7	36	6	6
Delayed motor development	209	54	16	245	50	15
Febrile convulsions	0	4	4	0	6	5
Other generalized convulsions	0	3	3	0	5	3
Focal Motor	0	1	0	0	1	1
Myoclonic seizures	0	0	1	0	1	0

Source: See Table 3.

The question of whether premature infants "catch up" as opportunities for compensation are experienced through learning, was investigated by Harper *et al.*[18] By evaluating 417 low-birth-weight children and 405 full-term children, eight to ten years old, "catching up" was not observed, to judge by the results obtained from Stanford Binet and Wechsler Intelligence Scale for Children. Some children have shown some improvement, but others had increasing mental impairment. The authors noted that the various impairments manifested by the low-birth-weight group were not secondary to socioeconomic factors or to the quality of "mothering."

Illegitimacy

Various studies have shown that unmarried pregnant women receive less prenatal care and have more complications of pregnancy than do married women. This is related to a score of factors among which are concealment of pregnancy, problems concerning arrangements to obtain medical care, attitudes to prenatal care, ineligibility for care, inability to pay medical fees, and inadequate or late referral.

Prenatal care per se is not an absolute safeguard against the emergence of various handicapping conditions in the children. The patients who receive suboptimal care during pregnancy generally include those who are of limited socioeconomic capacity and are exposed to the host of factors which typify this group: high rate of infection, poor nutrition, substandard housing. "Providing all women with obligatory prenatal care will not, in itself, eliminate mental retardation," or other handicapping conditions.[19]

TABLE 5. *Mean I.Q. of Four-year-old White Children by Education of Mother and Birthweight*

WHITES

Education Group of Mother	Birthweight in grams					
	≤1,500	1,501-2,000	2,001-2,500	2,501-3,000	3,001-4,000	≥4,001
I	0	75*	90	98	95	101*
II	92*	97	98	99	100	96
III	92*	101	103	103	104	104
IV	123*	98*	117	113	116	112
All education groups	94	99	103	103	105	103

* Indicates less than 10 cases.

Definition of Education of Mother: Group I = less than 7 years of schooling; Group II = 7 to 9 years of schooling; Group III = 10–12 years of schooling; Group IV = more than 12 years of schooling, including college education.

Source: See Table 3.

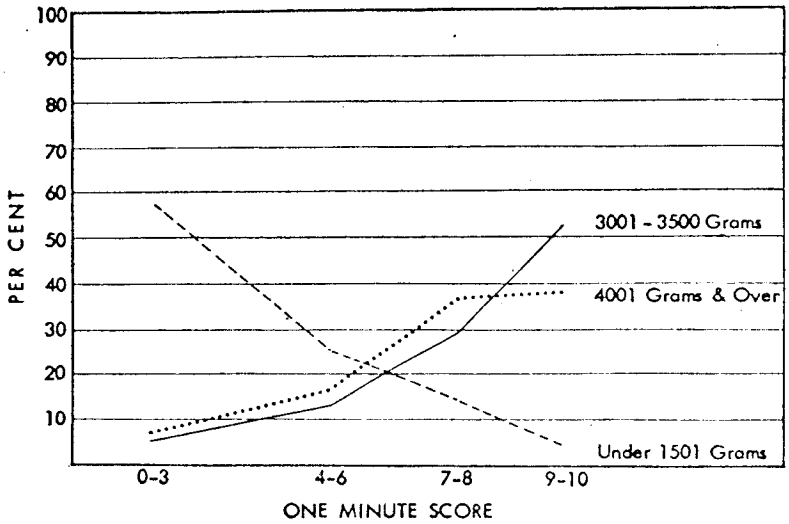

FIG. 3. Percentage distribution of one-minute scores for selected birth weights. Source: Drage, J. S. and Berendes, H. Pediat. Clin. N. Amer. 13: 635, 1966.

The rate of prematurity is higher among illegitimate than among legitimate children—14.6 per cent *vs.* 7.7 per cent in 1964. Infant mortality rate and fetal death ratio, the latter including stillbirths, miscarriages, and induced abortions, are also higher.

The rate of illegitimacy—defined as illegitimate births per 1,000 unmarried women, 15 to 44 years old—has been increasing over the past 25 years in the U. S. A. The rate, for example, nearly doubled from 1940 to 1950 (7.1 *vs.* 14.1), continued to rise rapidly until 1957 (21.0), and more slowly since then. By 1965 the rate was 23.5, or only 12 per cent higher than in 1957.

Although the measures of illegitimacy have always been higher for the nonwhite than for the white population, this differential has been declining in recent years. For example, in 1950 the illegitimacy rate for nonwhite women was 71.2, or nearly 12 times greater than the rate of 6.1 for white women. By 1965 this differential had declined to slightly more than eight times greater; the rates were 97.6 and 11.6 for nonwhite and white women, respectively.

The racial differences in illegitimacy are difficult to explain. Pratt [20] found that white couples are more apt to marry soon after discovery of conception whereas nonwhite couples may wait until after the birth of one or more children before marrying. Perhaps a second factor is that induced abortion is less frequent among Negro women. There is considerable evidence that among the lower socioeconomic status groups there may be less use of contraception, due either to lack of knowledge or inaccessibility of contraceptive devices. It is likely, however, that if it were possible to control for social class, much of the difference between these two groups would disappear.[21]

Early Identification of High-risk Infants

Successful management of abnormal pregnancy and defective products of conception is predicated upon early identification of the causative factor, and prompt application of appropriate remedial measures when available.

In 1953 Apgar[22] devised a scoring system which permits quick and accurate assessment of the newborn infant to predict survival, to compare methods of resuscitation, and through the infant's responsiveness after delivery, to contrast perinatal experiences in different hospitals. A score of 10 indicates an infant in the best possible condition. Infants with scores of 5 to 10 usually need no treatment. A score of 4 or below indicates the need for prompt diagnosis and treatment. Approximately 90 per cent of normal infants score 7 or more one minute after birth. This system has value for predicting neuromuscular deficit later in childhood.

In Drage's [23] study, 57.2 per cent of infants weighing under 1,501 Gm. at birth had Apgar scores of 0 to 3, and only 3.9 per cent had scores of 9 or 10. Infants weighing 3,001 to 3,500 Gm. showed 5.3 per cent with scores of 0 to 3 and 51.9 per cent with scores of 9 or 10 (Fig. 3). Correlation between birth weight and Apgar score was

maintained when the infants were observed five minutes after birth. This simple method of evaluating infants will help physicians in applying appropriate measures to prevent, or at least ameliorate, neuromuscular insult to the child.

Another method of identifying high-risk infants is by examining the umbilical cord.

Congenital malformations frequently are associated with absence of one umbilical artery. A single umbilical artery was found in 203 (0.76 per cent) of 26,539 placentas on gross and microscopic examination.[24] The incidence of single umbilical artery in white infants was 1.22 per cent compared to 0.44 per cent in Negro infants. The incidence of single umbilical artery was 1.98 per cent in infants of low birth weight (2,500 Gm. or less); 0.63 per cent in those weighing more than 2,500 Gm. The over-all incidence of associated malformations was 28.6 per cent. All organ systems were involved with the possible exception of the endocrine system. When borderline (in contrast to lethal or major and nonlethal) malformations were excluded, the incidence was 16.7 per cent.

The Future

Every child has a right to be wanted and a right to be born healthy. Development of safe and effective contraceptive devices or drugs which are available and accessible to those who need them must be continued. The President's Committee on Mental Retardation has recently recommended to the President that family planning services be made available on a voluntary basis to all Americans. Since infant mortality rates and prematurity rates correlate with socioeconomic status, minority group membership, maternal age, and many other medical and social factors, it is thought that effective family planning programs may significantly reduce the incidence of prematurity and the neuropsychiatric sequelae which afflict some of these children. Furthermore, if fertility control were encouraged for women who are approaching the twilight of their reproductive life, a decline in the incidence of certain congenital malformations, including mongolism, would be anticipated.

The future is encouraging, to judge by the results of current researches in the fields of biology, genetics, medicine and behavioral sciences.

Some of the more recent advances include:

1. Induction of enzymatic, metabolic functions through administration of drugs.[25]
2. Intrauterine diagnosis and management of genetic defects including cystic fibrosis of the pancreas,[26] and Lesch–Nyhan syndrome, a condition characterized by self-mutilation, increased level of uric acid in the blood, and choreoathetosis.
3. Diagnosis of carriers of potentially lethal conditions or diseases characterized by impairment of intellectual development.
4. Development of biologic products such as rubella vaccine and anti-Rh immunoglobulin.
5. The effect of nutrition on growth and development.

The quest for more knowledge must continue through research in the biomedical and behavioral sciences, independently and collaboratively, if the health of this most important resource is to be maintained and improved. It is necessary for all professional groups, community agencies and parents to work together for optimal, coordinated, accessible and continuous provision of health care for children.[27]

This health care should begin prior to the child's conception and must be continued throughout his infancy, childhood and adolescence. Emphasis must be on prevention. Only when primary prevention is no longer attainable should emphasis be thrown on curative or rehabilitative care.

It is difficult to predict how long one should delay before feeling reasonably sure that an infant is suitable for adoption both physically and mentally. If one defines health as a state of physical, mental and social well-being, and not only the absence of disease or infirmity, it is currently very difficult to predict whether or when a child will manifest organic, behavioral or antisocial traits which would make him a poor risk for adoption.

On the other hand, leaving an infant in a nursery or orphanage for several years while waiting to ascertain whether he is absolutely free from all disabilities that he may be declared a perfect candidate for adoption is not the most practical way of ensuring that he will ultimately grow into an emotionally well-balanced and intellectually and socially mature adult member of society.

Utilizing his very best judgment, and weighing all pertinent factors, the advising physician must strike a balance between these opposing considerations.

Acknowledgment

The assistance of Miss Pamela Ann Rabbitt is gratefully acknowledged.

References

1. Adoptions in 1967, Supplement to Child Welfare Statistics—1967, Children's Bureau Statistical Series 92, 1968.
2. Polk, M.: Facts on Adoption in Maryland, Maryland State Department of Social Services, November 1968.
3. Scrimshaw, N. S. and Gordon, J. E. (ed.): Malnutrition, Learning, and Behavior. Proceedings of an International Conference cosponsored by The Nutrition Foundation, Inc., and the Massachusetts Institute of Technology held at Cambridge, Massachusetts, March 1 to 3, 1967. Cambridge, M. I. T. Press, 1968.
4. Winick, M.: Changes in nucleic acid and protein content of the human brain during growth. Pediat. Res. 2: 352, 1968.
5. Cravioto, J. and Robles, B.: Evaluation of adaptive and motor behavior during rehabilitation from kwashiorkor. Amer. J. Orthopsychiat. 35: 449, 1965.
6. Hegnauer, H.: Geburtsh. u. Frauenh., 1951.
7. McIntosh, R., Merritt, K., Richards, M., Samuels, M. and Bellows, M.: The incidence of congenital malformations; a study of 5,964 pregnancies. Pediatrics 14: 505, 1954.
8. Alexander, G. J., Machiz, S. and Alexander, R. B.: Inherited abnormalities in three generations of offspring of LSD-treated rats. Fed. Proc. 27: 220, 1968.
9. Cohen, M. M., Hirschhorn, K. and Frosch, W. A.: *In vivo* and *in vitro* chromosomal damage induced by LSD-25. New Eng. J. Med. 277: 1043, 1967.
10. Irwin, S. and Egozcue, J.: Chromosomal abnormalities in leukocytes from LSD-25 users. Science 157: 313, 1967.
11. Cohen, M.: Evaluation of drug effects by cytogenetic investigation. *In* McKhann, G. M., Yaffe, S. J. and Sharon, G. S. (ed.): Drugs and Poisons in Relation to the Developing Nervous System. Proceedings of the conference on drugs and poisons as etiological agents in mental retardation, February 26–March 1, 1967, Palo Alto, California, pp. 37–46. U. S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1791.
12. Bender, L. and Siva Sankar, D. V.: Chromosome damage not found in leukocytes of children treated with LSD-25. Science 159: 749, 1968.
13. Loughman, W., Sargent, T. and Israelstam, D.: Leukocytes of humans exposed to LSD; lack of chromosomal damage. *Ibid.* 158: 508, 1967.
14. Sparkes, R., Melnyk, J. and Bozzetti, L. T.: Chromosomal effect *in vivo* of exposure to lysergic acid diethylamide. *Ibid.* 160: 1343, 1968.
15. Warkany, J. and Takacs, E.: Lysergic acid diethylamide (LSD); no teratogenicity in rats. *Ibid.* 159: 731, 1968.
16. Zellweger, H., McDonald, J. and Abbo, G.: Is lysergic acid diethylamide a teratogen? Lancet 2: 1066, 1967.
17. Apgar, V.: Drugs in pregnancy. JAMA 190: 840, 1964.
18. Wiener, G., Rider, R., Oppel, W. and Harper, P.: Correlates of low birth weight; psychological status at eight to ten years of age. Pediat. Res. 2: 110, 1968.
19. Barnes, A.: Prevention of congenital anomalies from the point of view of the obstetrician. Second International Conference on Congenital Malformations, New York City, July 14–19, 1963, pp. 377–385.
20. Pratt, W.: Premarital pregnancy in a metropolitan community. Paper presented at the 1965 meeting of the Population Association of America.
21. Trends in Illegitimacy, United States—1940–1965. National Center for Health Statistics, Series 21, Number 15, U. S. Department of Health, Education, and Welfare, February 1968.
22. Apgar, V.: A proposal for a new method of evaluation in the newborn infant. Anesth. Analg. 32: 260, 1953.
23. Drage, J. S. and Berendes, H.: Apgar scores and outcome of the newborn. Pediat. Clin. N. Amer. 13: 635, 1966.
24. Froehlich, L. and Fujikura, T.: Significance of a single umbilical artery. Amer. J. Obstet. Gynec. 94: 274, 1966.
25. Trolle, D.: Decrease of total serum-bilirubin concentration in newborn infants after phenobarbitone treatment. Lancet 2: 705, 1968.
26. Danes, B. S. and Bearn, A.: A genetic cell marker in cystic fibrosis of the pancreas. Lancet 1: 1061, 1968.
27. Wallace, H., Dooley, S., Thiele, R., Fraser, C. and Eisner, V.: Comprehensive health care of children. Amer. J. Public Health 58: 1839, 1968.