Fetal Alcohol Syndrome
PAST, PRESENT AND FUTURE

Kenneth R. Warren, Ph.D.
Deputy Director
National Institute on Alcohol Abuse and Alcoholism
Some Challenges in FASD

- The agent responsible for FASD is alcohol

- Alcohol has a diversity of toxic (teratologic) effects on the developing embryo and fetus, and these adverse effects can occur across the total embryonic and gestational course of pregnancy

- Some of the most serious adverse effects can occur in the early phase of pregnancy often before a woman’s self-awareness that a pregnancy has commenced
Some Challenges in FASD Prevention

- Coupled to these facts, the consumption of alcoholic beverages is an accepted and widely practiced social behavior, for both men and women, throughout a great part of the world.
- We now know that alcohol should be avoided during pregnancy, but during almost ¾ of the 20th century it was believed by the medical community and public that alcohol was safe in pregnancy, at any dose and at any time.
- Was this always the view of medicine?
- If not, what brought about this misunderstanding?
Some Historical Viewpoints

• Observations on the risks associated with alcohol in pregnancy have been noted in history

• One of the earliest occurred almost 300 years ago in 1725 as a partition from the London College of Physicians to the House of Commons during the London Gin Epidemic. It stated...
We... do think it our Duty most humbly to represent that we have with concern observed, for some years past, the fatal effects of the frequent use of several sorts of distilled Spirituous Liquors... and too often the cause of weak, feeble, distempered children, who must be instead of an advantage and strength, a charge to their Country.
25 Years Later…

GIN LANE
William Hogarth
1751
Depiction of the London Gin Epidemic

Pawn shop, coffin maker and ginneries prospering

Man hanging from rafters

Wasting disease

Baby dropped over railing

NIH National Institute on Alcohol Abuse and Alcoholism
Henry Fielding, Esq.

- Henry Fielding *An enquiry into the causes of the late increase of robbers...with some proposals for remedying this growing evil.* London: A. Millar; 1751.

- “What must become an infant who is conceived in Gin? With the poisonous distillations of which it is nourished, both in the Womb and at the Breast” -- 1751 quote of Henry Fielding

Hogarth and Fielding had more success in that Parliament shortly afterward ended the epidemic.
In the writings of the London College of Physicians, Henry Fielding, William Hogarth, etc., it is not alcohol, per se, that is considered to be the offending agent, but rather the distilled spirit Gin.
In William Hogarth’s etching *BEER STREET*, the drinking of beer is envisioned with health and prosperity.

Pawn shop is in decay

Brewery and all other businesses are thriving

No longer is there a coffin maker shop
19th Century and Stout

But malt products and their risk for pregnancy outcome do appear in writings by the 19th Century

Charles Dickens in 1836 *Pickwick Papers* presents the character Betsy Martin “...one child, one eye...knows her mother drank bottled stout, and shouldn’t wonder if that caused it”. 
Many of the writings are unclear as to whether alcohol effects on children were being ascribed to:

- alcohol consumption in pregnancy;
- male and/or female alcohol use at the time of conception or before conception;
- damage to genetic factors (germ cells);
- toxic damage to the fetus from alcohol-exposure in the womb (teratology);
- alcohol exposure post pregnancy;
- or even the direct feeding of alcohol, in place of breast milk, to the infant.
Sullivan 1899

• First true epidemiological study.

• Liverpool Jail
  
  600 children of 120 alcoholic women
  28 non-drinking relative controls

• Infant mortality 2-1/2 times higher

• Healthy children with forced abstinence in prison

*Image: the convict nursery at Brixton
1904 Ballantyne

• J.W. Ballantyne, in the 1904 *Manual of Antenatal Pathology and Hygiene*, divided pregnancy into the germinal, embryonic and fetal stages.

• He noted that alcohol can act in all three phases causing:
  – *structural abnormalities* in the first phases,
  – And, abortion, and premature labor in the latter two.
Alcohol and Pregnancy in Temperance Campaigns

• During the pre-prohibition era, Temperance societies mounted extensive campaigns that included research findings from early investigations on the adverse effects of alcohol, including those related to adverse fetal outcome, in their efforts to impose Alcohol Prohibition.

• Many brochures and posters published in the early 20th Century by Temperance organizations* conveyed findings from early epidemiologic studies of alcohol on pregnancy

* A misnomer since as early as 1850 these societies had already moved from advocating temperance to advocating total abstinence through prohibition.

FOR EXAMPLE........
W.C. Sullivan, M.D.  
1906  
“Alcoholism”
Deaths of Babies Increased as Mothers Became More Alcoholized
Studies of 444 Children of 120 Alcoholic Mothers

First Born 80 Children
33.7% Died

Second Born 80 Children
50% Died

Third Born 80 Children
52.6% Died

Fourth and Fifth Born 111 Children
65.7% Died

Sixth to Tenth Born 93 Children
72% Died

Of the Living Children 4.1% were Epileptic
Others were Mentally Defective

W.C. Sullivan, M.D. "Alcoholism" 1906
Laitinen XII
International Congress on Alcoholism, 1909

“Statistics of 19,519 children in 5,735 families”
Austria, 1914
Study from Berne, Switzerland
*Influence of Alcohol on the Child* 1878-1879

Compared children of 10 Temperant and 10 Intemperant Families

**Saint Vitus Dance** is a disease characterized by rapid, uncoordinated jerking movements affecting primarily the face, feet and hands. Sydenham’s chorea (SC) results from childhood infection with Group A beta-hemolytic *Streptococci.*
Parents' Drinking Weakens Children's Vitality

Comparison of Children in 50 Abstaining and 59 Drinking Families in One Village in Finland

<table>
<thead>
<tr>
<th>Category</th>
<th>Abstaining Families</th>
<th>Drinking Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakly children</td>
<td>1.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Children who died</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstaining Families</td>
<td>18.5%</td>
<td></td>
</tr>
<tr>
<td>Drinking Families</td>
<td></td>
<td>24.8%</td>
</tr>
</tbody>
</table>

Drink menaces vigor and lives of children

Prof. Toivo Luftinen, University of Helsingfors, Report XII. International Congress on Alcoholism, 1909.
The campaigns of the Temperance Societies did result in the introduction of Prohibition not only in the U.S. but in many European countries as well.
Alcohol Prohibition

- Russia (1914 – 1927)
- Canada (1917 – 1927)
- United States (1919 – 1933)
More Prohibition in Europe in Early 20th Century

- France (1916)
- Iceland (1915-1922) – beer was still prohibited until 1989
- Norway (1916–1927)–fortified wine and beer also prohibited from 1917-1923
- Hungary (1919)
- Finland (1919-1932)
Post-Prohibition Backlash

Impact on Views of Safety of Alcohol in Pregnancy
Post-Prohibition Mid-20th Century Views on Alcohol and Pregnancy Risk

- Post-Prohibition literature rejected all pre-prohibition literature, perhaps because of its moralistic tone.
- “...the idea of germ poisoning by alcohol in humans may be safely dismissed..., Jellinek, E.M., and Jolliffe, N. Journal of Studies on Alcohol. Vol. 1, Number 1, pg 110-181 (1940)
- …mental deficiencies are due to “poor stock” of alcoholic families. Alcohol Explored, Haggard and Jellinek, 1942
- Mark Keller (1955) “the old notions about children of drunken parents being born defective can be cast aside…”

* Popular Pamplet #3, Rutgers Centers for the Study of Alcohol
Alcohol Enters Obstetric Practice

- Given the accepted safety of alcohol with respect to pregnancy, it is not surprising that the danger of using alcohol in a new obstetric procedure would be missed.

- In the mid-1960s the use of very high dose alcohol to treat threatening pre-mature labor – the “alcohol drip” was introduced.

With alcohol now accepted for use in obstetric practice – it is not surprising that the publications in 1973 by Ken Jones and David Smith – and the uncovering of a similar report from 1967 by Paul Lemoine – did not initially garner overwhelming endorsement from any medical group.
Confirmatory Research

- But the Jones and Smith findings did ignite an interest in a small group of researchers who used animal models and human epidemiologic exploration to confirm the initial reports on FAS (1973 – 1977).
- In 1977, NIAAA organized the first international meeting on FAS for researcher to present and discuss their findings to date.
- Findings were sufficiently compelling that attendees recommended the issuance of a health advisory on FAS.
- Advisory was released in U.S. on June 1, 1977.
- Tone of advisory was “conservative” – only cautioned against heavier drinking.
“Recent research reports indicate that heavy use of alcohol... during pregnancy may result in... The Fetal Alcohol Syndrome.”

“Given the... evidence available... pregnant women should be particularly conscious of the extent of their drinking. While safe limits are not known... risk is established... above 6 drinks per day....”

Recommended not more than 2 drinks per day.

June 1, 1977
As evidence increased and public reaction changed, an updated FAS Advisor was issued in the U.S. by the Surgeon General.

This time, the perspective had changed from “safe until proven dangerous, to advise caution until proven safe.”

“The Surgeon General advises women who are pregnant (or considering pregnancy) not to drink alcoholic beverages and to be aware of the alcoholic contents of food and drugs….”

May 1981
The Bottle Label Issue

- In the U.S. Hearings were held in 1988
- Became Law November 1988
- Became Effective November 1989
- Department of Treasury (not Health) sets regulations on size, placement and appearance of label
French Bottle Warning Icon
TODAY

- NIAAA maintains an active research agenda to aid in the continual pursuit of Prevention of FASD and improved Clinical Care for those adversely affected by prenatal alcohol exposure.

There are multiple research issues pursued toward these goals.
Improve Diagnostic Capabilities to:
• Identify Women and Children in Need of Care and Services, and

• Determine the full Prevalence of all of the disorders that lie within the spectrum of FASD.
Even FAS and pFAS (no less ARND) remain under-diagnosed because:

- facial features are subtle, particularly in newborns
- The neurobehavioral deficits necessary for diagnosis may not be obvious <age 3 years
- In epidemiology, one approach that has been used to obtain more accurate prevalence is Active Case Ascertainment (Phil May presentation – upcoming)
  - It involves assessment among an entire, or representative sample population such as all 1st grade school entry students
  - It is the most expensive in money and time – but it affords the most reliable prevalence rates – especially for FAS and pFAS
- This method reveals prevalence up to 10 times greater than previous estimates which were based primarily on clinic based prospective studies, other clinical studies and registries
Prevention of drinking in pregnancy through detection of risk drinking:

- Though self-reports of drinking can be informative – biomarkers of alcohol use disclose far greater levels of risk.

- One biomarker shown to be effective in clinical setting is the non-oxidative alcohol metabolites – fatty acid ethyl esters (FAEES) obtained from newborn meconium.
  - Limitation: reveals 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester drinking only!
  - Since obtained at birth, it is a good prevention indicator for subsequent pregnancies, but not for current one.
  - Still useful because a leading indicator of a subsequent FAS birth is having already given birth to an FAS child (77% probability).

- Research continues on other potential biomarkers including miRNA, proteomic and metabolomic profiles, as well as metabolites ethyl-glucuronide and phosphatidyl ethanol.
Given the subtlety of FAS facial deficits – to improve the acumen for FAS facial recognition through 3-D photography and computer analysis

Advantages:

- The 3-D image is suitable for **telemedicine**
- Computer is free of human eye bias
- “Machine learning” approach may be used where the computer on its own identifies key feature from known cases and controls
- The computer may even be able to see more subtle facial feature signatures in ARND. (Peter Hammond presentation –upcoming)
• Refining our understand of the complexities in the neurobehavioral phenotype associated with FAS, pFAS and ARND (i.e. ND-PAE):
  - So as to achieve more facility in the recognition of these disorders
  - And to use this knowledge in the pursuit of appropriate interventions to help those with prenatal alcohol deficits

• This is particularly important in differentiating from other developmental disorder which may have similar phenotypes but which require distinct pharmacologic or behavioral interventions – such as ADHD – and genetic disorders…
Answering the question: Is the face a window on the brain?

As we refine our understanding of the specific CNS deficits – clues to guiding us to the appropriate interventions may derive from an enhanced understanding of the relationship between facial features and underlying CNS structural deficits in FASD

– Imaging research over the past 20 years has demonstrated structural brain deficits in specific brain areas:

- Corpus callosum (hypoplasia or total absence)
- Anterior Vermis of the Cerebellum (hypoplasia)
- Frontal lobes (too blunt)
- Parietal lobes (too narrow)
- Subcortical structures
Correlating Changes in the Face with the Brain

Courtesy of Kathy Sulik, University of North Carolina
Positive correlations between brain volume and palpebral fissure length after controlling for scan location, age, sex, and ICV in subjects with FASD. (N = 52)
Negative correlations between brain volume and lipometer scores after controlling for scan location, age, sex, and ICV in subjects with FASD. (N = 52)
Research Challenge VI: Etiology of FASD

Establishing the **Mechanisms** through which alcohol causes FAS and FASD to be able to **apply this knowledge to the Prevention and Treatment of these disorders.**

**Complication:** Alcohol appears to have many distinct actions whereby it can **elicit harm** to the developing **embryo and fetus**
Etiology of FASD

The multiple sites of alcohol’s actions in FASD include:

- Early Embryologic genes - Pax6, Otx 6, Sox 3 and NCAM, TBX5, VAX2
- Oxidative stress
- Altered apoptosis
- Epigenetic Effects on histones and DNA – (e.g., HPA axis)
- Impaired cell adhesion mechanisms, e.g., the L1 molecule and binding
- Altered response to trophic factors: IGF, NGF, ADNF (SAL), and ADNP (NAP)
- Neurotransmitter system: glutamate (NMDA); Serotonin; plus others
- Impaired glia development and migration,
- Impaired myelination
Animal model research has shown promise with respect to two different approaches:

- Stimulation through physical exercise – particularly for cerebellum related deficits
- Pre- or postnatal nutritional supplementation
Postnatal Choline Reduces the Severity of FASD

- Animal research (Jennifer Thomas) has shown that choline supplementation can mitigate alcohol’s effects on activity level and learning tasks (_hippocampal-associated_)
- Choline is effective even when administered after alcohol exposure and during a period of development equivalent to early postnatal development in humans
- The beneficial effects are observed even months after choline treatment is complete as demonstrated in a Delayed Discrimination Task…
Choline Supplementation

- NIAAA is currently supporting research with nutritional supplementations, including supplementation with choline:
  - In pregnancy
  - In young children with FAS
Other Research Challenges

- Determining the most effective approaches to incorporate interventions for at-risk drinking into pre-pregnancy and prenatal care, as well as methodology for the identification of alcohol dependence (alcoholism) in these population, and the most effective treatment approaches.

- Examining the effectiveness of Community Prevention Approaches to reduce risk drinking in pregnancy – including enhancing the public's understanding of the risks of alcohol use in pregnancy –
Recognizing that 50% of pregnancies are unplanned so that substantial prenatal alcohol exposure may have occurred before pregnancy recognition

Working to change the social norms surrounding drinking behavior whenever there is a risk of a pregnancy —
Thank You!

Kenneth R. Warren, Ph.D.
Deputy Director
National Institute on Alcohol Abuse and Alcoholism