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

The potential teratogenic effects of alcohol have been suspected for centuries, but it was not until the work of Lemoine in 1968 and the independent observations of Jones and Smith in 1973 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. 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. We have now evaluated 65 patients with the syndrome. Majewski and his colleagues 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. Recent studies place the frequency at between one and two live births per 1000, with the frequency of partial expressions at perhaps three to five live births per 1000.

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.

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 anomalies; 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. 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.

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

*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. In one series, four brains showed similar malformations caused by failure or interruption in neuronal and glial migrations. Although the same malformations were noted in a single 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. One case in which the malformations were primarily in the cerebrum, and there was associated microcephaly. Subtential 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 neuropsychological and psychological studies demonstrate, microcephaly does not necessarily predict normal brain structure or function after intrauterine alcohol exposure. Furthermore, hydrocephaly can be an occasional variant in the fetal alcohol syndrome, because limited brain growth during the early fetal period results in the neurocranial fluid and the brain occupying the space normally occupied by bone. Since cerebrospinal-fluid dynamics are usually normal in patients with anencephaly, hydrocephaly does not appear to be a predominant feature of the syndrome.

Neurologic abnormalities at birth in the fetal alcohol syndrome are usually irritability with hyperactivity, not the self-regulating behavior usually last for days to weeks. Children have mandibular hypoplasia in cerebral dysgenesis. However, abnormal phenotypic features have been noted in culture-reared children of alcohol-exposed mothers. In one study, children have had mental retardation, seizures, hypotonia, and dysmorphisms.

Hyperactivity associated with the fetal alcohol syndrome may be crucial for youngsters sometimes living in crowded rooms. The extent of hyperactivity versus environment is still under investigation.

Growth Deficiency

Most infants with growth deficiency have been described in early reports of cases. Growth deficiency, or failure to thrive, has been recognized as an important feature, and has been noted in greater deficits in alcoholics. In addition, children have been noted with poor weight in the first few months of life. With their poor weight gain, infants have been noted to have delay for failure to thrive. The syndrome of alcohol syndrome has also been described in infants below the 5th or 10th percentile weight being more common in affected children than in normal infants, only to become normal by 3 years of age.

Although it is unknown how many reports in the literature on growth-deficient infants with excess adipose tissue and with the fetal alcohol syndrome are associated with alcoholic parents bringing their children to medical attention.
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 intrauterine ethanol exposure.13,14 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 meningomyelecele 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.10,12 These abnormalities usually last for several weeks or months. Older children have most frequently shown mild alterations in cerebellar function10,12,13,15 and hypotonicity.24,37,38 However, severe hypotonicity has been observed in at least one older patient,22 and mixed toxicity 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,3 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-

Figure 1. Patients at 17 (A) and 2 1/2 (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 Mid-face.

The older boy’s face has been further altered by mild downsant of the eyes and a relative prognathism resulting from the mid-facial hypoplasia.
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. Two children with gestational histories of substantial ethanol exposure have also been reported to resemble somewhat patients with the Noonan syndrome. 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.

We are indebted to Drs. James W. Hanson and Kenneth Lyons Jones, who evaluated many of the 65 patients whose features were summarized here, and to Mrs. Lyle Harrah for help in collecting and translating much of the foreign-language literature.

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