MEDICAL PROGRESS

THE FETAL ALCOHOL SYNDROME

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Behold, thou shalt conceive, and bear a son; and now drink no wine or strong drink....(*Judges* 13:7)

THE potential teratogenic effects of alcohol have been suspected for centuries, but it was not until the work of Lemoine in 1968[1] and the independent observations of Jones and Smith in 1973[2] that a distinct, dysmorphic condition associated with maternal, gestational alcoholism was described in medical literature.

Since alcoholics frequently abuse other drugs, notably caffeine, nicotine and diazepam, and generally have unbalanced diets, it was initially questioned if ethanol could be isolated as the etiologic agent responsible for the "fetal alcohol syndrome." Extensive animal studies have now demonstrated the specific teratogenic properties of ethyl alcohol in a variety of species, many of the abnormalities being similar to those found in man.[3-9] In man, the fetal-alcohol-syndrome phenotype has not been documented in malnourished populations in which alcohol is not abused. Alcohol has remained the only common variant in the ingestion histories of the large number of women now known to have produced affected offspring.

Because of the widespread use of alcohol, the potential magnitude of birth defects stemming from ethanol exposure is relevant. In 1976, only three years after Jones's original article, the Dysmorphology Unit at the University of Washington could report 41 affected patients with fetal alcohol syndrome.[10] We have now evaluated 65 patients with the syndrome. Majewski and his colleagues[11-13] have studied 85 patients with fetal alcohol syndrome in Tübingen, Germany, and over 100 other cases have been reported elsewhere in the United States and Europe.[14-32] Recent studies place the frequency at between one and two live births per 1000,[29-33] with the frequency of partial expressions at perhaps three to five live births per 1000.[33,34]

The United States Food and Drug Administration recently advocated the placement of warning labels on whiskey bottles. Yet in spite of the growing awareness of the clinical manifestations of the fetal alcohol syndrome, recognition has been minimal in many areas where alcoholism rates might suggest a sizable number of affected offspring. Consequently, the purpose of this article is to summarize United States and world experience with the clinical features of ethyl alcohol teratogenesis to aid in the early recognition of those affected and to facilitate appropriate family preventive counseling and patient management.

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VARIABLE EFFECTS OF ALCOHOL ON THE FETUS

Variability of severity is an important principle in the appreciation of the effects of any teratogen. In medical centers where large numbers of children affected by ethanol have been studied, a wide spectrum of effects of alcohol on the fetus have been appreciated. At the most severe end of the spectrum are patients with the unique constellation of anomalies initially termed "fetal alcohol syndrome." Along the rest of the continuum toward normal are persons with every subcombination of fetal-alcohol-syndrome anomalies. Each anomaly can independently vary in severity and grade into the normal range.

The abnormalities most typically associated with alcohol teratogenicity can be grouped into four categories: central-nervous-system dysfunctions; growth deficiencies; a characteristic cluster of facial abnormalities; and variable major and minor malformations. Tables 1 and 2 show the frequency of specific malformations within each category. Since alcohol teratogenicity presents such a broad range of abnormalities, any specific list of individual features that are claimed to be essential to the diagnosis could be arbitrary and misleading. In general, however, there has been a reluctance to positively identify a person as affected by ethanol without some alteration in brain function, growth and facial appearance. Until more knowledge has been accumulated, less complete partial expressions can only be referred to as "suspected fetal alcohol effects."

The variability of phenotype probably results from variable dose exposure at variable gestational timings offset by the genetic background of the individual fetus. Nearly all patients recognized as having the full fetal-alcohol-syndrome phenotype have been born to daily heavy alcohol users or relatively frequent heavy intermittent alcohol users. The evidence to date suggests that chronic consumption of 89 ml of absolute alcohol or more per day — the equivalent of about six hard drinks — constitutes a major risk to the fetus.[35] Lower levels of consumption or less frequent use of alcohol carries an unknown risk and may be shown to be associated with less seriously affected children. No absolutely safe level of ethanol consumption has yet been established.

Table 1. Principal Features of the Fetal Alcohol Syndrome Observed in 245 Persons Affected.

FEATURE	MANIFESTATION
Central-nervous-system dysfunction:	
Intellectual	Mild to moderate mental retardation*
Neurologic	Microcephaly*
	Poor co-ordination, hypotonia†
Behavioral	Irritability in infancy*
	Hyperactivity in childhood†
Growth deficiency:	
Prenatal	<2 SD for length & weight*
Postnatal	<2 SD for length & weight*
	Disproportionately diminished adipose tissue†
Facial characteristics:	
Eyes	Short palpebral fissures*
Nose	Short, upturned†
	Hypoplastic philtrum*
Maxilla	Hypoplastic†
Mouth	Thinned upper vermilion*
	Retrognathia in infancy*
	Micrognathia or relative prognathia in adolescence†

*Feature seen in >80% of patients. †Feature seen in >50% of patients.

Central-Nervous-System Dysfunction

Mental retardation has been one of the most common and serious problems associated with ethanol teratogenicity. Of 126 patients described with specific mention of standardized testing of performance, 107 (85 per cent) scored more than 2 standard deviations below the mean.[10,14,17,19,20,28,32,36] Although not all persons affected are retarded, rarely has an affected patient displayed average or better than average mental ability.

The question has been asked whether the mental deficiency in these patients is the result of prenatal exposure to ethanol or the consequence of postnatal exposure to life with alcoholic parents. Much evidence has now accumulated to support a prenatal origin for much of the problem.

In one study, intelligence was evaluated in 20 patients with the fetal alcohol syndrome who had varying severity of growth deficiency and dysmorphic features.[36] The patients ranged in age from nine months to 21 years. The average IQ was 65, with a range from 16 to 105. In general, the more phenotypically involved patients had the lower IQ scores, suggesting that the prenatal insult that resulted in the dysmorphic features also produced the mental deficiency.

A review of the offspring of 23 women with chronic alcoholism from the National Collaborative Perinatal Project of the National Institute of Neurologic Diseases and Stroke demonstrated that 44 per cent of the surviving offspring had IQ scores that were below 80.[37] Differences in intelligence scores were not statistically significant between children raised with their alcoholic parents and those raised by relatives or in foster homes.

In the Soviet Union, 23 children born to women who had been alcoholic during gestation were compared to 19 children born to women who became alcoholic after pregnancy.[38] The children exposed to alcohol in utero displayed neonatal neurologic impairments, and 14 were eventually found to be mentally retarded. The children raised with an alcoholic mother after a normal gestation displayed "vegetative, emotional and behavioral" disorders that became manifest in middle childhood and improved with better social circumstances.

The most impressive evidence for the prenatal effect of ethanol on the brain has come from neuropathological studies. Structural alterations have recently been demonstrated in the brains of infants exposed to alcohol in utero.[11,39,40] In one series, four brains showed similar malformations caused by failure or interruption in neuronal and glial migrations.[40] Although the type of malformation was similar in each case, the location of the malformations varied from subject to subject. The most consistent anomalies were cerebellar dysplasias and heterotopic cell clusters, especially on the brain surface. In one case the malformations were primarily in the cerebrum, and there was associated microcephaly. Subtentorial anomalies produced hydrocephalus in two cases and had no untoward effects on head size in another.

Microcephaly has been an important feature of the fetal alcohol syndrome. Generally, it has been of prenatal onset, though occasionally it has only become apparent with time. Microcephaly reflects deficient brain growth, but as the neuropathological and psychologic studies demonstrate, normocephaly does not necessarily predict normal brain structure or function after intrauterine alcohol exposure. Furthermore, hydrocephaly can be an occasional variant in the fetal

Table 2. Associated Features of the Fetal Alcohol Syndrome Observed in 245 Persons Affected.

AREA	FREQUENT*	OCCASIONAL†
Eyes	Ptosis, strabismus, epicanthal folds	Myopia, clinical microphthalmia, blepharophimosis
Ears	Posterior rotation	Poorly formed concha
Mouth	Prominent lateral palatine ridges	Cleft lip or cleft palate, small teeth with faulty enamel
Cardiac	Murmurs, especially in early childhood, usually atrial septal defect	Ventricular septal defect, great-vessel anomalies, tetralogy of Fallot
Renogenital	Labial hypoplasia	Hypospadias, small rotated kidneys, hydronephrosis
Cutaneous	Hemangiomas	Hirsutism in infancy
Skeletal	Aberrant palmar creases, pectus excavatum	Limited joint movements, especially fingers & elbows, nail hypoplasia, especially 5th, polydactyly, radioulnar synostosis, pectus carinatum, bifid xiphoid, Klippel–Feil anomaly, scoliosis
Muscular		Hernias of diaphragm, umbilicus or groin, diastasis recti

*Reported in between 26 & 50% of patients.
†Reported in between 1 & 25% of patients.

alcohol syndrome if the malformations that usually cause limited brain growth also interfere with cerebrospinal-fluid dynamics. We are aware of two surviving patients with the fetal alcohol syndrome and hydrocephaly not yet reported on.

Since alcohol has been shown to interfere with brain organization, ethanol could be one etiologic agent in the production of neural-tube defects. Exencephaly has in fact been produced in mice after in utero ethanol exposure.[3,6] We are aware of one infant with anencephaly born to a frequent alcohol abuser, and a similar patient was described elsewhere.[22] We have also observed a child with the fetal alcohol syndrome and meningomyelocele and a child with the syndrome and a lumbosacral lipoma. Clearly, this is an area that deserves closer investigation.

Neurologic abnormalities may be present from birth in the fetal alcohol syndrome, again reflecting the prenatal nature of this condition. Newborns are usually irritable and tremulous, have a poor suck and have apparent hyperacusis.[10,42] These abnormalities usually last for several weeks or months. Older children have most frequently shown mild alterations in cerebellar function[10,19,23,33,36] and hypotonicity.[24,27,36] However, severe hypertonicity has been observed in at least one older patient,[22] and mixed tonicity with hypotonic arms and hypertonic legs has been noted in one other case.[30] Seizures beyond the neonatal period have been surprisingly rare. Neonatal seizures have occasionally been observed by us and by others.[22,41,42]

Hyperactivity is a frequent component of the fetal alcohol syndrome in young children. Affected youngsters sometimes seem to fly about the examining room. The extent to which this behavior is organic versus environmentally determined has not been established.

Growth Deficiency

Most infants with the fetal alcohol syndrome are growth deficient at birth for both length and weight. Early reports stressed greater deficits in prenatal linear growth than in weight at birth,[2] but it has now been recognized that many affected infants have greater deficits in prenatal weight than in length. Few infants have demonstrated postnatal catch-up growth. With their poor suck and poor growth many affected infants have been initially and repeatedly evaluated for failure to thrive. In general, children with the fetal alcohol syndrome remain more than 2 standard deviations below the mean for height and weight, with weight being more severely limited. Occasionally, affected children have shown normal prenatal growth, only to become increasingly growth deficient with time.

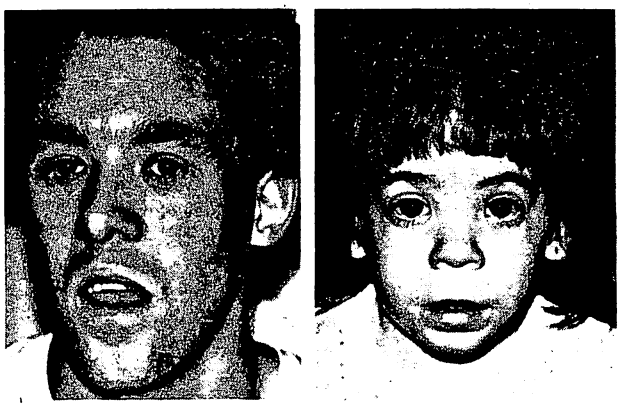
Although it is not always mentioned in the patient reports in the literature, in our experience, decreased adipose tissue is a nearly constant feature of persons with the fetal alcohol syndrome. A major complaint of parents bringing their children to our clinic for follow-up examination has been their inability to "fatten up" their "skinny little kid."

The failure of these children to grow at a normal rate has prompted some endocrinologic studies. Children with the fetal alcohol syndrome have demonstrated appropriate levels of growth hormone, cortisol and gonadotropins.[28,43] We believe the growth deficiency in this condition reflects the prenatal insult to cell proliferation leading to diminished fetal cell numbers and eventual limitation of size.

Distinctive Face

There is a rather typical facial appearance in persons with the fetal alcohol syndrome. Although many disorders feature mental deficiency and growth deficiency, it is the facial similarities among children with the syndrome that unite them into a discernible entity (Fig. 1 and 2). Whereas these facial similarities are clear from the photographs of affected children presented by numerous authors, the written descriptions have not always emphasized the same features, and these discrepancies have led to some confusion. In our experience, the facies is characterized by a few key features: short palpebral fissures; a hypoplastic upper lip with thinned vermilion; and diminished to absent philtrum. Frequently, the face is further altered by mid-facial and mandibular growth deficiency.

The growth of the eye, like the rest of the nervous system, is adversely affected by fetal exposure to alcohol. On rare occasion eye growth has been so deficient that frank microphthalmia has been seen.[10] Typically, modest growth deficiency of the eye is reflected in shortened palpebral fissures. Unfortunately, standards for size of palpebral fissure in children are based on rather old data, and the means and stan-



A B

Figure 1. Patients at 17 (A) and 2½ (B) Years of Age, with the Usual Facial Appearance Observed in the Fetal Alcohol Syndrome, Which Results from a Cluster of Minor Anomalies, Including Short Palpebral Fissures, Short Nose, Hypoplastic Philtrum, Thinned Upper-Lip Vermilion and Flattened Midface.

The older boy's face has been further altered by mild downslant of the eyes and a relative prognathism resulting from the mid-facial hypoplasia.

A B

Figure 2. Patients at 1½ (A) and Six (B) Years of Age, Showing on Overall Facial Appearance Differing Somewhat from That in Figure 1 because of Normal Maxillary Growth and Differing Racial Backgrounds

The principal cluster of facial abnormalities is present in each case, however, and includes short palpebral fissures, short nose, hypoplastic philtrum and thinned upper-lip vermilion. In addition, they have mild ptosis.

dard deviations are inadequately established.[44,45] We have viewed short palpebral fissures as one of the most important findings in making the diagnosis, and 59 of our patients with the fetal alcohol syndrome (91 per cent) have had this facial feature. Twelve other authors have described short palpebral fissures in 54 of 74 patients (73 per cent). Only Majewski did not find this abnormality to be a frequent feature. He reports short palpebral fissures in less than 10 per cent of 76 patients.[11] Strabismus and myopia are frequent eye problems, and ptosis and blepharophimosis have been reported frequently in some series.[12] Structural alterations within the eye have been observed in individual cases.

The face, in general, has a drawn appearance that is produced principally by the thinned upper vermilion and hypoplastic philtrum and is further accentuated by the frequent additional feature of mid-facial hypoplasia. The retrusive maxilla contributes to the accompanying flattened profile and occasional downslanting of the palpebral fissures. The nose is frequently short, with a low bridge and associated epicanthal folds and anteverted nostrils. The short, upturned nose gives the real or apparent impression that the distance from the alae nasae to the upper lip is long. Cleft lip and cleft palate have occasionally been observed.

The ear and mandible are involved in some patients. Posterior rotation of the helix is common, and alteration in conchal shape occurs occasionally. The mandible is generally small at birth. In some children, micrognathia remains with increasing age; in others the jaw grows relatively better than the midface, and an apparent prognathism may be seen in adolescence.

Taken as a whole, the face of patients with the fetal alcohol syndrome is as distinctive as that of patients with the Down syndrome and is as readily appreciated in the newborn period as in later life. However, the important abnormalities, taken individually, are subtle and not likely to be found in standard listings of malformations. It has been our experience that although untrained observers generally notice the face of patients with the syndrome to be unusual, they most frequently are not able to describe their observations accurately and generally do not record them. Consequently, retrospective chart-search studies for cases are difficult to conduct, since without the facial description it is quite difficult to make the diagnosis of the fetal alcohol syndrome.

Associated Major and Minor Anomalies

Although there is an increased frequency of malformations in children with the fetal alcohol syndrome, no one major malformation occurs in the majority of cases. Table 2 lists the major and minor malformations that have been found in at least two of the available 245 reports.

Differential Diagnosis

In a few severely affected children we have noted a superficial facial resemblance to patients with the de Lange syndrome, and such a resemblance has also been recorded by Barry and O'Nuallain.[14] Two children with gestational histories of substantial ethanol exposure have also been reported to resemble somewhat patients with the Noonan syndrome.[18,29] Generally, however, the fetal-alcohol-syndrome phenotype is distinct and not readily confused with other recognized patterns of malformation.

Final Comments

Maternal abuse of ethanol during gestation produces a readily identifiable dysmorphic condition and appears to be the most frequent known teratogenic cause of mental deficiency in the Western world. Extensive animal experiments and scores of affected children reported on leave little doubt of the reality and origin of this disorder.

The issue of the existence of the fetal alcohol syndrome is behind us. Needed now are answers to questions such as the risk to a woman, given a specific drinking history, of producing a seriously affected offspring. How does intermittent binge drinking as opposed to steady consumption alter the phenotype? How do commonly associated drugs like coffee, nicotine and diazepam alter or potentiate the effects of alcohol? What are the mechanisms through which alcohol or its breakdown products produce their effect on the embryo and fetus? Can prenatal diagnostic technics be used to detect this disorder?

There are relatively few forms of mental retardation that can be diagnosed before birth. Through accurate understanding of the intrauterine effects of ethanol and widespread public awareness, this major cause of birth defects and mental retardation could be largely reduced and, ideally, eliminated.

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