

Incidence of Fetal Alcohol Syndrome and Prevalence of Alcohol-Related Neurodevelopmental Disorder

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ABSTRACT We critique published incidences for fetal alcohol syndrome (FAS) and present new estimates of the incidence of FAS and the prevalence of alcohol-related neurodevelopmental disorder (ARND). We first review criteria necessary for valid estimation of FAS incidence. Estimates for three population-based studies that best meet these criteria are reported with adjustment for underascertainment of highly exposed cases. As a result, in 1975 in Seattle, the incidence of FAS can be estimated as at least 2.8/1000 live births, and for 1979–81 in Cleveland, ~4.6/1,000. In Roubaix, France (for data covering periods from 1977–1990), the rate is between 1.3 and 4.8/1,000, depending on the severity of effects used as diagnostic criteria. Utilizing the longitudinal neurobehavioral database of the Seattle study, we propose an operationalization of the Institute of Medicine's recent definition of ARND and estimate its prevalence in Seattle for the period 1975–1981. The combined rate of FAS and ARND is thus estimated to be at least 9.1/1,000. This conservative rate—nearly one in every 100 live births—confirms the perception of many health professionals that fetal alcohol exposure is a serious problem. *Teratology* 56:317–326, 1997. © 1997 Wiley-Liss, Inc.

Phillips and Krueger, '92; Ward and West, '92; Dumas and Rabe, '94; Bonthius et al., '96; Sutherland et al., '97). Considerable confusion exists, however, about how to diagnose FAS and how to estimate the incidence of FAS and related adverse reproductive outcomes of women using alcohol during pregnancy (Dehaene et al., '77, '81, '91; Olegård et al., '79; Larsson, '83; May et al., '83; Abel and Sokol, '87, '91; Robinson et al., '87; Chavez et al., '88; Lesure, '88; Kaminski, '92; Abel, '95).

Here, we discuss traditional criteria necessary for the estimation of FAS incidence. We then review published data from large population-based studies in order to arrive at reasonable estimates of FAS incidence. We also present new data and propose a new methodology for operationalizing the recent Institute of Medicine (IOM) definition of alcohol-related neurodevelopmental disorder (ARND) and estimating its prevalence (IOM, '96).

CHARACTERISTICS OF FAS AND ARND

Clinical criteria for any birth defect syndrome are based on a characteristic pattern of major and minor anomalies and deficits that, as a group, are satisfactorily unique to that disorder. No list is ever fully specific. Owing to ordinary human biologic variability, any list of clinical criteria for any condition will include the occa-

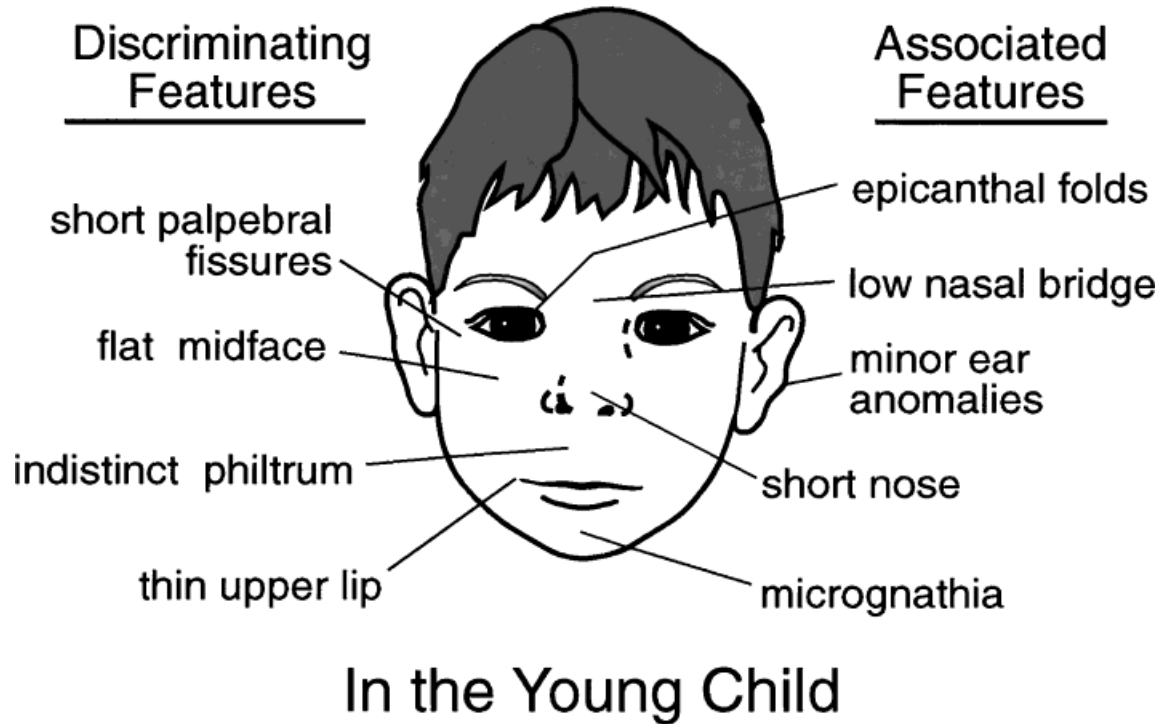
Alcohol is well established as a teratogenic drug capable of causing miscarriage, stillbirth, malformation, growth deficiency, and central nervous system dysfunction by interfering with normal proliferation and migration of neuronal and glial cells, by direct toxic effects of ethanol and acetaldehyde upon cells, by hemodynamic-induced hypoxia, and by other mechanisms (West, '86; Schenker et al., '90; Randall et al., '90; Clarren et al., '92; Goodlett and West, '92; Miller, '92;

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The Face in Fetal Alcohol Syndrome



In the Young Child

Fig. 1. The face in fetal alcohol syndrome.

sional individual with an alternate condition (phenocopy) and exclude some individuals with incomplete expressions of the condition under consideration. This confusion is noticeably alleviated when a specific biologic marker or pathophysiologic test is linked to the cause of the diagnosis; however, no specific test is yet available for the birth defects caused by ethanol.

The diagnosis of fetal alcohol syndrome (FAS), which has changed little since the mid-1970s (Clarren and Smith, '78; Rosett, '80; Smith, '82; Sokol and Clarren, '89), rests on a combination of growth deficiency and neurobehavioral effects with a recognizable pattern of minor facial anomalies. Children with the clearest FAS phenotype have complex brain dysfunction combining elements of cognitive impairment, behavioral disturbance, and neurological damage. They may have small crania and are typically below the tenth centile in height and/or weight. From late infancy to the onset of adolescence, their faces are characteristic of this disorder. Some of the more distinctive minor anomalies contributing to the characteristic appearance include short palpebral fissures, relatively short nose, flat philtrum, thin upper lip, and flattened medial midface. Figure 1 diagrams these characteristic features (many demonstrated in Fig. 2, a photograph of a child diagnosed FAS). When this characteristic clinical expression is complete, many diagnosticians believe that the



Fig. 2. Photograph of a child diagnosed FAS. Reprinted with permission from the Institute of Medicine report on FAS (IOM, '96).

FAS diagnosis can be made without knowledge of maternal alcohol exposure.

The studies used for estimating the incidence of FAS in this work were carried out between 1974 and 1993 and used the standard criteria of the times, as described above. They did not utilize the new criteria for FAS suggested by the 1996 IOM report (see Table 1), in which the emphasis on structural CNS deficits and neurological hard and/or soft signs would eliminate many of the children traditionally diagnosed as FAS.

The term "fetal alcohol effect" (or FAE) was first used in 1978 in reference to the cognitive or behavioral problems, growth aberration, or physical (dysmorphic) deviations that occurred at higher frequencies in alcohol-exposed populations than in unexposed populations (Clarren and Smith, '78; Hanson et al., '78). Recently, however, some workers in the field have questioned whether or not FAE is a clinically useful diagnostic term outside of animal or human population studies in which maternal alcohol consumption during pregnancy is the independent variable being studied (Aase et al., '95). More specific terms, such as "physical FAE" or "neurobehavioral FAE," also have been used on occasion. These correspond now to the definitions of alcohol-related birth defects (ARBD) and alcohol-related neurodevelopmental disorder (ARND) recently proposed in the IOM report (Table 1). These are clinical conditions in which there is a history of maternal alcohol exposure and where clinical or animal research has linked maternal alcohol ingestion to observed outcomes: congenital anomalies in the case of ARBD, and CNS or behavioral abnormalities in the case of ARND.

It is difficult to estimate the incidence or prevalence of ARBD and ARND. Some diagnosticians have estimated the relative ratio of FAS to ARND cases from counts of referrals (May et al., '83; Robinson et al., '87), but such estimates depend on referral patterns as well as incidence. This study utilizes empirical methods to estimate the incidence of FAS, defined with traditional criteria, and the prevalence of ARND, defined in a manner consistent with the recent IOM ('96) report, in birth cohorts of children ascertained by maternal self-reported alcohol use rather than by clinical referral.

ESTIMATING INCIDENCE OF FETAL ALCOHOL SYNDROME

Defining incidence

An incidence requires two key pieces of information: (1) a well-defined population to be studied over a given period, and (2) stated criteria used to define a new case of the condition. If risk of having the condition under study is related to an exposure, information on the rate of this exposure in the population is needed in order to interpret the incidence fully.

These criteria for obtaining accurate estimates of incidence pose special problems when the condition is FAS. There are difficulties both in defining the appropriate outcome state and in estimating incidence once a definition of the outcome has been accepted.

Given a specific population and period, *what is the group at risk for the condition?* (What is the denominator for the FAS incidence?) Is it all conceptuses, all clinically recognized pregnancies, all births of viable gestational age, or all liveborn infants? Only the latter provides a reasonable quantifiable basis. Variations in maternal drinking are considered as variations in the exposure of the cohort, rather than as an adjustment to the denominator for the rate.

What are the criteria for an FAS case? The diagnosis of FAS is particularly prone to unreliability and bias because few clinicians are trained to recognize it and because there are no validated checklists or laboratory tests by which the inexperienced examiner may calibrate his/her judgments based on published characterizations (Clarren and Smith, '78; Rosett, '80; Smith, '82; Sokol and Clarren, '89; IOM, '96). Abel et al. ('93) report ratings of facial features of FAS by medical providers and biomedical scientists to be significantly correlated; however, the findings reported seem to imply low sensitivity and specificity for FAS. Also, the stigma attached to FAS could decrease the likelihood of a clinician entering an FAS diagnosis in the official medical record, especially for families of higher income or social class.

A different problem arises when noting anomalies one-by-one rather than making clinical judgments about FAS as a discrete entity (Kaminski, '92). Even in the Seattle study, using a checklist designed by D.W. Smith and examiners trained by him, the total number of anomalies did not correspond well to clinical diagnosis of FAE in 4-year-olds (Graham et al., '88).

Astley and Clarren ('95) suggest that objective measures of FAS facial features can be combined in a scoring system to discriminate the FAS ratings of one trained dysmorphologist. However, this study does not establish the accuracy of the rating system in an objective clinical context; indeed, it is intended mainly as a screening tool. Sokol et al. ('93) are using a computer program for identifying cases of FAS based on a clinician's rating of facial, congenital and neurobehavioral anomalies, but there is not yet any published validation of this procedure.

Once a definition of the incidence and a protocol for classifying cases are adopted, *how are the cases ascertained?* Ascertainment in registries is notoriously inadequate, especially when the diagnosis is difficult or stigmatizing (NCHS, '92; CDCP, '95b). Because of the logistical difficulty of conducting clinical examinations, a population may be screened first for maternal alcohol use to eliminate many infants at low risk of FAS. This strategy assumes that: (1) verbal screening tools provide a sufficiently valid estimate of the amount of ethanol ingested in the critical period for FAS (Streissguth et al., '76), (2) below some threshold, FAS does not occur, and (3) clinical examination by trained examiners does not result in false positives (phenocopies of

TABLE 1. Diagnostic criteria for fetal alcohol syndrome (FAS) and alcohol-related effects (IOM, '96)*

Fetal alcohol syndrome		
1. FAS with confirmed maternal alcohol exposure ¹		
A. Confirmed maternal alcohol exposure ¹		
B. Evidence of a characteristic pattern of facial anomalies that includes features such as short palpebral fissures and abnormalities in the premaxillary zone (e.g., flat upper lip, flattened philtrum, and flat midface)		
C. Evidence of growth retardation, as in at least one of the following: low birth weight for gestational age decelerating weight over time not due to nutrition disproportional low weight to height		
D. Evidence of CNS neurodevelopmental abnormalities, as in at least one of the following: decreased cranial size at birth structural brain abnormalities (e.g., microcephaly, partial, or complete agenesis of the corpus callosum, cerebellar hypoplasia) neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination		
2. FAS without confirmed maternal alcohol exposure		
B, C, and D as above		
3. Partial FAS with confirmed maternal alcohol exposure		
A. Confirmed maternal alcohol exposure ¹		
B. Evidence of some components of the pattern of characteristic facial anomalies Either C or D or E		
C. Evidence of growth retardation, as in at least one of the following: low birth weight for gestational age decelerating weight over time not due to nutrition disproportional low weight to height		
D. Evidence of CNS neurodevelopmental abnormalities, as in: decreased cranial size at birth structural brain abnormalities (e.g., microcephaly, partial, or complete agenesis of the corpus callosum, cerebellar hypoplasia) neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination		
E. Evidence of a complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone, such as learning difficulties, deficits in school performance, poor impulse control, problems in social perception, deficits in higher level receptive and expressive language, poor capacity for abstraction or metacognition, specific deficits in mathematical skills, or problems in memory, attention, or judgment		
Alcohol-related effects		
Clinical conditions in which there is a history of maternal alcohol exposure, ^{1,2} and where clinical or animal research has linked maternal alcohol ingestion to an observed outcome. There are two categories that may co-occur. If both diagnoses are present, then both diagnoses should be rendered.		
4. Alcohol-related birth defects (ARBD)		
Congenital anomalies, including malformations and dysplasias:		
Cardiac	Atrial septal defects Ventricular septal defects	Aberrant great vessels Tetralogy of Fallot
Skeletal	Hypoplastic nails Shortened fifth digits Radioulnar synostosis Flexion contractures Camptodactyly	Clinodactyly Pectus excavatum and carinatum Klippel-Feil syndrome Hemivertebrae
Renal	Aplastic, dysplastic, hypoplastic kidneys Horseshoe kidneys	Scoliosis Ureteral duplications Hydronephrosis
Ocular	Strabismus Retinal vascular anomalies	Refractive problems secondary to small globes
Auditory	Conductive hearing loss	Neurosensory hearing loss
Other	Virtually every malformation has been described in some patient with FAS. The etiologic specificity of most of these anomalies to alcohol teratogenesis remains uncertain.	
5. Alcohol-related neurodevelopmental disorder (ARND)		
Presence of:		
A. Evidence of CNS neurodevelopmental abnormalities, as in any one of the following: decreased cranial size at birth structural brain abnormalities (e.g., microcephaly, partial or complete agenesis of the corpus callosum, cerebellar hypoplasia) neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination and/or:		
B. Evidence of a complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone, such as learning difficulties, deficits in school performance, poor impulse control, problems in social perception, deficits in higher level receptive and expressive language, poor capacity for abstraction or metacognition, specific deficits in mathematical skills, or problems in memory, attention, or judgment.		

¹A pattern of excessive intake characterized by substantial, regular intake or heavy episodic drinking. Evidence of this pattern may include frequent episodes of intoxication, development of tolerance or withdrawal, social problems related to drinking, legal problems related to drinking, engaging in physical hazardous behavior while drinking, or alcohol-related medical problems such as hepatic disease.

²As further research is completed and as, or if, lower quantities or variable patterns of alcohol use are associated with ARBD or ARND, these patterns of alcohol use should be incorporated into the diagnostic criteria.

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FAS in truly unexposed children). We are not aware of any incidence study in which FAS has been diagnosed in an "unexposed" child. Instead, but too rarely, a sample of these "unexposed" infants may be drawn to compare to the "exposed" infants. This is done not to obtain a stratified sample but, rather, to permit examiners to be blinded to exposure status (Hanson et al., '78). Incidence estimates cannot be generated from case-control studies, from most studies testing group differences, or from registries. A representative sample of an entire cohort must be examined.

When are cases ascertained? Timing of ascertainment affects the estimated incidence of FAS as it does many other syndromes. Birth is a convenient time to make the diagnosis of FAS, but only the most severely affected infants are likely to be identified then (Darby et al., '81).

If children are followed after birth, the criteria for diagnosis may change in adolescence or adulthood, owing to changes in facial morphology associated with puberty (Streissguth et al., '85, '91; Spohr et al., '93). The easiest time to establish the diagnosis is between 8 months and 8 years of age.

Studies of FAS incidence

We are not aware of any studies that fully meet all the above criteria. However, we have identified three investigations that meet almost all of these requirements, and these are reviewed in detail. Others that satisfy most of the criteria are described briefly.

U.S. studies. Two studies of prenatal alcohol effects in the United States meet most of the criteria enumerated above. One is from Seattle and the other is from Cleveland. Both are prospective cohort studies in which a population of prenatal patients was screened and a group of exposed infants selected, along with a group of unexposed, in order to blind the clinicians who examined the infants after delivery for FAS status. Neither population alone is representative of the U.S. population. The number of FAS cases is divided by the number in the (screened) population to obtain an estimate of incidence.

The prospective study in Seattle, Washington, considered all obstetrical patients at a health maintenance organization and a teaching hospital during a 1-year period (1974–1975) before there were any official recommendations about drinking and pregnancy (Streissguth et al., '81, '93). They were interviewed at their fifth month of pregnancy; those who did not receive prenatal care by that time were not eligible for the study. The sample, although heterogeneous, was primarily white, married, and middle-class. In all, 1,439 of the women interviewed delivered a live infant at the study hospitals. Neonates in the "exposed" and "unexposed" categories were examined shortly after birth in the hospital by a dysmorphologist (JWH) without knowledge of exposure history.

For the dysmorphology substudy (Hanson et al., '78), an "exposed" infant (for the purpose of this analysis) was one whose mother reported drinking prior to

recognition of pregnancy, or in midpregnancy, either (1) an average of at least one ounce of absolute alcohol per day, or (2) more than 17.5 drinks per month with ingestion of five or more drinks on at least one occasion. This defines the "high priority" exposure category in the protocols for the Seattle study (Streissguth et al., '81, '93). If two "exposed" infants were born on the same day, the one with the higher exposure code was selected for pairing with the "unexposed" infant for examination. A matched "unexposed" cohort was selected from study infants born the same day at the same hospital whose mothers were abstainers or infrequent drinkers (<0.10 oz absolute alcohol per day and no intoxications). This protocol allowed only one pair of infants to be scheduled per day. Eighty of the exposed infants (39%) were seen; the balance were either born before the dysmorphology component was begun, were born the same day as a baby having a higher priority due to higher exposure, were born when no control was available, left the hospital early, or were available only when the examiner was unavailable. Two of these 80 exposed infants were diagnosed "blind" at birth as having FAS, using criteria comparable to those set out earlier in this paper (Hanson et al., '78). None of the unexposed were so diagnosed.

The unweighted incidence is 2/1439, or ~1.4/1000 live births. However, this is an underestimate due to less-than-full ascertainment of the "exposed" infants in the screening population. Assuming that the infants examined represent a random sample from the cohort of exposed infants in the population, we obtain an appropriate estimate of the incidence in the population by weighting the diagnosed cases according to the number of exposed infants in the screening population relative to the number actually examined.

The dysmorphologist saw 80 children out of the 204 "exposed." Another 22 of these were not seen owing to birth of a higher priority baby the same day. Assuming that (1) no two cases of FAS were ever born on the same day, and (2) FAS is generated only at the very highest levels of dose, then the effective number of exposed infants screened was 102 (80 + 22). One would then expect a full screening to have found (204/102) times as many cases, or 4 per 1,439 live births, an incidence of 2.8 per 1,000. More detailed analysis of this calculation shows that it is not sensitive to the threshold defining the "exposed" subpopulation.

The sample for the Cleveland Fetal Alcohol Study was drawn over the period 1979–1981 from a hospital that served mainly poor, innercity patients (Sokol et al., '81, '86). The Michigan Alcoholism Screening Test (MAST) was used as the screening tool for exposure (Selzer, '71). This instrument focuses on psychosocial problems related to alcohol abuse and dependence, and so, although not a measure of exposure per se, is similarly able to discriminate the highest stratum of alcohol abusers. About 11% of 8,331 consecutive patients were MAST-positive; 600 of them were recruited as mothers of the "exposed" group of infants, along with a matched group of MAST-negative mothers, whose

infants were assumed not to be at risk. Infants were examined within 72 hours after birth, using criteria published by the Research Society on Alcoholism (Rossett, '80). Twenty-five FAS cases were diagnosed among the infants of the 1,200 patients examined. The authors calculated an incidence of $25/8331 = 3.0/1,000$ total live births. As not all MAST-positive infants in the study were examined, true incidence can be no lower and may be higher. Correcting for the underascertainment of "exposed" cases in the Cleveland population as we did for the Seattle study, the incidence is 4.6 per 1,000.

Sokol et al. ('93) screened a population of 14,707 black women in Detroit, with follow-up of the children of all heavy drinkers leading to an estimated incidence of 3.9/1,000. However, assessment of FAS was done using a computer program (as noted above) rather than the judgment of a trained clinician or dysmorphologist.

Other U.S. studies with smaller numbers of subjects have also estimated incidences for FAS. In Boston, at a hospital serving a poor innercity population of prenatal patients, 322 live infants, including 42 (of 58) "exposed," were examined by a pediatric neurologist (Ouellette et al., '77). The cohort was not systematically examined after birth. Incidence was originally estimated at 0, but rose to 3.1/1,000 when one FAS case was later diagnosed at 1 year of age (cited in Abel and Sokol, '87). A subsequent study of 1,690 infants in the same hospital estimated incidence at 0.6/1000—again, this is one case—but among examined infants there were only 45 whose mothers reported having as many as two drinks daily (Hingson et al., '82). We are not aware of any other U.S. studies in which a systematic attempt at complete ascertainment of a birth cohort was made to determine FAS incidence using a trained examiner.

Studies in other countries. One of us (PD) has been conducting an extensive prospective study of FAS in Roubaix, France, since 1975 (Dehaene et al., '77, '81, '91). All newborns (~2,500 per year) are screened, with selected infants examined by a neonatologist (PD) or one of two colleagues, all using the same case criteria derived from extensive experience with FAS. A tentative diagnosis is made at birth and confirmed at subsequent visits to the pediatric clinic. As this is a clinical population rather than a research sample, diagnoses are not necessarily made blind. The rate of "heavy drinking," defined as >30 g ethanol daily (~1 oz absolute alcohol, or two drinks) on average, was estimated at 8.9% for women in the beginning of pregnancy (Dehaene et al., '85).

The case definition in Roubaix differs somewhat from the definition used in the United States. Three degrees of fetal alcohol effects are used. Type I, or "moderate FAS," represents growth retardation (weight, length, or head circumference below the 25th percentile for gestational age) and one or two clear dysmorphic facial features (including short palpebral fissures, retrognathia, deep nasal bridge with short upturned nose, and long smooth philtrum with thin upper lip). Type II, or "full FAS," requires growth deficiency and at least four

craniofacial dysmorphic features. Type III, "severe FAS," requires severe dysmorphic features, growth retardation (height, weight, or head circumference under the third percentile for gestational age), and one or more major malformations (cleft lip or palate, cardiac defects, hip dislocation). All infants known to be "exposed" are examined at birth; those initially classified as FAS Type I, II, or III at birth are re-evaluated later to confirm the final diagnosis.

FAS subtypes were not separated prior to 1977. For the years of complete ascertainment, 1977–79 (Dehaene et al., '81) and 1986–90 (Dehaene et al., '91), 74 cases of Types I and II combined and 28 cases of Type III have been seen in a total of 21,402 births. This yields an incidence of 3.5/1,000 total births for Types I and II combined, and 1.3/1,000 for Type III. (Note: the total rate of 6.0 per 1,000 reported by the IOM ('96) for combined types I, II, and III over the years 1986–90 is in error.) The criteria for Type III are more stringent than the U.S. FAS criteria, and Types I and II combined contain more cases than would be called FAS in the U.S. P.D. estimates that the fraction of "U.S. FAS" represented in the Type I and II classes combined is ~30%. Under that assumption, the total incidence of FAS in Roubaix over this period would be approximately $(0.30)(74) + 28 = 50$, for an estimated incidence of $50/21,402 = 2.3/1,000$ live births.

A study from Stockholm, Sweden, was designed as an intervention in which pregnant women were counseled not to drink; thus exposure may have been lower than usual in this population (Larsson, '83). It otherwise meets many of the required criteria for incidence estimation. Of 464 consecutive prenatal patients who were recruited and interviewed, 399 women delivered infants at participating hospitals. Heavy drinkers (at least 30 g ethanol/day) were provided with various types of support to encourage them not to drink. A blind exam of all infants was carried out by a neonatologist, using the criteria of the U.S. studies. One case of FAS was identified, for an incidence of 2.5/1,000 births.

Among all births in Göteborg, Sweden, from May 1977 until November 1987 (~7,600), 12 cases were diagnosed FAS using the U.S. criteria (Olegård et al., '79). Newborns were admitted to one of two neonatal units staffed by a group that included a research team carrying out a series of prenatal alcohol studies. The rate of identified cases at birth (considered by the authors to be likely an underestimate) was 1.6/1,000.

Other researchers have examined cohorts of infants with various protocols, but these studies did not achieve systematic ascertainment, so their rates are possibly underestimates of incidence. One such study was carried out on Ile de la Réunion, a French island in the Indian Ocean, with an impoverished population of black, Asian Indian, and white inhabitants having a death rate from alcoholism seven times the French rate (Lesure, '88). Only "severe" FAS cases were enumerated, using the Dehaene criteria described earlier. Maternal alcoholism was confirmed by biologic mark-

ers. The frequency of FAS full cases between 1976 and 1982 was estimated at 6/1,000 live births.

Several large population-based studies (e.g., Lumley et al., '85) have relied on medical records with unspecified examiners and diagnostic criteria to estimate incidence. The CDC Birth Defects Monitoring Program has most recently reported the incidence of reported cases of FAS as .67/1,000, a rate that has been increasing in recent years (CDCP, '95a). We do not review these studies since they are subject to many of the biases of passive surveillance systems and registries.

Evaluation of existing data

Our estimate of the Seattle incidence, 2.8/1,000 live births, lies between the higher rate, 4.6/1,000, in the more disadvantaged group from Cleveland and the lower rates typically found in lower risk populations. Systematic studies of FAS on the European mainland have yielded similar, although slightly lower incidences, depending on the diagnostic criteria used and, of course, on the exposure profile of the target population.

Clearly, some subgroups of women with a high proportion of problem drinkers have higher rates of FAS. In North America, some populations of American Indians are at particularly high risk. There are no adequate incidence data, to our knowledge, but the prevalence (not incidence) of FAS (existing cases) has been reported to be between 1.3 and 10.3/1,000 (May et al., '83), depending on attitudes and customs regarding alcohol abuse in different American Indian communities. Robinson and colleagues ('87) found an FAS prevalence of 125/1,000 in a small Canadian Indian community where alcoholism was rampant. Both black and American Indian women have been identified by Center for Disease Control surveillance systems as at high risk of producing an alcohol-affected child (Chavez et al., '88). The risk of FAS appears to be greater in the presence of the low socioeconomic status, poverty, and lack of education that often accompany abusive drinking; women who drink and have these characteristics appear to be at higher risk of having an FAS child than women who are more advantaged. However, if drinking continues long enough, many women will become poor, malnourished, and of low economic status.

In the Seattle study, both FAS babies identified at birth without prior knowledge of exposure history were from mothers living on public assistance, although only 8% of the Seattle study mothers had this characteristic (Hanson et al., '78). One mother was black and the other American Indian, although only 9% and 0.7% of the sample mothers were black and American Indian, respectively. (Note: Abel, '95, and the IOM, '96, incorrectly report both of these cases as black.) In Seattle, Cleveland, and Roubaix, the mothers of children identified with FAS were most likely to be both alcoholic and poor. Those in Cleveland and Seattle were racial minorities, but in Roubaix they were all white.

A series of reports by Abel ('95) and Abel and Sokol

('87, '91) have estimated FAS incidence "in the Western world" first as 1.9/1,000, then .33/1,000, and most recently .97/1,000. The most recent report by Abel ('95), pools the data from 29 prospective studies, varying immensely in sample size and ascertainment strategy; most do not meet the minimal criteria for FAS incidence estimation discussed above. It is difficult to imagine a statistical sampling design justifying an estimate of incidence for the "Western world."

ESTIMATING INCIDENCE OF ARND

The "diagnosis" of fetal alcohol effects or ARBD and ARND and the estimation of their incidence are more difficult than that of FAS. The specificity of the FAS diagnosis for alcohol makes it clinically useful and scientifically meaningful. ARBD and ARND, however, are not syndromes in the classic sense, but the presentation of FAS signs individually associated with, but not specific to, prenatal alcohol exposure. They can be "lower dose" manifestations of FAS, but they can also reflect the timing of exposure, dose of teratogen, genetic factors in mother or fetus affecting metabolism or susceptibility, and interactions with other environmental exposures, all known to modify outcome to potentially teratogenic exposures (Chernoff, '80; Hanson, '90; Goodlett and West, '92; Streissguth and Dehaene, '93).

In this section, we utilize the extensive neurobehavioral data base of the Seattle study to identify cases of "true" ARND (i.e., effects specific to alcohol exposure) in 7-year-old children, and thereby estimate a minimum rate (not really an incidence, as explained below) for these effects.

In the Seattle study already described, 581 children had sufficient psychometric assessments from birth through age 7 to be considered for analysis (Streissguth et al., '93). These consisted of all the "exposed" subjects as defined above and a sample of all subjects with lower levels of exposure. Through age 7, there were five waves of psychometric observations in the laboratory from which 474 separate neurobehavioral outcome variables were selected for a longitudinal analysis. These outcome variables were divided into 15 blocks of variables according to age of measurement and type of outcome: *Attention* and *Neuromotor* at ages 1 day, 8 and 18 months, and 4 and 7 years, *Mental* at ages 8 and 18 months and 4 and 7 years, and *Learning Disability* at age 7 years.

The definition of "exposed" subjects refers to measures of average maternal consumption of absolute alcohol in ounces per day, together with indications of binge consumption (5 or more drinks on an occasion) in each of two periods, prepregnancy recognition, and midpregnancy. These are four of a total of 13 different measures of alcohol consumption used to encode variations in the timing and pattern of drinking behavior. Other measures included number of drinking occasions per month, average number of drinks per drinking occasion, maximum number of drinks on a drinking occasion, and a quantity-frequency-variability scale

published by Cahalan et al. ('69). An alcohol latent variable (LV) was computed as a linear combination of these 13 (nonlinearly transformed) alcohol scores to show the highest mean squared covariance with the set of 474 outcomes as a whole. Simultaneously, for each of the 15 blocks, an outcome LV was computed as a linear combination of the corresponding outcome scores to show the highest covariance with the alcohol LV, which is considered as an estimate of true alcohol dose. High scores on the outcome LVs represent neurobehavioral deficits. This Partial Least Squares approach to analysis is explained in detail elsewhere (Sampson et al., '89; Carmichael Olson et al., '92; Streissguth et al., '93; Bookstein et al., '96).

This resulted in 16 LV scores for each of the children in our study: one for dose (alcohol) and one for each of the 15 outcome (neurobehavioral) blocks. The alcohol LV weights the binge measures more heavily than the average volume measures, and the prepregnancy recognition measures more than those for midpregnancy. The most salient outcomes span the 7 years, including items from the Brazelton neonatal exam (e.g., habituation to light and incurvation threshold) as well as items from our age 7 neuromotor exam. These include tests of copying designs, memory for designs, memory for stories, and differentiating rhythmical patterns. Salient outcomes from other blocks defining the pattern of alcohol-related deficits at 4 and 7 years include IQ and achievement measures of arithmetic, teacher ratings of attention and cooperation/impulsivity, overall ratings of academic adjustment, and false alarms on laboratory vigilance tests.

For each outcome LV, we explored the top 5% of its values, the top 7.5%, etc., to see which of those cases exceeded the corresponding percentile of alcohol dose. Then, for each of the resulting "high-dose, high-deficit" cases, we examined all the earlier or later outcome blocks to see which of these cases were systematically high (although not necessarily in the extreme tail) on all of these other outcomes.

Of all of these tentative screenings, the best, in our judgment, was for the 7.5 percentile of the Neuromotor outcome block at age 7. For this outcome we found the largest number of children who were in the extreme percentile range of both alcohol exposure and outcome and had nearly uniformly high deficit scores (substantially worse than average) on all the other outcome blocks. Of the 44 children in the top 7.5 percentile of this LV score, 13 were also in the top 7.5 percentile range for alcohol dose. Of these 13, 11 had never been better (i.e. less deficient) than average on *any* of the earlier outcome blocks. Further detail is available in Streissguth et al. ('93).

One of the two children with FAS identified at birth was examined but not included in the analysis just described (because of extreme outlying alcohol scores). Restoring this child to the analysis, this computational filter identifies 12 children showing a continuing pattern of *alcohol-related deficits* in repeated exams across

the full spectrum of neurobehavioral measures; all having high levels of alcohol exposure. We, therefore, regard them as "true ARND," i.e., having enduring alcohol-related deficits consequent to prenatal alcohol exposure, even though we cannot observe this causation in any more direct way. This rate of $12/1439 = 8.3/1,000$ for cases considered FAS and/or ARND is approximately three times the incidence of FAS alone in the sample. (As the "observations" involved here range over 7 years of life, this number is not a birth incidence.) Only four additional children in the screening sample of 1439 were "exposed" (had alcohol LV scores above the 7.5 percentile cutoff used here) but not included in the follow-up study. Adjustment for this under-ascertainment of "exposed" cases increases the estimated rate slightly, to $(12/1439) \times (49/45) = 9.1/1,000$.

DISCUSSION

Our procedure here may be construed as a tentative operationalization of the new definition of ARND recently published by the Institute of Medicine ('96). The definition, given under the heading of "Diagnostic Criteria" (their Table 1), is a subtle one, worth citing in full (see Table 1).

The diagnostic criteria suggested by the IOM report involve five conceptual entities: (1) a history of prenatal alcohol exposure involving "a pattern of excessive intake," (2) research linking that exposure to an observed outcome, and either (3) the presence of CNS neurodevelopmental abnormalities, or (4) evidence for a pattern of neurobehavioral abnormalities for which, furthermore, there is (5) insufficient explanation by "familial background or environment alone." The procedure just reviewed combines aspects (1), (2), and (4) in a single empirical computation.

We have combined (1), (2), (4), above, and a subset of (3) (excluding structural or morphometric abnormalities) in a "dose-response calibration" of alcohol teratogenesis. We specify a complex "pattern of excessive intake" combining separate dose measurements (the items included in IOM footnote [1]) and a comparably complex pattern of neurobehavioral anomalies by requiring the dose pattern to optimally explain (covary with) the outcome pattern, and vice versa. In this setting, there is no further role to be played by IOM concern (5), competing explanation by "familial background or environment"; as we showed in Streissguth et al. ('93), neither factor helps explain the particular complex "patterns" of outcome that emerge, and so this concern is nullified.

Our recommendation in this matter is strongly conditioned by our interest in providing a diagnosis of ARND that can actually serve as the basis for epidemiology; a diagnosis that characterizes individual cases stably over development. Our "diagnosis" is a diachronic observation, a matter of consistency over time in the apparent sequelae of alcohol teratogenesis. It is stringent in contrast to the usual clinical setting in that it would

exclude children observed to be atypically deficient in performance at only a single testing age. Also, we do not wish a diagnosis that, by excluding patterns that can "be explained by familial background or environment alone," requires us to decide what constitutes such an "explanation" in the individual case, and so systematically lowers the rates of ARND in disadvantaged groups for which the extent of that competing "explanation" is most uncertain. We circumvent the confound of joint socioeconomic causes of behavioral deficits by observing a wide variety of such outcomes, wider than can be collected by any single test battery or at any single age of evaluation.

Because our detection protocol is built around a dose-response relation between exposure and a pattern of outcomes, it can be used toward three goals that have hitherto proved refractory in the epidemiology of fetal alcohol effects: (1) the adjustment of differences in population rates for differences in population patterns of alcohol abuse, (2) the actuarial estimation of the numbers of cases "saved" as a result of changes in those drinking patterns induced by governmental actions such as labeling laws or taxation, and, most importantly (3) the assessment of the effects of active interventions on cases once they are labeled as ARND at early ages.

This protocol for estimating ARND required extensive examination of the birth cohort over many years. We would encourage additional studies to validate this approach. Studies in which the profile of effects of alcohol exposure can be distinguished from those of other teratogens used by the drinking population are also needed. We hope to see studies that attempt to characterize ARND using a single screening profile, rather than the 15 neurobehavior profiles used here, or that otherwise extend this laboratory-based neuromotor score into a more realistic screening protocol in the clinical setting. As the studies described here were initiated over 20 years ago, and Little et al. ('90) have shown that alcohol-affected babies are not being systematically screened at birth, further research on improved screening diagnostic procedures is needed.

The identification of alcohol-affected offspring is complicated by the absence of biological markers. The only biomarker of alcohol's impact on the fetus is the face of FAS and that alone is not a very good indicator of the known neuropsychological effects of alcohol. To date, there are no other biological features known that are sufficiently specific as markers. The logical place to look for such biomarkers of the neuropsychological effects of fetal alcohol exposure is in the brain itself. Modern neuroimaging methods (MRI, fMRI, PET, and associated statistical methods of analysis) may in the future yield such markers. If we are able to find neurological markers, then these could supplant the 7-year testing sequence that we have resorted to in this study.

The only U.S. studies permitting reliable estimation of the incidence of FAS show rates of 2.8/1,000 and 4.6/1,000. These rates reflect, respectively, a relatively

low-risk, middle-class population in Seattle in the mid-1970s and a low SES, high-risk population in Cleveland of the late 1970s. Comparable rates have been reported by similar studies in Europe. These figures for major prenatal alcohol effects, together with our estimate of a combined FAS and ARND prevalence of 9.1/1,000 in Seattle, confirm the perception of many public health and medical professionals that fetal alcohol exposure is a serious problem.

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