Slide 1

Background

Fetal alcohol syndrome is among the most common known causes of mental retardation and as such, it is a major public health problem. The purpose of this lecture is to provide a basic overview of what we know about the effects of prenatal alcohol exposure. It is certainly not meant to be comprehensive. For more detailed overview, the following references might be helpful.

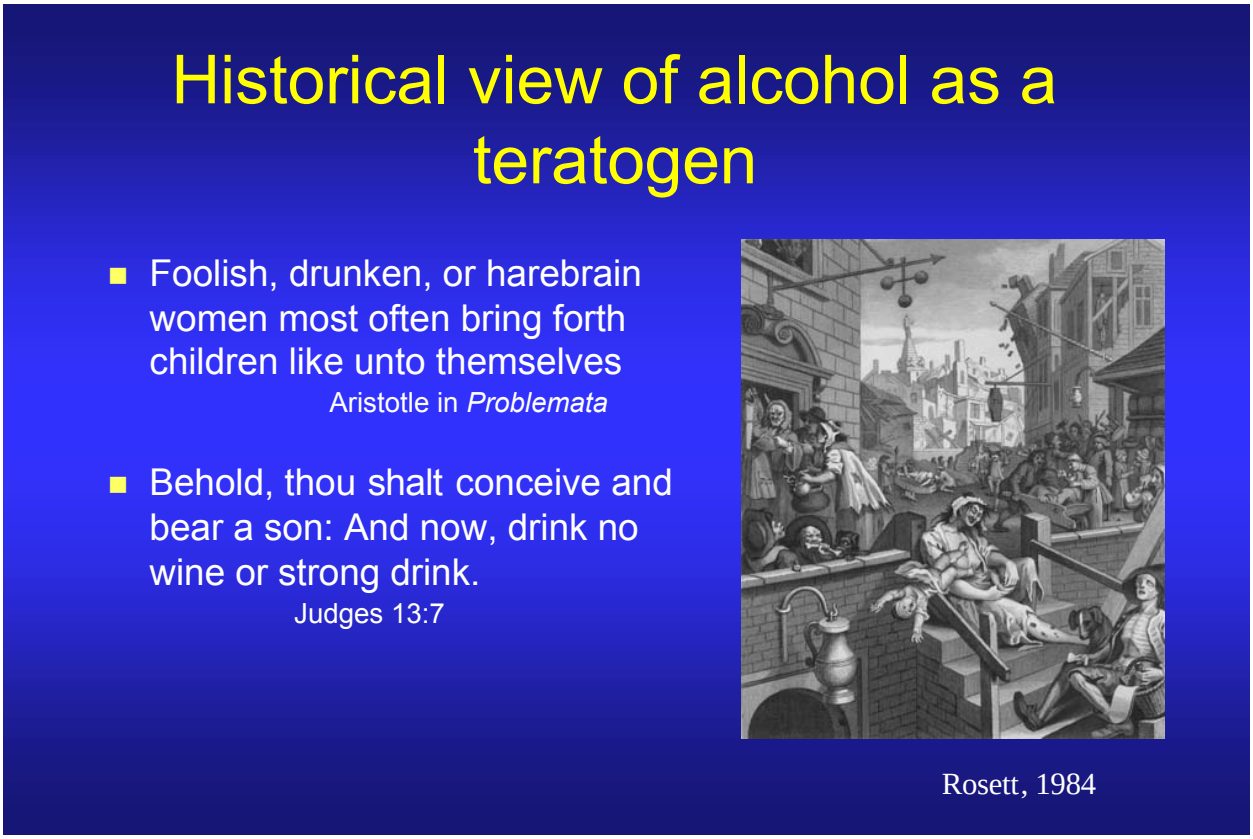
It is important to remember that as the mother consumes alcohol and her blood alcohol level rises, that alcohol is freely crossing the placenta and the embryo or fetus is being exposed to the same blood alcohol levels.

References

Stratton, K., Howe, C., & Battaglia, F. (1996). *Fetal alcohol syndrome: Diagnosis, epidemiology, prevention, and treatment*. Washington, DC: National Academy Press.

Streissguth, A. P. (1997). *Fetal Alcohol Syndrome: A Guide for Families and Communities*. Baltimore: Paul H. Brookes Publishing Co.

Slide 2



Background

The possible detrimental effects of prenatal alcohol exposure have been known for some time. On the left side of the slide are quotes to get people thinking about this; one from Aristotle and the other from the bible. The lithograph is entitled "Gin Lane" and was done by William Hogarth (1697-1764). It depicts a condition that occurred in England during the first part of the 1700s. Gin was available cheaply due to a lifting of the tax. During this period, the birth rate declined, infant mortality increased and the incidence of epilepsy increased. These were all reversed when the British College of Physicians urged the Parliament to reimpose the taxation.

There were also numerous studies conducted both in animals and in humans at the end of the 19th and beginning of the 20th centuries. All of these showed the detrimental effects of prenatal alcohol. However, for a variety reasons, including prohibition, the effects of prenatal alcohol exposure did not attract much attention. While people recognized that the offspring of alcoholics had problems they felt that these were the result of poor genetic stock rather than to any direct effects of the alcohol. For example the Journal of the American Medical Association in 1946 stated "The offspring of alcoholics have been found defective not because of alcoholism of the parents but because the parents themselves came from a defective stock." (Journal American Medical Association, 132:419, 1946). The modern era of the recognition of the detrimental effects of prenatal alcohol exposure began when Ken Jones, David Smith and associates published two papers in 1973, describing a common set of features in 11 children whose mothers were known to be alcoholics or heavy drinkers during their pregnancies. Subsequently, it was

discovered that a common pattern of anomalies had been described previously in the French medical literature in 1967 by a French physician, Philip Lemoine.

References

Jones, K. L., & Smith, D. W. (1973). Recognition of the fetal alcohol syndrome in early infancy. *Lancet, 2*, 999-1001.

Jones, K. L., Smith, D. W., Ulleland, C. N., & Streissguth, A. P. (1973). Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet, 1*, 1267-1271.

Lemoine, P., Harousseau, H., Borteyru, J.-P., & Menuet, J.-C. (1968). Les enfants de parents alcooliques: Anomalies observees. A propos de 127 cas [Children of alcoholic parents: Abnormalities observed in 127 cases]. *Ouest Medical, 21*, 476-482.

Rosett, H. L. a. W., L. (1984). *Alcohol and the Fetus: A Clinical Perspective*. New York: Oxford University Press.

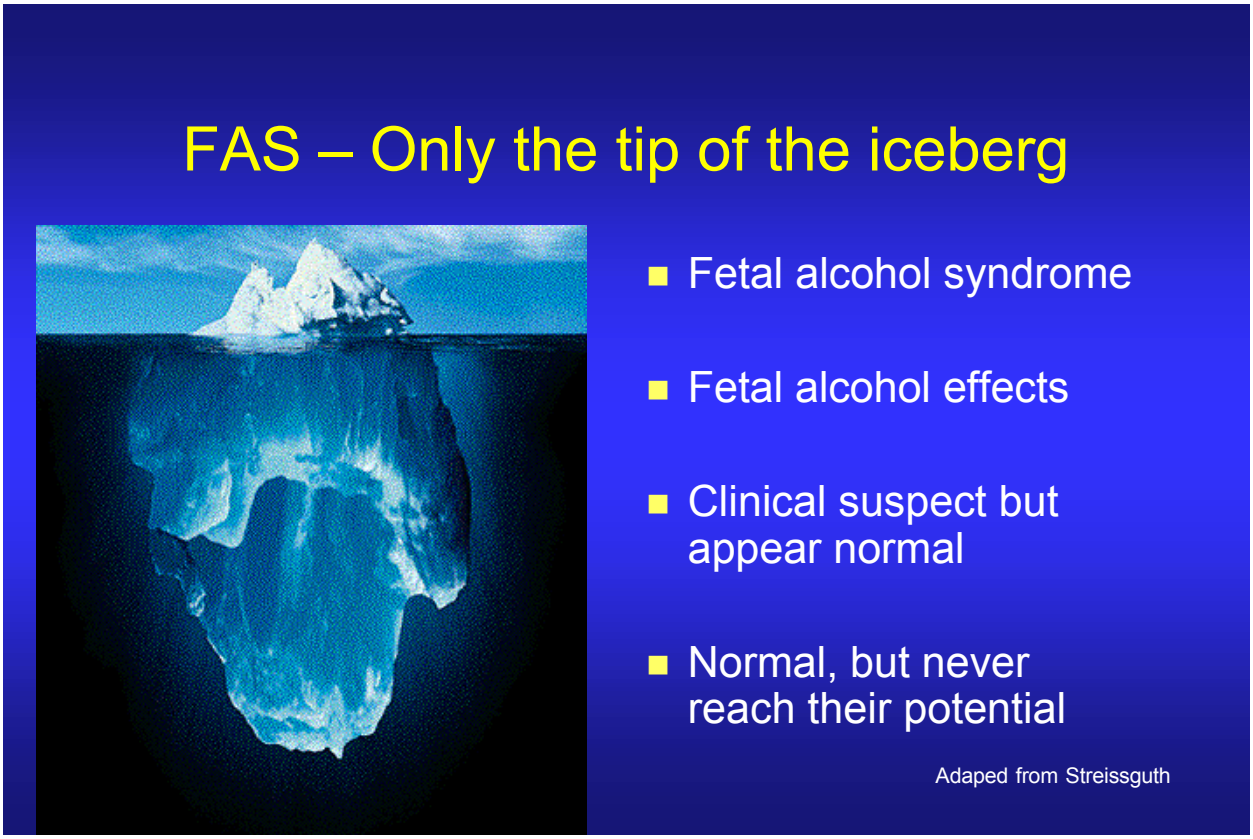
Slide 3

Background

What each of these papers described was a common set of features that could occur in the offspring of mothers who drank heavily during their pregnancies. This constellation of features was named the Fetal Alcohol Syndrome in 1973 by Jones and colleagues. In order to be diagnosed as having FAS, the individual MUST meet all three criteria. There is a specific pattern of facial anomalies, which will be shown shortly. There is pre and or postnatal growth deficiency. Usually the children are born small (<25th percentile) and remain small, at least until puberty. Finally, there must be evidence of central nervous system dysfunction. This CNS dysfunction might be physical (e.g. microcephaly) or behavioral (hyperactivity, mental retardation). There are pitfalls in the diagnosis of FAS. Sometimes the complete pattern of anomalies is not present. Various terms have been proposed for these cases (FAE – Fetal alcohol effects, ARBD – Alcohol related birth defects, ARND – Alcohol related neurobehavioral disorder), but each has its limitations and no fixed terminology has been accepted. Another problem relates to the age at which the diagnosis is conducted. It appears to be easier to diagnose this condition in young children, while the diagnosis in the neonatal period may be more difficult. Furthermore, changes in the face may occur as the individual grows into adulthood and obscure the typical facial appearance of FAS. For a more thorough discussion of the diagnosis of FAS and various related conditions, the reader is referred to the IOM report (Stratton et al, 1996).

Of concern is the 1) the necessity of documenting the exposure history of the mother, 2) the reluctance of physicians to inquire about the drinking histories of pregnant women, or women contemplating pregnancies, and 3) the fact that many physicians are not well trained or not confident in their ability to recognize these effects.

Slide 4

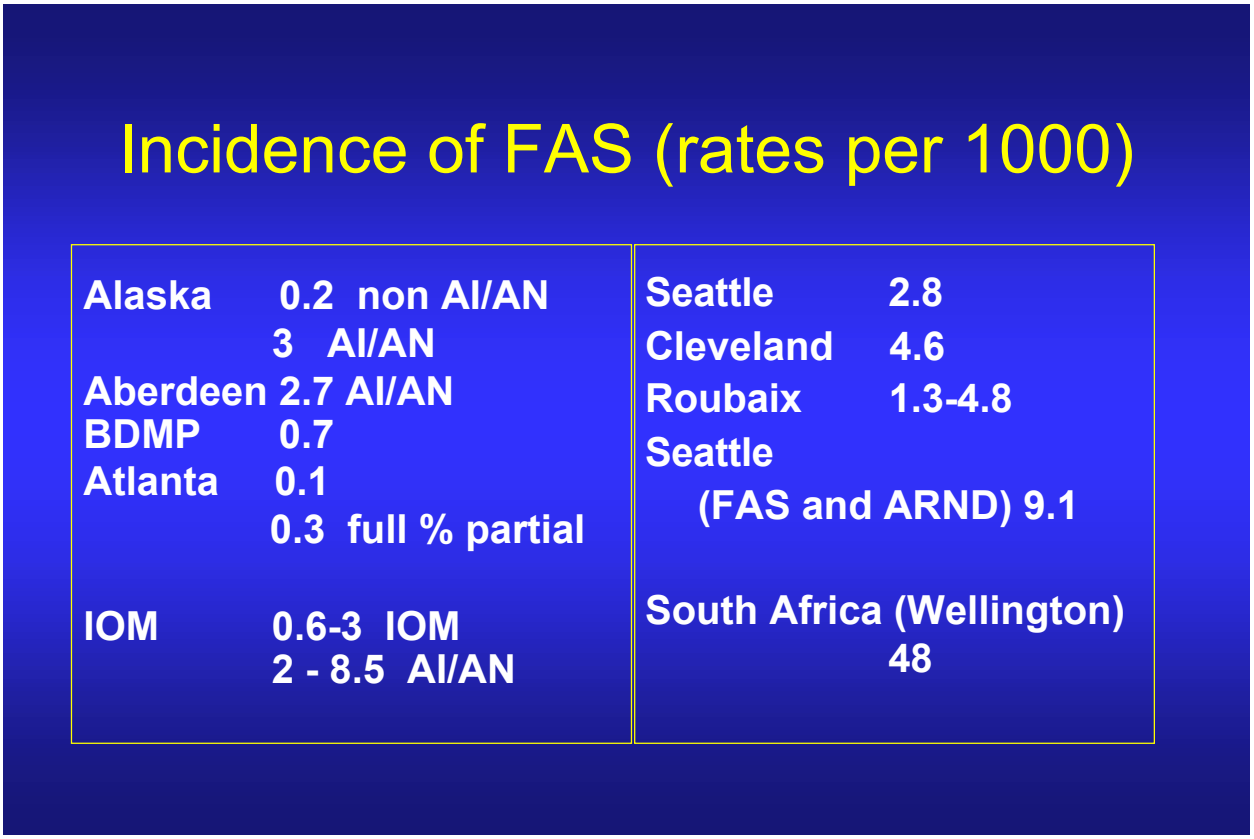


Background

This slide illustrates an extremely important point. Fetal alcohol syndrome only represents one point on what appears to be a continuum of effects from prenatal alcohol exposure. Towards one end may be fetal death and FAS. As one moves to the other end of the continuum, one may find isolated effects resulting from prenatal alcohol: maybe only some of the facial characteristics or maybe only behavioral problems. The point is that FAS represents only a small sampling of the effects of prenatal alcohol. Many more children are included when we consider those with FAE who might or might not have obvious signs of alcohol exposure, and those that do not manifest any physical features of FAS, but have behavioral problems. FAS is only the tip of the iceberg.

Interestingly only 10 – 40% of children of chronic alcohol abusers can be diagnosed as having FAS. However, there is very good data suggesting that these non-FAS children are affected, most notably behavioral and cognitive deficits. Even in children with normal IQs who have been exposed to alcohol prenatally, there is evidence that they do not live up to their true potential.

Slide 5



Background

The epidemiology of FAS is quite variable. Here are the results of recent surveys on the incidence of FAS.

The incidence of FAS is somewhere between .1/1000 and 3/1000. These are not very precise estimates, but vary depending upon the methodologies used. Also, rates can be ethnically, culturally, and regionally dependent. The incidence of FAE is considerably higher, but there are really no good estimates given the wide range of outcomes. Finally, about 12.5% of childbearing age women are at risk drinkers (>7drinks/week - 5 or more drinks per occasion).
The data on the left side of the slide come from Louise Floyd of the CDC. The first four studies were sponsored by the CDC and the other two estimates on the left side come from the IOM report (Stratton, 1996). AI/AN stands for American Indian/Alaska Native.

The numbers on the right side are from a recent study by Sampson et al., (1997). They demonstrated rates of FAS of at least 2.8/1000 live births in Seattle, 4.6/1000 in Cleveland, and between 1.3 and 4.8/1000 in Roubaix, France. Interestingly, in this study they estimate the prevalence in Seattle for FAS and ARND at 9.1/1000 births. This would mean that nearly 1 in every 100 children is affected by prenatal alcohol exposure. The last number from South Africa is from recent work done by Phil May and colleagues.

References

Egeland G, Perham-Hester KA, Gessner BD, Ingle D, Berner JE,Middaugh JP. Fetal Alcohol Syndrome in Alaska, 1977 through 1992: An administrative prevalence derived from multiple data sources. American Journal of Public Health. 1998. 88(5): 781-786.

Aberdeen IHS Area (1995) MMWR. vol 44(#):253-261. BDMP (1995): MMWR Vol. 44(13):249-253. Atlanta, Ga. (1997) MMWR Vol. 46(47): 1118-1120.

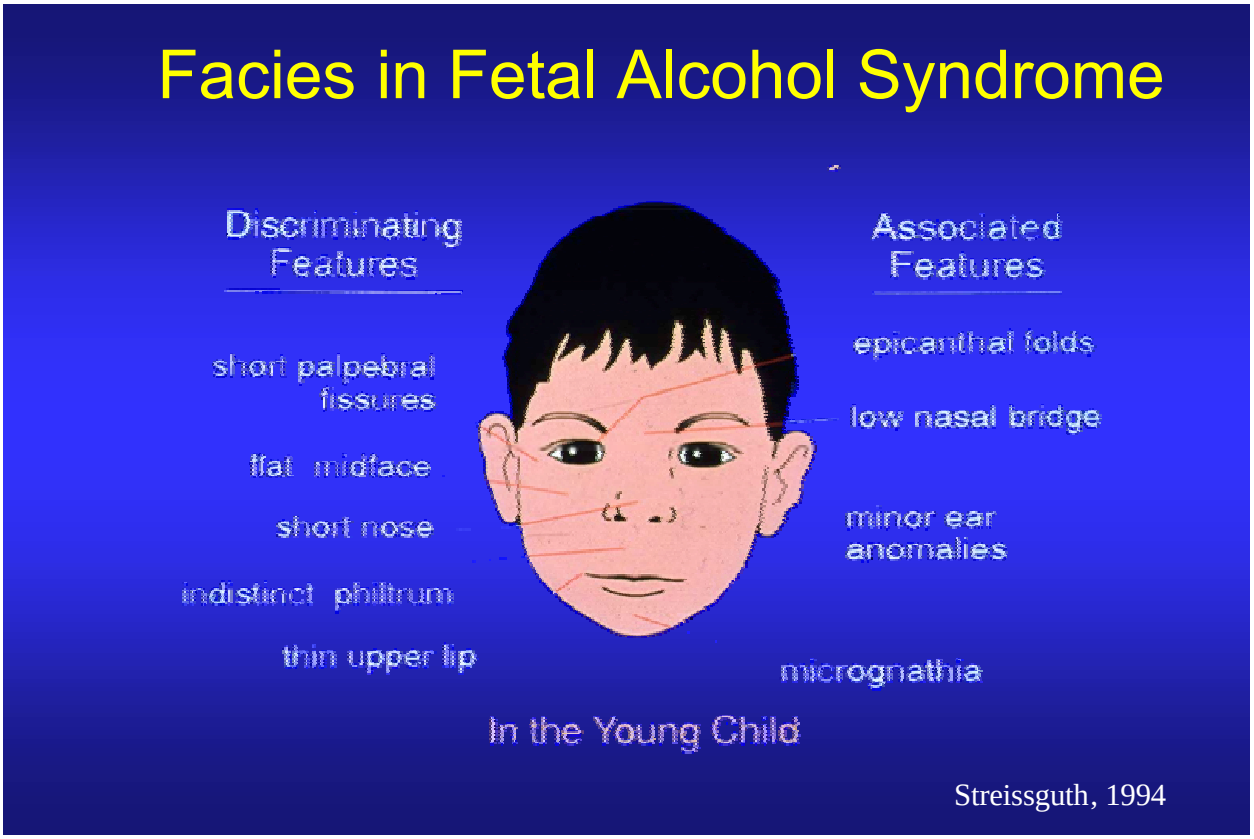
Sampson, P. D., Streissguth, A. P., Bookstein, F. L., Little, R. E., Clarren, S. K., Dehaene, P., Hanson, J. W., & Graham, J. M., Jr. (1997). Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology, 56*(5), 317-326.

Stratton, K., Howe, C., & Battaglia, F. (1996). *Fetal alcohol syndrome: Diagnosis, epidemiology, prevention, and treatment.* Washington, DC: National Academy Press. Institute of Medicine: 1996 Clinic-based (page 89), American Indian/Alaskan Native (page 88)

May, P., Viljoen, D., Gossage, J., Brooke, L., Croxford, J. (1999). An epidemiological analysis of data from children with fetal alcohol syndrome and controls in Wellington, South Africa. Alcoholism: Clinical and Experimental Research, 23 (5), 110A.

May, P., Viljoen, D., Gossage, J., Brooke, L., Croxford, J (1999). An update on the maternal risk factors associated with the prevalence of fetal alcohol syndrome in Wellington, South Africa. Alcoholism: Clinical and Experimental Research, 23 (5), 91A

Slide 6



Background

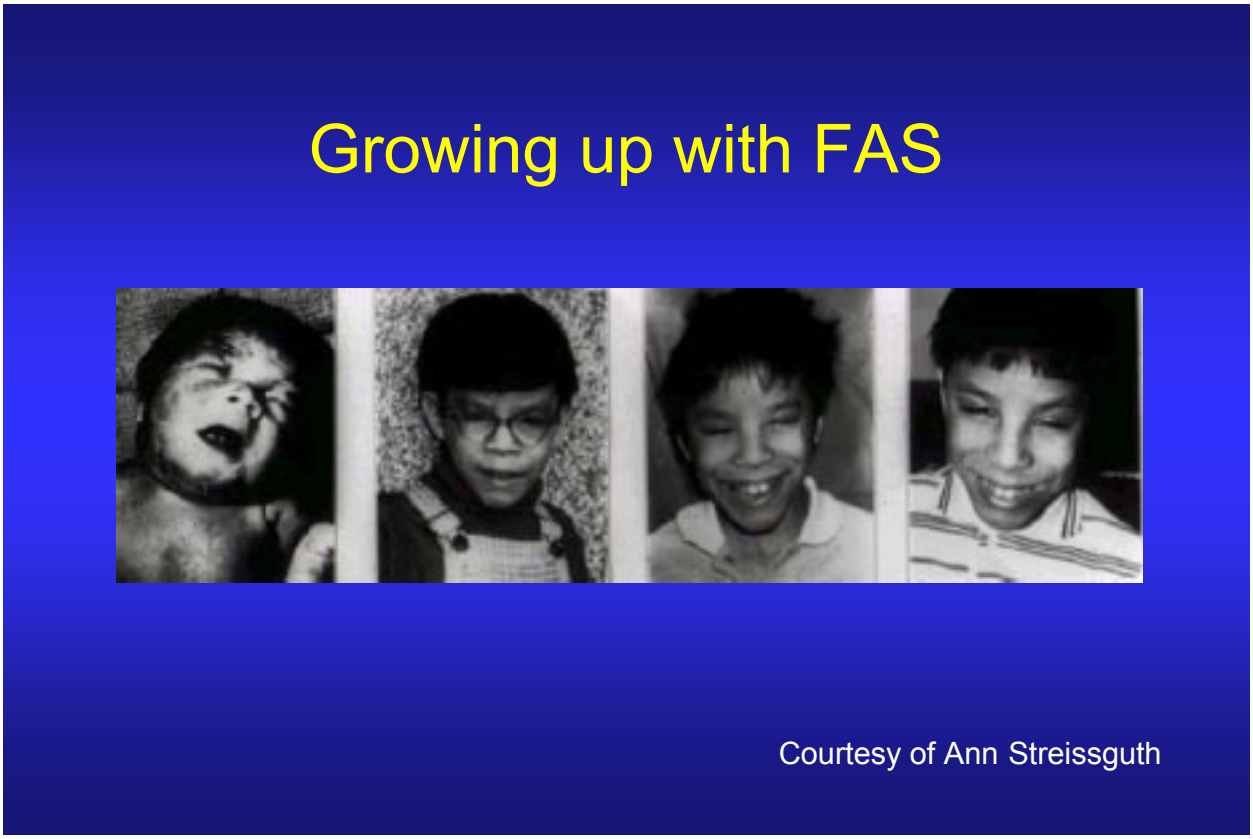
It must be stressed that the facial characteristics basically define FAS. Without these facial features, one cannot be diagnosed with FAS. In particular, the discriminating features are short palpebral fissures (the length of the eye opening), a flat midface, an indistinct or flat philtrum (the ridge under the nose), and a thin upper vermillion (lip). While each of these can occur in a variety of disorders, the combination of these features appears to be consistent with heavy prenatal alcohol exposure. Children with FAS can also have other facial features, such as epicanthal folds (tiny folds of tissues along the eye opening), a low nasal bridge, an underdeveloped jaw and minor ear anomalies.

These individuals can also have a variety of associated features. Heart defects, skeletal anomalies, altered palmar creases (those creases on your hands), and urogenital anomalies are among the anomalies found more frequently in FAS.

Reference

Streissguth, A. P. (1994). A long-term perspective of FAS , *Alcohol Health & Research World* (Vol. 18, pp. 74-81).

Slide 7



Here are two other children with FAS at four different ages. The FAS features are apparent even as these children mature.

Slide 8

Background

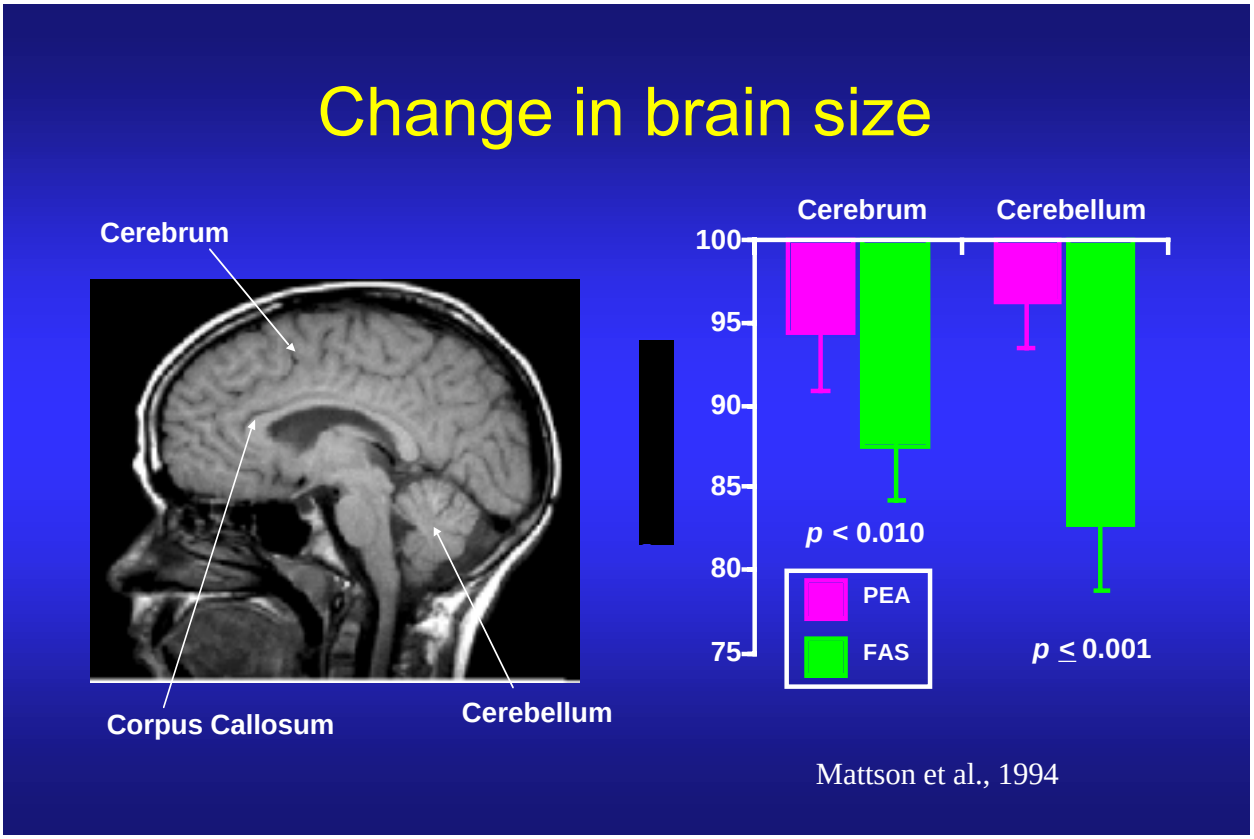
The brain on the left was obtained from a 5-day-old child with FAS while the brain on the right is a control. The effects are obvious. The brain on the left suffers from microencephaly (small brain) and migration anomalies (neural and glia cells did not migrate to their proper location in the brain, but instead many of them simply migrated to the top of the cortex). Although it cannot be seen here, there is also agenesis of the corpus callosum and the ventricles are dilated.
The corpus callosum is the major fiber tract connecting the two hemispheres of the brain (more on this later). Major findings of other autopsies of children with FAS have found microcephaly, hydrocephaly, cerebral dysgenesis, neuroglial heterotopias, corpus callosum anomalies, ventricle anomalies, and cerebellar anomalies. It must be pointed out, however, that these autopsies have typically been conducted only on the most severe cases, since these children often have enough problems that they do not survive. The interested reader on the pathological changes that occur in FAS is referred to the following articles.

References

Clarren, S. K. (1986). Neuropathology in fetal alcohol syndrome. In J. R. West (Ed.), *Alcohol and Brain Development* (pp. 158-166). New York: Oxford University Press.

Roebuck, T.M., Mattson, S.N., and Riley, E.P. (1998). A review of the neuroanatomical findings in children with fetal alcohol syndrome or prenatal exposure to alcohol. Alcoholism: Clinical and Experimental Research, 22 (2),339-344.

Slide 9



Background

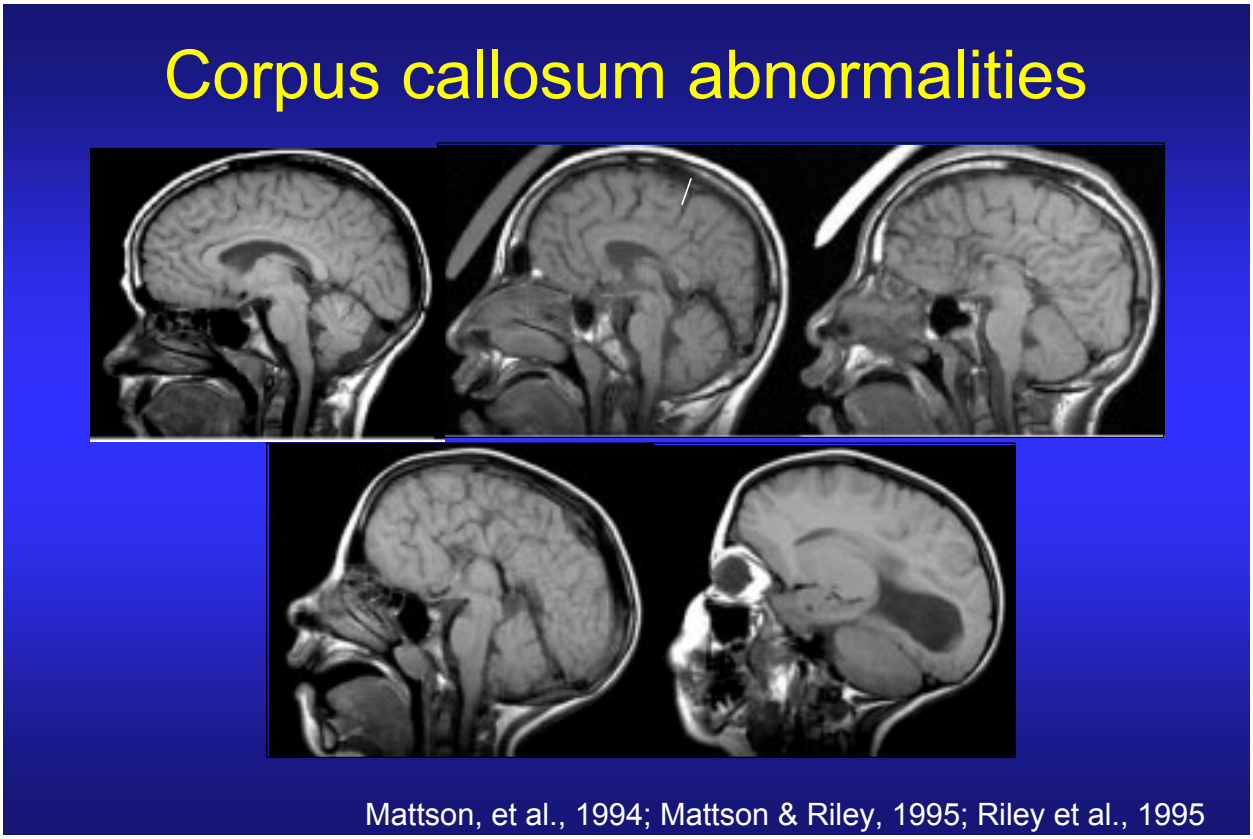
The image on the left is a normal midsaggital MRI scan of the human brain with the cerebrum and cerebellum pointed out. The data on the right show the reduction in size of the these two areas in children with FAS and PEA. PEA stands for Prenatal Exposure to Alcohol, and includes children with known histories of heavy prenatal alcohol exposure, but who lack the features necessary for a diagnosis of FAS. As can be seen, the extent of reduction in the volume of both the cerebrum and cerebellum is significant. While the PEA group shows a reduction in volume, with these sample sizes, this is not a significant difference. Other brain imaging studies indicate disproportionate size reductions in the basal ganglia, cerebellum, and corpus callosum. The data are presented as percent of normal matched controls.

References

Mattson, S. N., Jernigan, T. L., & Riley, E. P. (1994a). MRI and prenatal alcohol exposure. *Alcohol Health & Research World, 18*(1), 49-52.

Archibald, S.L., Fennema-Notestine, C., Gamst, A., Riley, E.P., Mattson, S.N., and Jernigan, T.L. (submitted, 2000). Brain dysmorphology in individuals with severe prenatal alcohol exposure.

Slide 10



Background

One anomaly that has been seen in FAS is agenesis of the corpus callosum. While not common, it occurs in FAS cases (~6%) more frequently than in the general population (0.1%) or in the developmentally disabled population (2-3%). In fact it has been suggested that FAS may be the most common cause of agenesis of the corpus callosum.

In the top left picture, is a control brain. The other images are from children with FAS. In the top middle the corpus callosum is present, but it is very thin at the posterior section of the brain. In the upper right the corpus callosum is essentially missing. The bottom two pictures are from a 9 year old girl with FAS. She has agenesis of the corpus callosum and the large dark area in the back of her brain above the cerebellum is a condition known as coprocephaly. It is essentially empty space.

Most children with FAS do have a corpus callosum, although it may be reduced in size. The reduction in size occurs primarily in the front and rear portions (genu and splenium). One interesting item is that this same pattern of reduction in the genu and splenium has been found in ADHD children. The behavioral problems seen in FAS frequently are similar to those seen in ADHD.

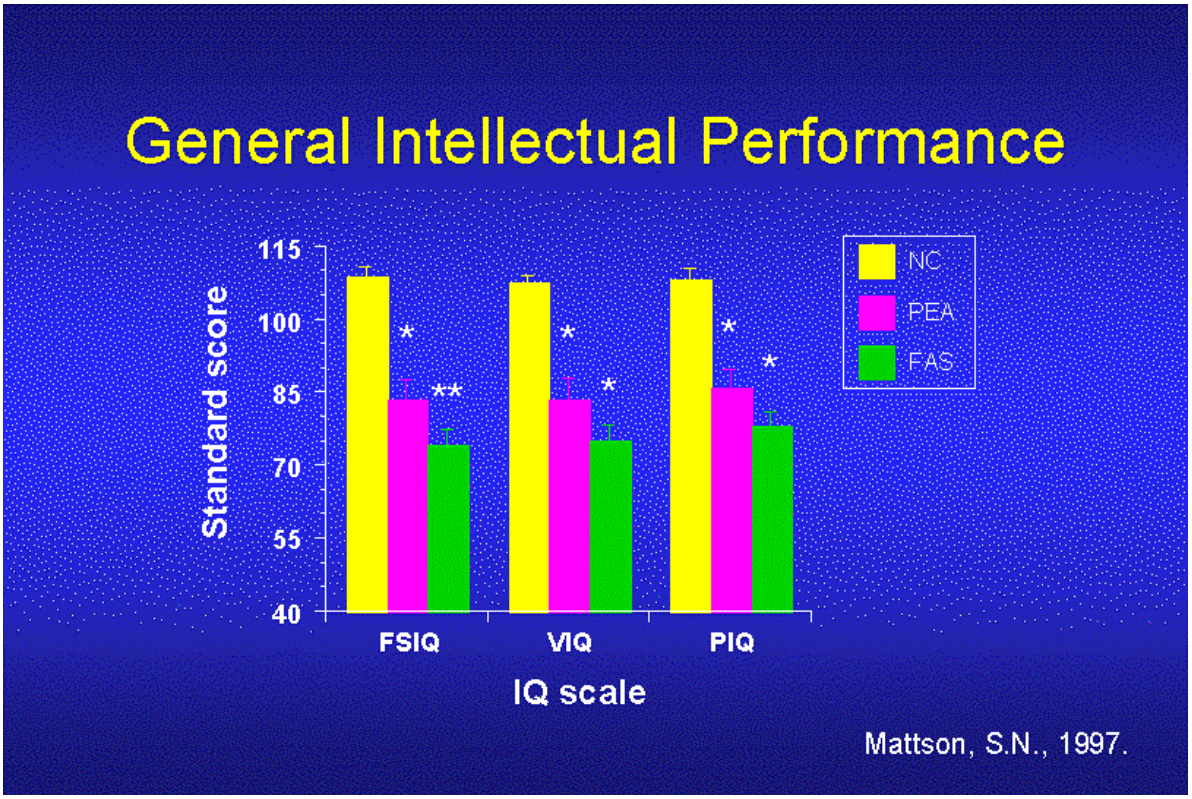
References

Mattson, S. N., Jernigan, T. L., & Riley, E. P. (1994a). MRI and prenatal alcohol exposure. *Alcohol Health & Research World, 18*(1), 49-52.

Mattson, S. N., & Riley, E. P. (1995). Prenatal exposure to alcohol: What the images reveal. *Alcohol Health & Research World, 19*(4), 273-277.

Riley, E. P., Mattson, S. N., Sowell, E. R., Jernigan, T. L., Sobel, D. F., & Jones, K. L. (1995). Abnormalities of the corpus callosum in children prenatally exposed to alcohol. *Alcoholism: Clinical and Experimental Research, 19*(5), 1198-1202.

Slide 11



Background

There have been over a dozen retrospective studies of children with FAS (total N = 269). Overall, these studies, such as the Seattle studies or studies out of Germany, reported an overall mean IQ of 72.26 (range of means = 47.4-98.2). The data presented here were collected in San Diego, CA as part of a project at the Center for Behavioral Teratology.

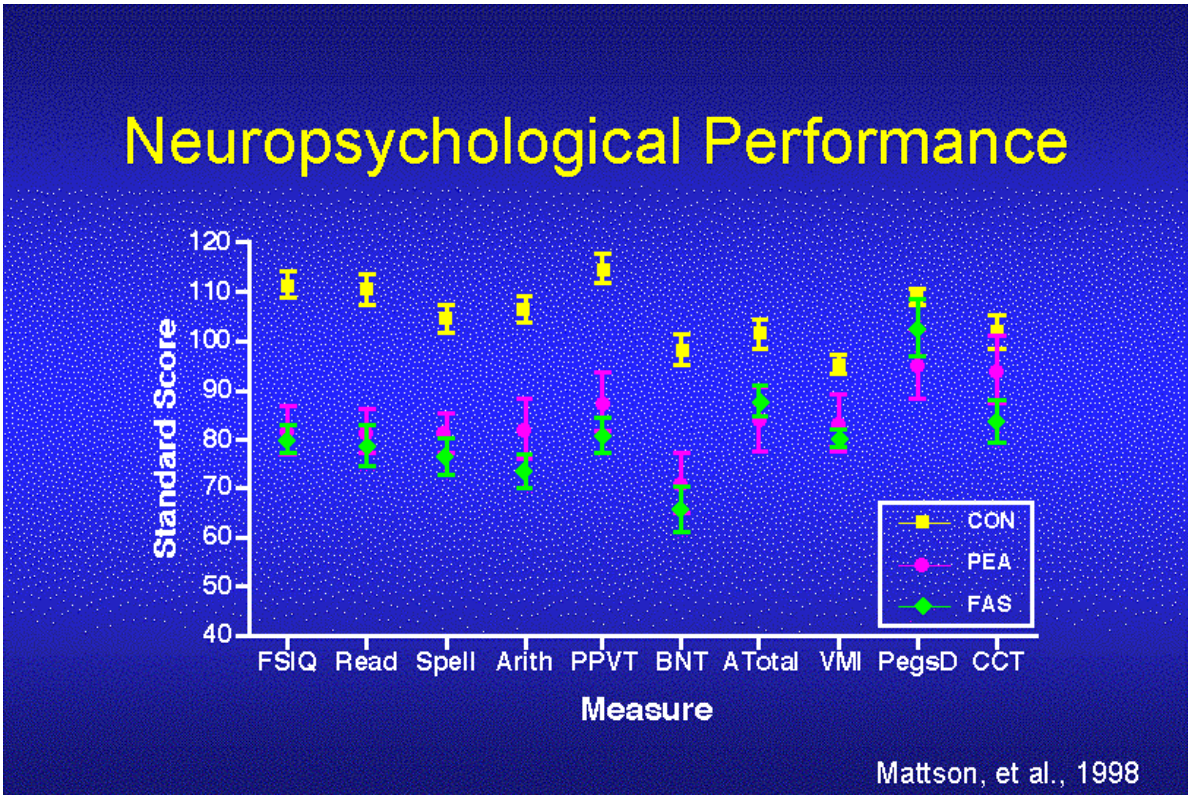
The mean IQ performances of children with FAS were compared to alcohol-exposed children with few if any features of FAS. All children in this study were exposed prenatally to high amounts of alcohol, however only the FAS group displayed the craniofacial anomalies and growth deficits associated with the diagnosis. The other group was designated as having prenatal exposure to alcohol (PEA) and had documented exposure to high levels of alcohol but were not dysmorphic, microcephalic, or growth-retarded. In comparison to normal controls, both groups of alcohol-exposed children displayed significant deficits in overall IQ measures as well as deficits on most of the subtest scores. While the PEA subjects usually obtained marginally higher IQ scores than those with FAS, few significant differences were found between the two alcohol-exposed groups. These results indicate that high levels of prenatal alcohol exposure are related to an increased risk for deficits in intellectual functioning and that these deficits can occur in children without all of the physical features required for a diagnosis of FAS. Our PEA subjects may be somewhat similar to individuals identified by other groups as having FAE, however individuals with PEA display few if any of the facial features of FAS, and are not growth retarded or microcephalic.

References

Streissguth AP, Aase JM, Clarren SK, Randels SP, LaDue RA, Smith DF (1991). Fetal alcohol syndrome in adolescents and adults. Journal of the American Medical Association 265:1961-1967.

Mattson, S.N., Riley, E.P., Gramling, L., Delis, D.C., and Jones, K.L. (1997). Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. Journal of Pediatrics, 131 (5), 718-721. Mattson, S.N. and Riley, E.P. (1998). A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. Alcoholism: Clinical and Experimental Research, 22 (2), 279-294.

Slide 12



Background

This was a study of a broad range of neuropsychological tests, such as: The Wide Range Achievement Test- which assesses academic skills, the Peabody Picture Vocabulary Test and the Boston Naming test-both assessment of basic language functioning, the California Verbal Learning Test-a list learning and memory test, the Visual-Motor Integration Test which measures basic visual-perceptual skills, the Grooved Pegboard test-a test of fine-motor speed and coordination, and the Children's Category Test-a measure of nonverbal learning.

Along the x-axis are the tests included in the battery; for comparison purposes, all scores were converted to standard scores with a mean of 100 and an SD of 15.

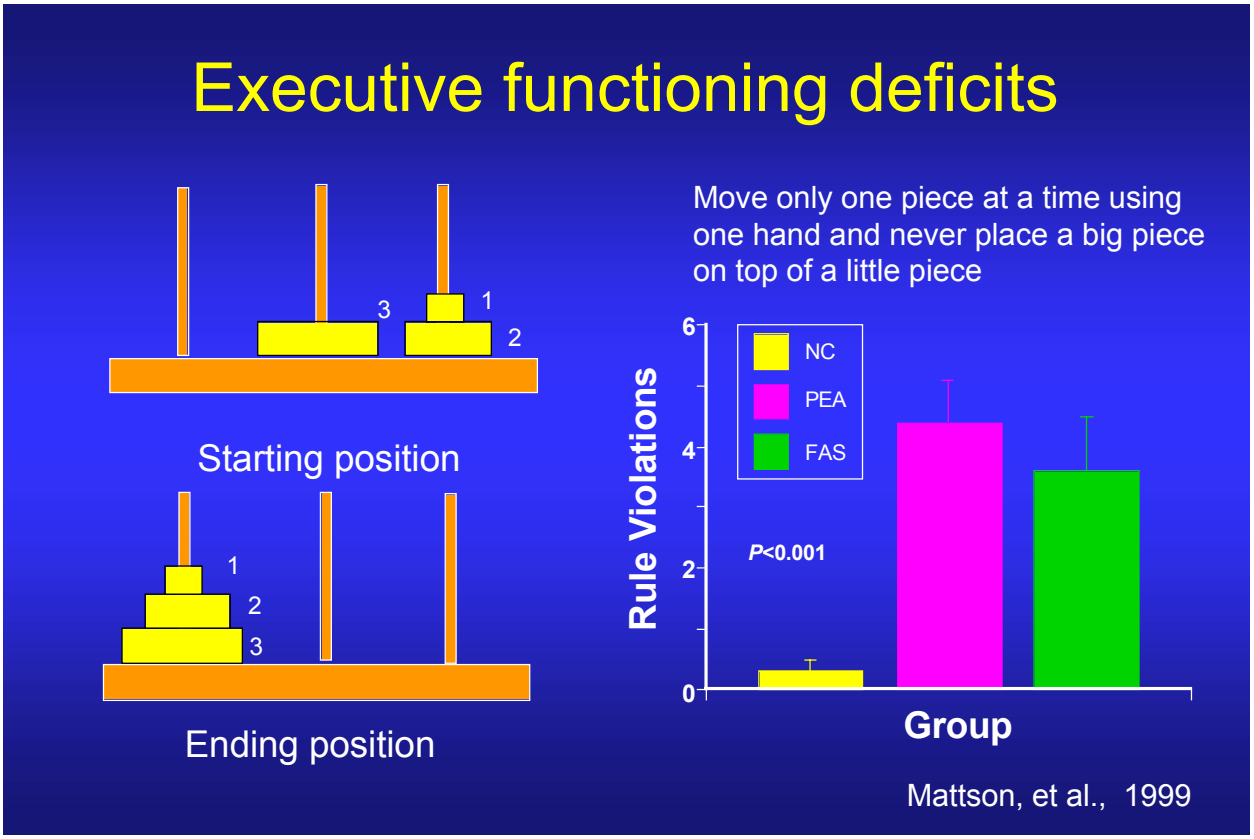
Children with FAS or PEA showed deficits in comparison to controls and they were very similar to each other. There does seem to be some indication that the nonverbal measures (on the right of the slide) are not as impaired as the verbal and academic measures, which are on the left and center of the slide.

The take home message is that children with FAS and those exposed to high amounts of alcohol, but without the characteristics required for a diagnosis of FAS, are similarly impaired. The FAS children tend to be a bit worse than the PEA children, but the pattern of behavioral deficits is fairly similar over a wide range of tests.

References

Mattson, S. N., Riley, E. P., Gramling, L., Delis, D. C., & Jones, K. L. (1998). Neuropsychological comparison of alcohol-exposed children with or without physical features of fetal alcohol syndrome. *Neuropsychology, 12*(1), 146-153.

Slide 13



Background

In addition to the abilities already discussed, a few studies have documented other specific neuropsychological deficits in individuals with FAS. Children with prenatal alcohol exposure, with and without FAS, have demonstrated various deficits on measures of executive functioning. These measures have revealed problems in areas such as planning (tower task-shown above), cognitive flexibility (trails test), inhibition (stroop test), and concept formation and reasoning (word context tests). Generally, performance on these measures is characterized by increased errors and more difficulty adhering to rules. Therefore, children are less successful overall. For example, on the tower measure shown above (Tower of California-similar to Tower of London), children with FAS and PEA passed fewer items overall and made more rule violations than controls. The only two rules were to never place a larger piece on top of a smaller one and to move only one piece at a time. As can be seen the alcohol exposed children had many more rule violations.

In addition, deficits have been found on the WCST (Wisconsin Card Sort Test), a nonverbal measure of problem solving. The WCST test requires both problem solving and cognitive flexibility and has been proposed to be sensitive to frontal system dysfunction. This test is a gold standard in the measure of executive functioning in neuropsychology. Children with prenatal exposure to alcohol made more errors and had more difficulty with the conceptual nature of the task than controls. New data indicate that they have trouble identifying and defining concepts.

Finally, tests of planning ability are also thought to be sensitive to frontal systems dysfunction although few such studies have been done in individuals with FAS. On the Progressive Planning Test which is similar to the Tower of London test children with FAS/FAE had difficulty with planning ahead and tended to perseverate on incorrect strategies. So far the results could be summarized as:

1) Heavy prenatal alcohol exposure is associated with a wide range of neurobehavioral deficits including visuospatial functioning, verbal and nonverbal learning, and executive functioning
2) Heavy prenatal alcohol exposure causes microcephaly and disproportionate reductions in the corpus callosum, basal ganglia, and cerebellum
3) Children with and without physical features of the fetal alcohol syndrome display qualitatively similar deficits

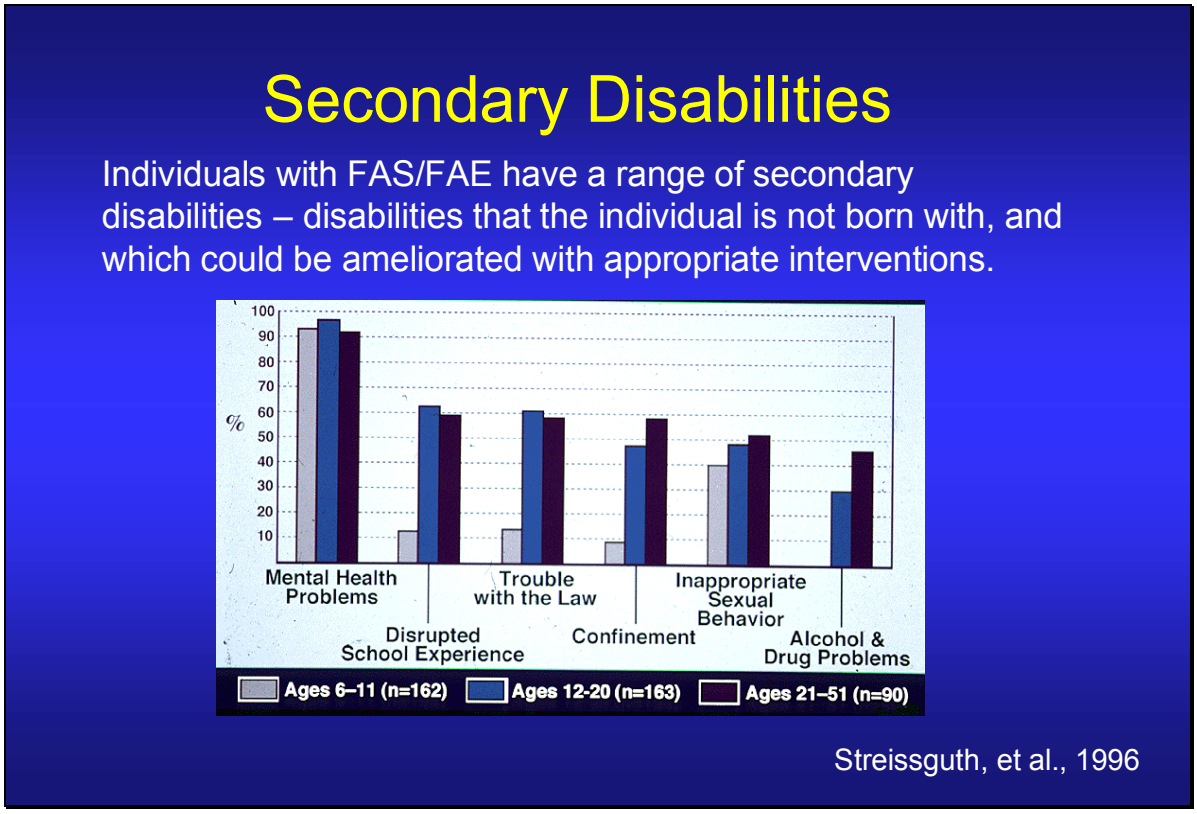
References

Carmichael O.H., Feldman JJ, Streissguth AP, Gonzalez RD: Neuropsychological deficits and life adjustment in adolescents and adults with fetal alcohol syndrome. Alcoholism: Clinical and Experimental Research 16:380, 1992

Kodituwakku PW, Handmaker NS, Cutler SK, Weathersby EK, Handmaker SD: Specific impairments in self-regulation in children exposed to alcohol prenatally. Alcoholism: Clinical and Experimental Research 19:1558-1564, 1995

Mattson, S. N., Goodman, A. M., Caine, C., Delis, D. C., & Riley, E. P. (1999). Executive functioning in children with heavy prenatal alcohol exposure. *Alcoholism, Clinical and Experimental Research, 23*(11), 1808-1815.

Slide 14



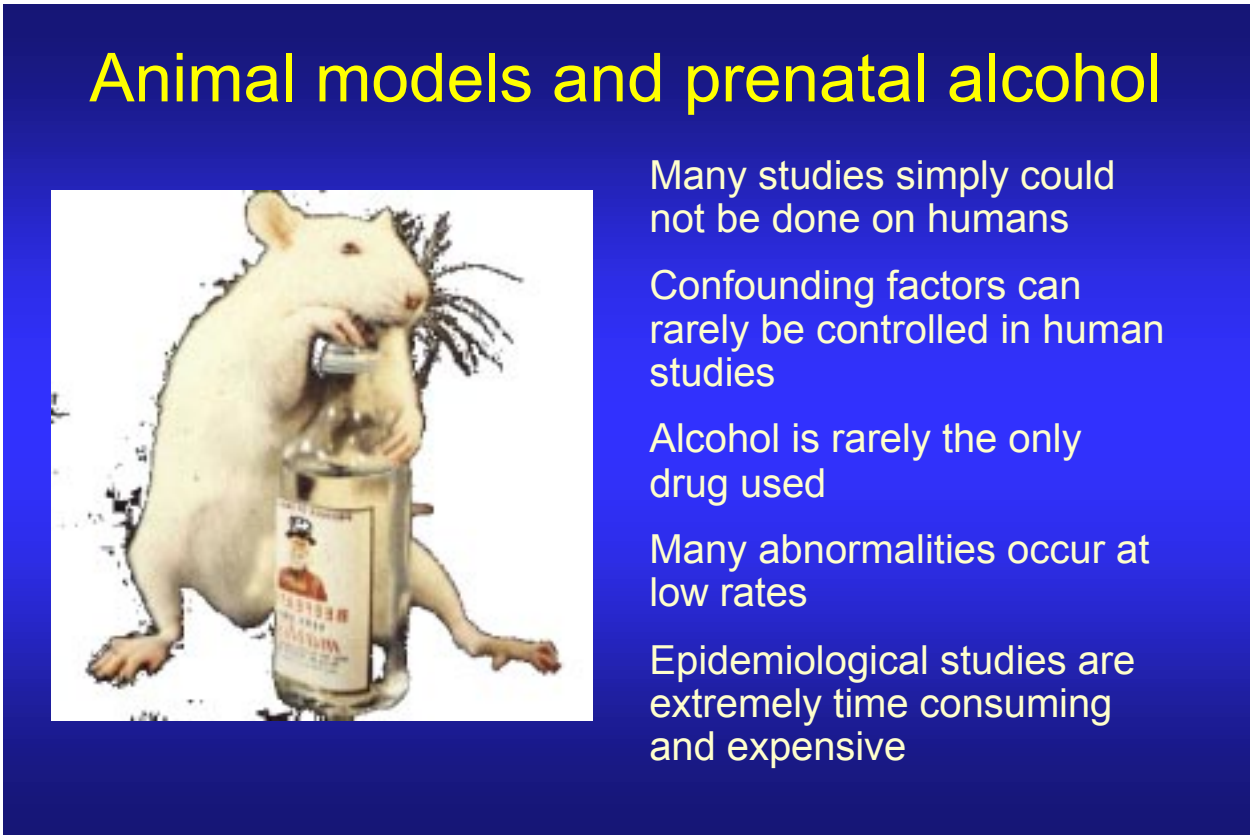
Background
Secondary disabilities are those disabilities that the individual is not born with, and hopefully with appropriate intervention could be ameliorated.

This slide illustrates the extent of these secondary disabilities as a function of age. These are individuals with FAS and FAE. As can be seen over 90% of these individuals have mental health problems and about 50% of those over the age of 12 have disrupted school experiences, trouble with the law, which is frequently severe enough to require confinement. They also engage in relatively high rates of inappropriate sexual behavior and a significant number have alcohol and drug abuse problems.

Interestingly, the factors that are protective against these secondary disabilities are: Being raised in a stable, nurturant home, diagnosis before the age of 6, no sexual or physical abuse, not changing households every few years, not living in a poor quality home, and receiving Developmental Disabilities services.

References
Streissguth, A. P., Barr, H. M., Kogan, J., & Bookstein, F. L. (1996). *Final Report: Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE).* Seattle, WA: University of Washington Publication Services.

Slide 15



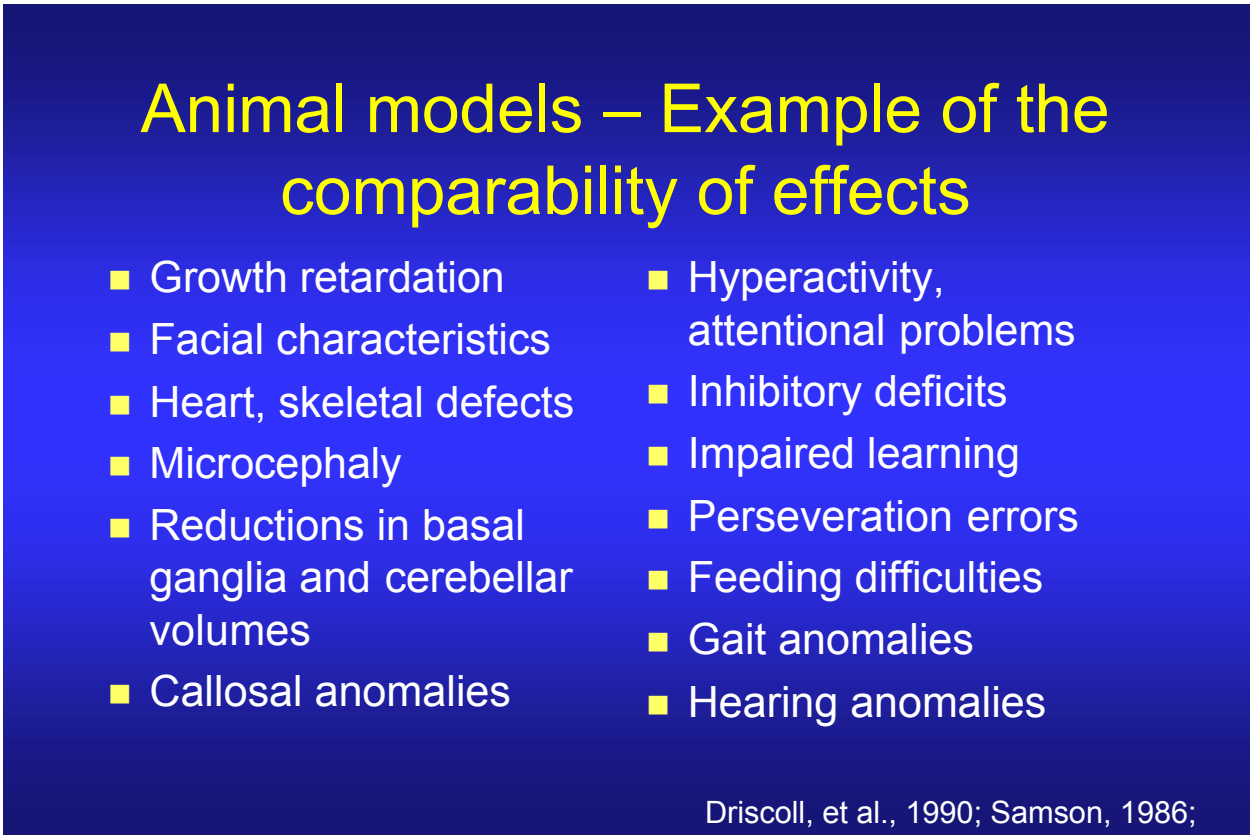
Background

Much of what we know about FAS and the effects of prenatal alcohol exposure is the result of work on animal models. After FAS was identified it became important to demonstrate that the effects were indeed the result of alcohol exposure and not due to factors such as other drugs, maternal conditions, or nutritional variables. The development of appropriate animal models was very important in this regard. Models were developed for assessing physical features of FAS as well as the behavioral, neuroanatomical, and neurochemical profiles of prenatal alcohol exposure.

The ideal test animal would absorb, metabolize and eliminate alcohol similar to human, transport alcohol and metabolites across placenta similar to human, have embryos and fetuses with developmental and metabolic patterns similar to that of human, be easily bred with large litters and a short gestation length, be inexpensive to maintain under laboratory conditions, and importantly not bite, scratch, kick, howl or squeal. No one animal meets all these requirements and the vast amount of work has been done in rodents (e.g. rats and mice). However, models have been developed in primates, sheep, pigs, and dogs. There is a continued need for animal research to answer questions that simply cannot be answered in humans: including the identification of risk factors, the elucidations of mechanisms by which alcohol damages the brain, and brain behavior relationships.

One can also mention the important reasons for conducting animal research and why it is done. Besides the ones listed on the slide the following factors could also be mentioned. We can assess mechanisms to help us understanding how alcohol does damage which might lead to ways to prevent or remediate this damage. We can also study genetic factors with the large number of selected lines or strains that are available. We can examine physiological outcomes not readily available for study in humans (e.g. anatomical or neurochemical changes). Finally, since the availability of FAS subjects for research is limited, these animal studies can act as a guide for studies on humans.

Slide 16



Background

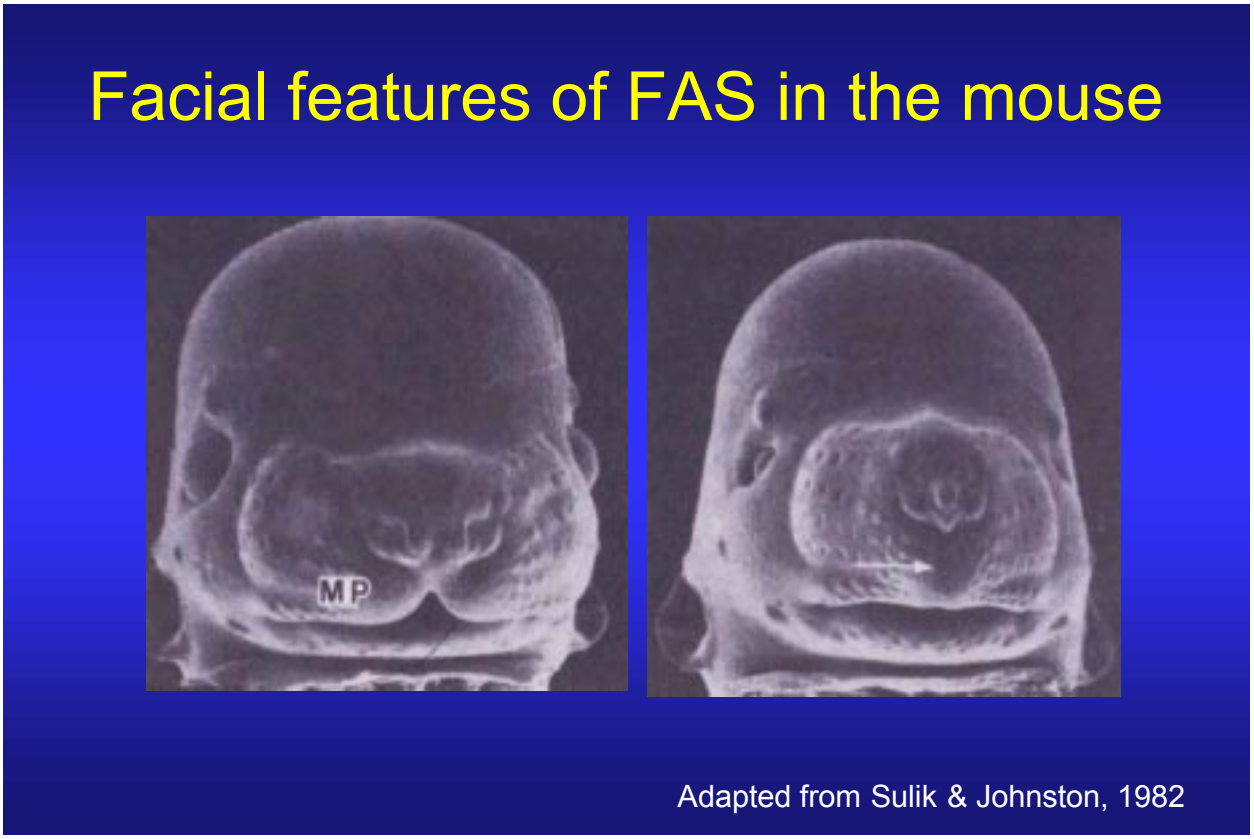
This slide shows areas where similar findings have been found both with the animal models and with humans. The point is that the models appear to be valid for studying FAS. In fact, the amount of concordance between the animal models and the human condition is rather remarkable.

References

Driscoll, C. D., Streissguth, A. P., & Riley, E. P. (1990). Prenatal alcohol exposure: Comparability of effects in humans and animal models. *Neurotoxicology and Teratology*, *12*, 231-237.

Samson, H. H. (1986). Microcephaly and fetal alcohol syndrome: Human and animal studies. In J. R. West (Ed.), *Alcohol and Brain Development* (pp. 167-183). New York: Oxford University Press.

Slide 17



Background

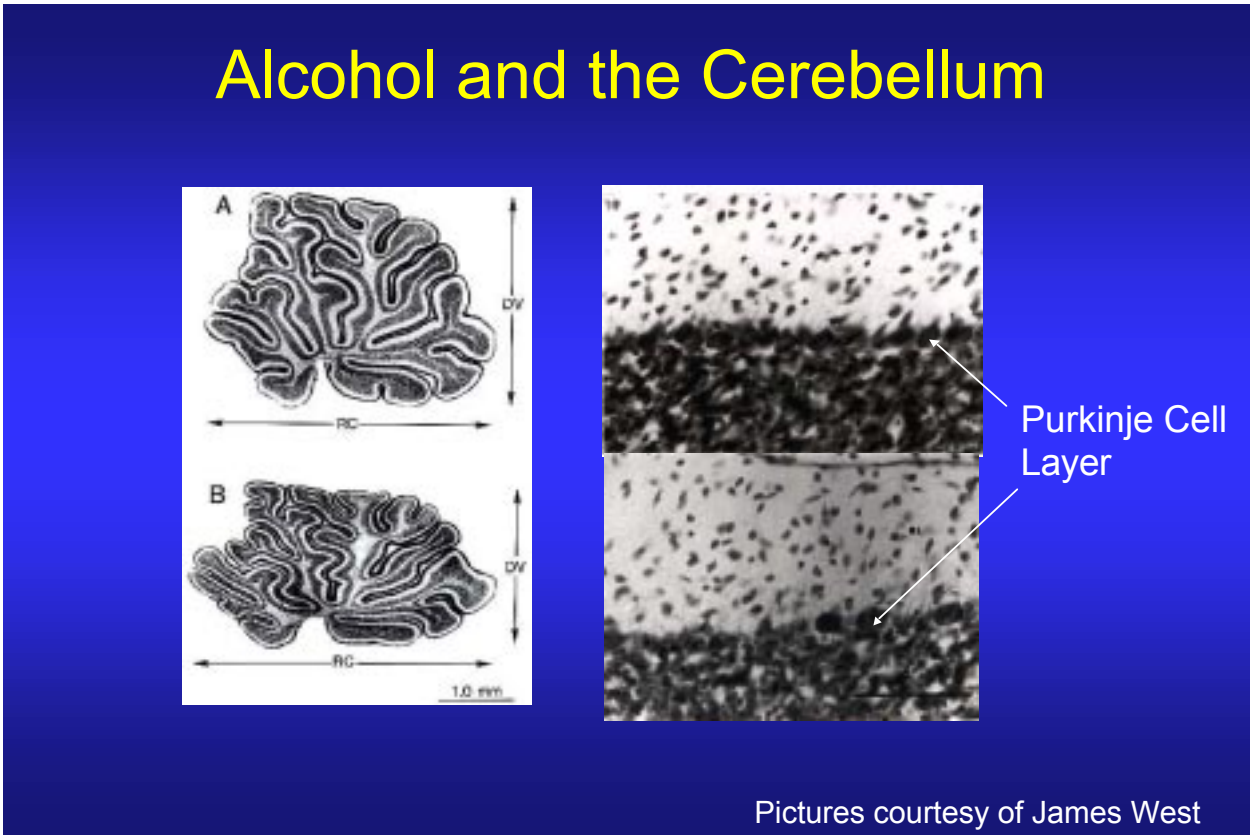
One model developed by Kathy Sulik uses mice. By exposing pregnant mice to high doses of alcohol during brief periods of gestation, she has been able to produce a mouse with the facial features of FAS. On the left is the control animal and the right the alcohol exposed animal. Note the small eye openings (palpebral fissures) and the long flat area under the nose (philtrum). Utilizing this model, Sulik and colleagues have been able to demonstrate that neural crest cells are especially sensitive to the effects of embryonic alcohol exposure and that the death of these cells may be responsible for the cranial facial defects in FAS.

References

Kotch, L. E., and Sulik, K.K. Experimental fetal alcohol syndrome: Proposed pathogenic basis for a variety of associate craniofacial and brain anomalies. Am. J. Med. Genet. 44, 168-176, 1992.

Sulik, K. K., & Johnston, M. C. (1982). Embryonic origin of holoprosencephaly: Interrelationship of the developing brain and face , *Scanning Electron Microscopy* (Vol. 1, pp. 309-322).

Slide 18



Background

Pre and/or early alcohol exposure can cause gross reduction in brain size. Alcohol can alter a number of brain regions, including the cortex, hippocampus, and corpus callosum. The cerebellum is one area that is particularly vulnerable to prenatal alcohol. On the left we see a sagittal view through the vermis of the cerebellum for a control rat and a rat exposed to alcohol during the third trimester equivalent brain growth spurt. Alcohol treatment during the brain growth spurt significantly reduces granule cell number and Purkinje cell number in the cerebellum. In the panel on the right, on the top you can see the monolayer of Purkinje cells in a control subject. On the bottom is an animal exposed to early alcohol treatment, which significantly reduced the number of Purkinje cells.

It is interesting that the cerebellar vermis, particularly lobules 1-5 have been shown to be reduced in area in children exposed to large amounts of alcohol prenatally.

References

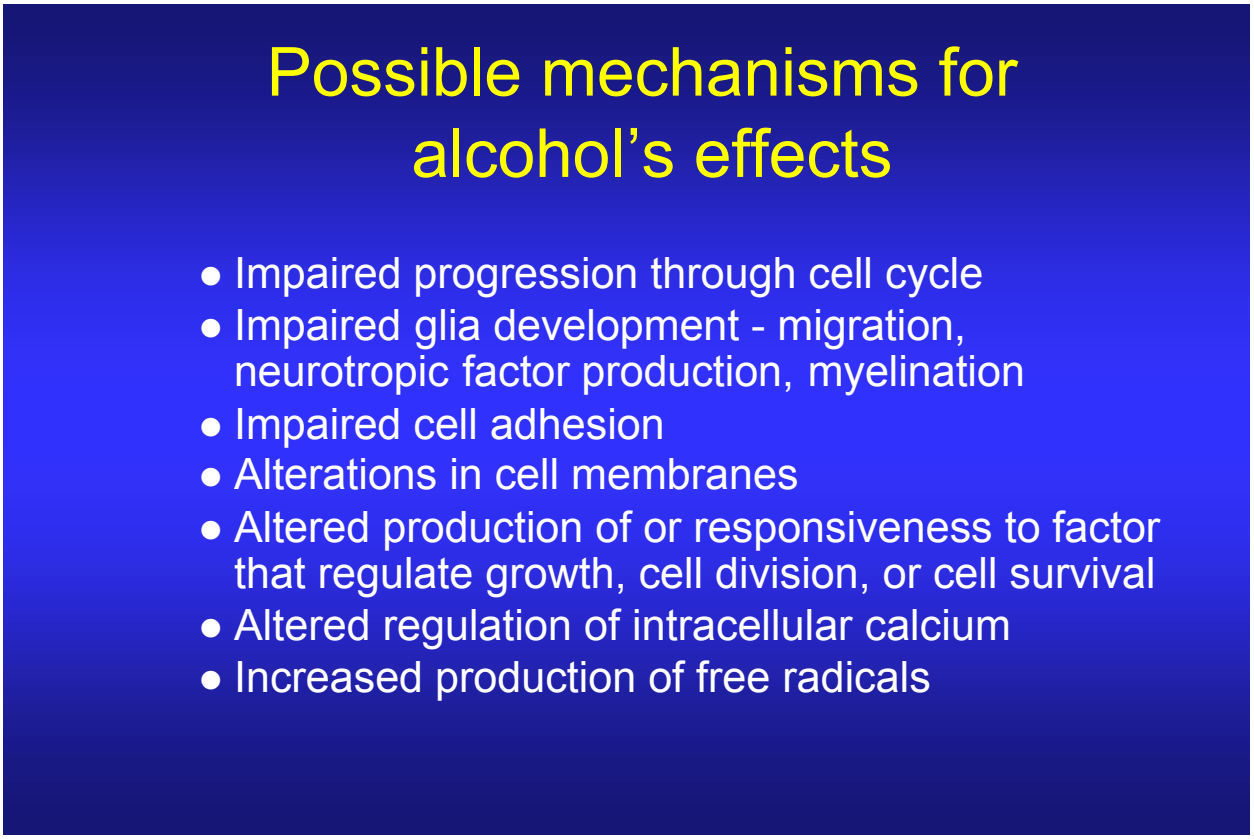
West, J.R., Chen, W-J. A., & Pantazis, N.J. (1994) Fetal alcohol syndrome: The vulnerability of the developing brain and possible mechanisms of damage. Metabolic Brain Disease, 9, 291-322.

Sowell ER; Jernigan TL; Mattson SN; Riley EP; Sobel DF; Jones KL. Abnormal development of the cerebellar vermis in children prenatally exposed to alcohol: size reduction in lobules I-V. Alcoholism, Clinical and Experimental Research, 1996, 20(1):31-4.

Pierce.D. R., and West, J.R. (1987) differential deficits in regional brain growth inducted by postnatal alcohol. Nuerotox. And Terat. 9, 129-141.

Thomas, J.D., Goodlett, C. r. (1998) Alcohol-induced Purkinje cell loss depends on developmental timing of alcohol exposure and correlates with motor performance. Dev. Brain Res. 165, 159-166.

Slide 19



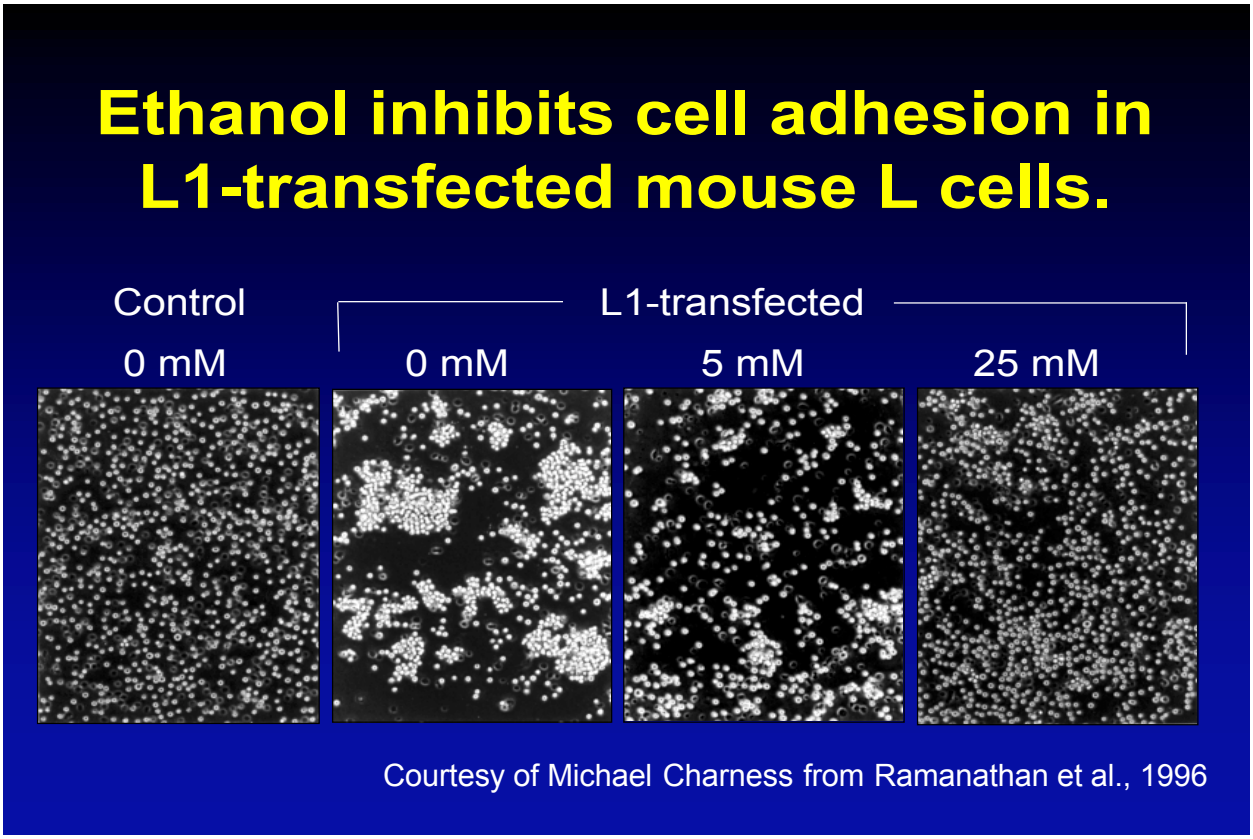
Background

One use of animal models is to examine mechanisms by which alcohol might damage the embryo and fetus. No one is postulating that all of the effects seen following prenatal alcohol exposure are the result of a single mechanism. Rather, alcohol can influence development via a number of both direct and indirect mechanisms. Alcohol can alter the proliferation, migration, differentiation and cell survival of neuronal cells. Alcohol can also disrupt the development of glial cells, leading to alterations in cell signaling and myelination. Alcohol may act on the cell membrane. For example, alcohol can disturb membrane fluidity, which can affect cell adhesion, migration and cell communication. Prenatal alcohol can also have effects on glutamate receptors and GABA receptors. Prenatal alcohol can also act on intracellular messengers. For example, alcohol can decrease or increase intracellular calcium; an optimal level of intracellular calcium is necessary for normal outgrowth of neuronal fibers. Yet, despite this multitude of possible mechanisms, not all neuronal cell populations are equally affected by prenatal alcohol. One of the challenges for alcohol researchers is to determine why some cells are resistant whereas others are relatively vulnerable to prenatal alcohol.

References

West, J.R., Chen, W-J. A., & Pantazis, N.J. (1994) Fetal alcohol syndrome: The vulnerability of the developing brain and possible mechanisms of damage. Metabolic Brain Disease, 9, 291-322.

Slide 20



Background

Ethanol seems to alter cell responses to molecules that regulate neuronal proliferation, migration, and differentiation. One interesting mechanism involves L1 and other cell adhesion molecules. These are essential for normal human nervous system development. L1 and other cell adhesion molecules guide neuronal migration and tract formation during nervous system development and mutations in the gene for L1 result in brain malformations.

Scientists recently recognized that children born with L1 mutations exhibit mental retardation, spastic gait, and a variety of brain malformations including enlarged ventricles (hydrocephalus), and agenesis of the corpus callosum. Noting that retardation, hydrocephalus, and agenesis of the corpus callosum also occur in FAS, Michael Charness and colleagues asked whether alcohol inhibits the adhesiveness of cells bearing the L1 molecule.

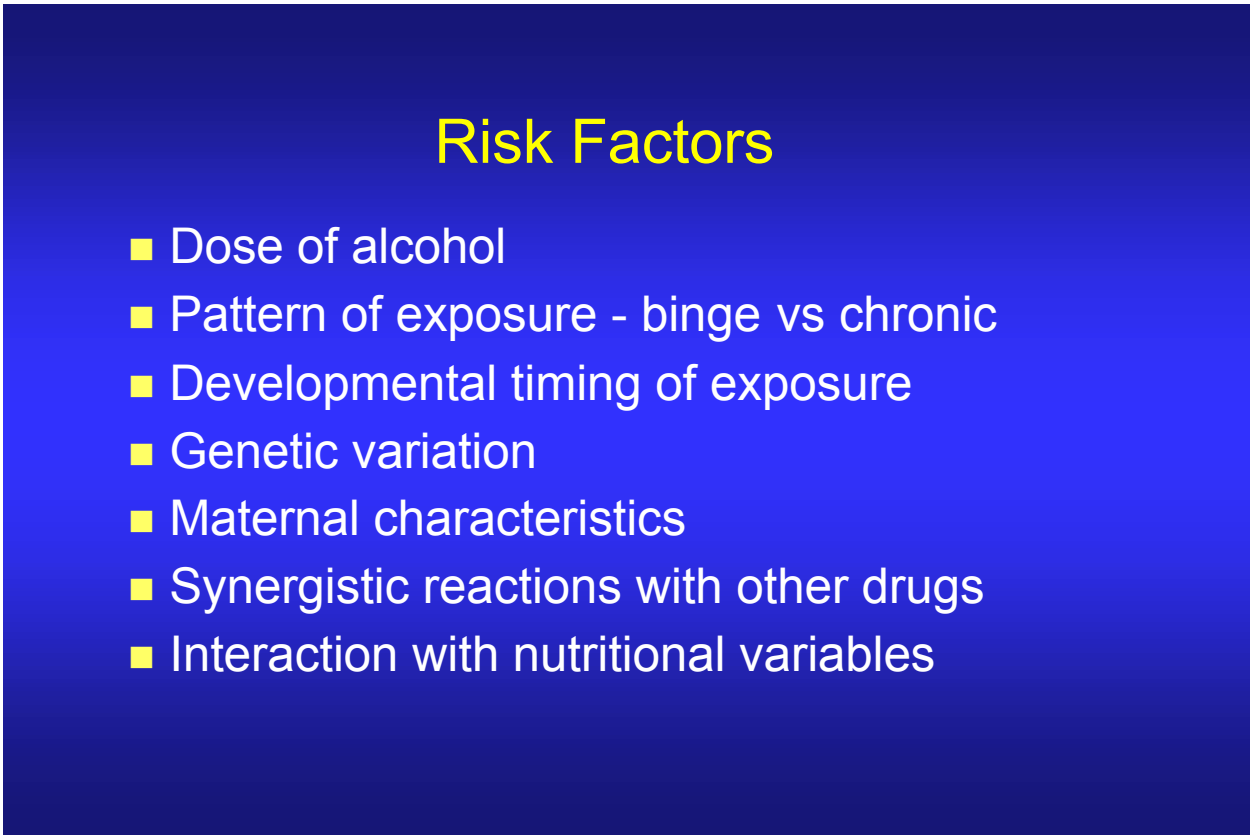
L cells (mouse fibroblasts) were engineered to express the human gene for the cell adhesion molecule L1. These are the 3 slides labeled L1-transfected. The cells were allowed to aggregate by gentle shaking for 30 minutes. Control cells (left most picture) form few clusters of adherent cells. Cells transfected with human L1, cell adhesion molecule aggregate much more than control cells. The second picture from the left shows this aggregation (the white clumps) when alcohol is not added to the system. The right two pictures show a dose dependent decrease in aggregation when ethanol is added to the medium. This increase in cell adhesion is inhibited by

ethanol in a dose-dependent manner. ethanol seems to alter cell responses to molecules that regulate neuronal proliferation, migration, and differentiation.

References

Ramanathan R; Wilkemeyer MF; Mittal B; Perides G; Charness ME. Alcohol inhibits cell-cell adhesion mediated by human L1. Journal of Cell Biology, 1996 Apr, 133(2):381-90.

Slide 21



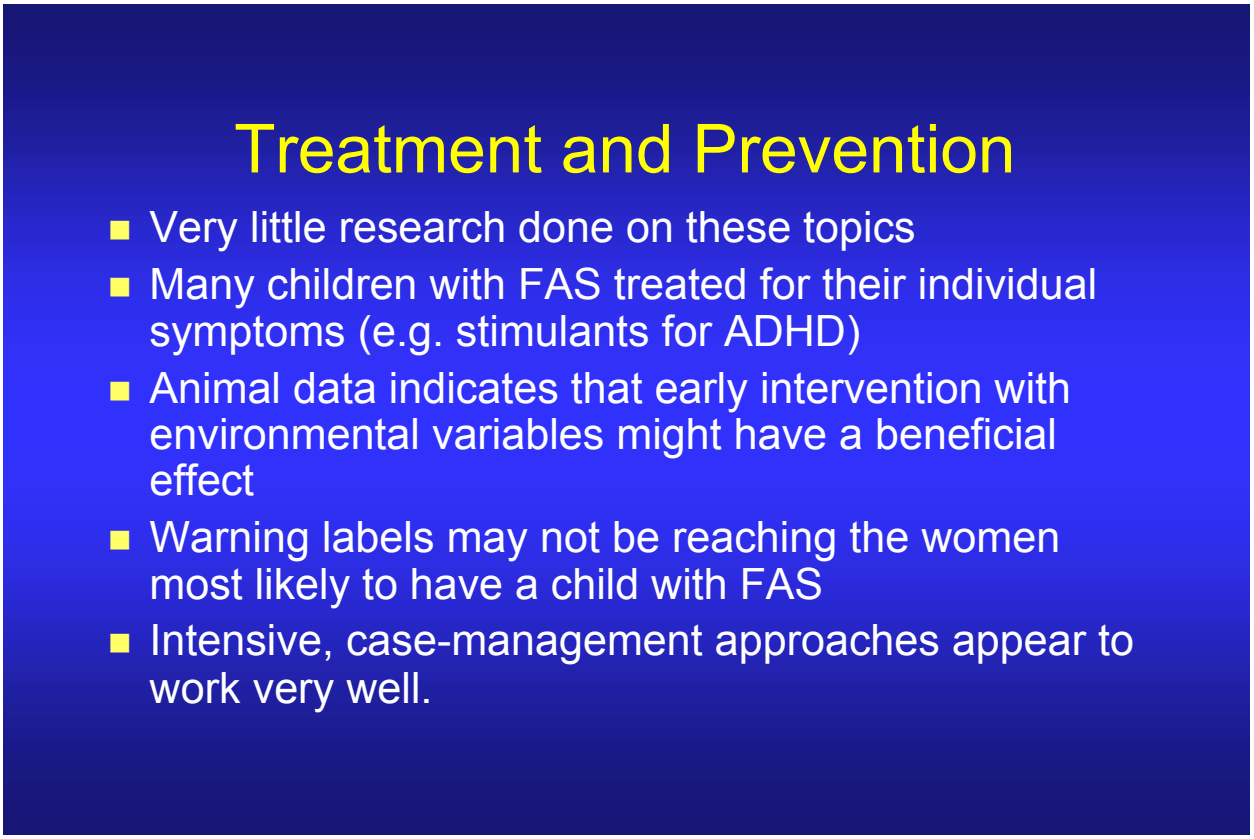
Background

FAS is only the tip of the iceberg in terms of outcomes. In fact, only a minority (10-40%) of the children of chronic alcoholic women are diagnosed with FAS. What makes some individuals more susceptible than others?. What are the risk factors associated with prenatal alcohol exposure? There are a number of factors that may contribute to increased risk to the adverse effects of prenatal alcohol. First, the higher the dose of alcohol, the greater the likelihood that the child will exhibit fetal alcohol effects. The pattern of exposure is also important. Both human and animal studies have found that binge drinking (drinking a large amount of alcohol in a short period of time), which produces high blood alcohol levels, is more damaging to the fetus than chronic alcohol exposure that produces lower blood alcohol levels. Thus, peak blood alcohol level may be an important factor.

In addition, the developmental timing of alcohol exposure may influence the outcome. For example, the facial features associated with prenatal alcohol treatment appear to be related to alcohol exposure during the first trimester. Obviously, as different organs undergo development at different times, when the embryo or fetus is exposed is going to be important in determining the outcome. The brain undergoes a very prolonged developmental course and therefore, may be susceptible to fetal alcohol effects throughout gestation. In addition, genetic factors, nutritional factors, parity, and synergistic reaction with other drugs may influence the effects of prenatal alcohol exposure.

It is important to realize that some fetal alcohol effects might occur even before a women realizes she is pregnant.

Slide 22



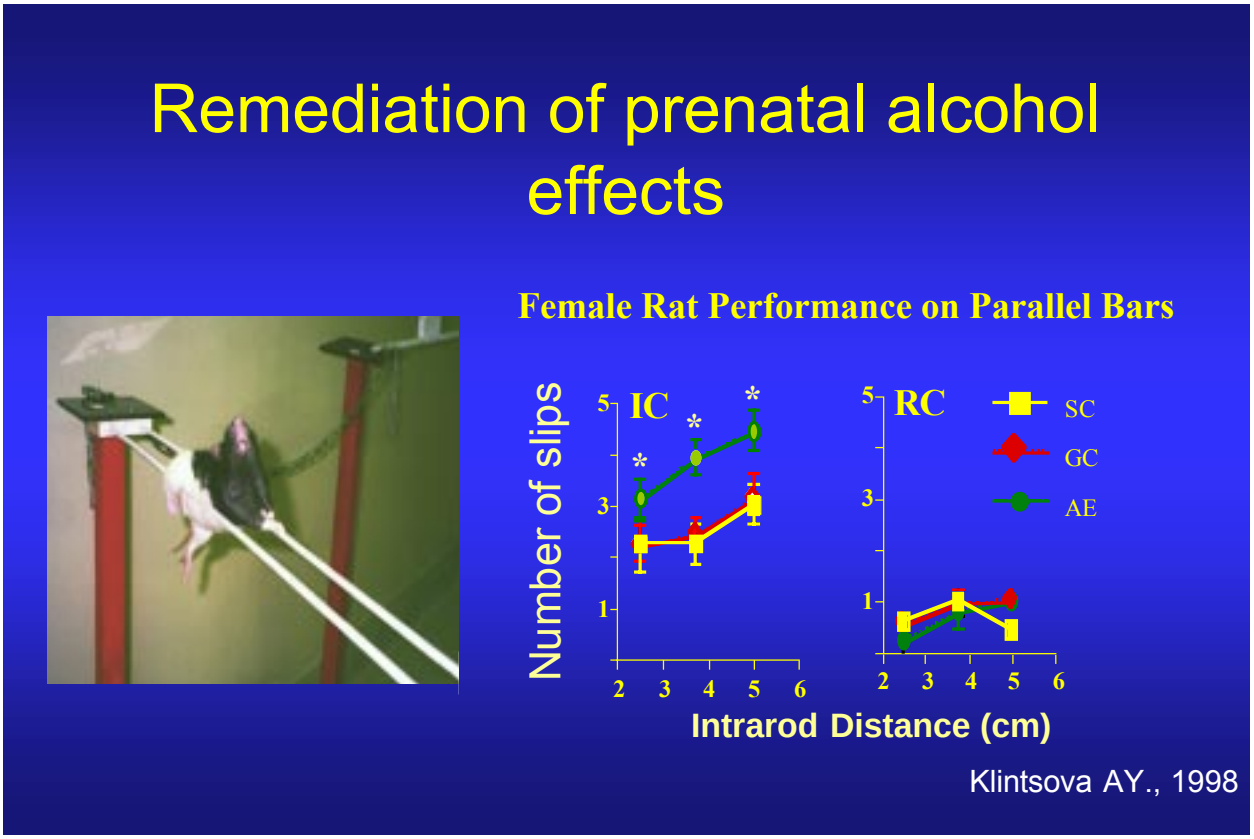
Background

Very little work has been done in these two areas. In terms of the treatment of FAS children, basically the individuals symptoms appear to be treated without regard to the etiology. The data on stimulants for this group of children is mixed. The animal data indicates that the stimulants should not be very effective in children. However, there are data showing that some of the FAS children with ADHD do indeed respond favorably to stimulant medication.

There is some interesting work using animal models showing the effectiveness of early motor training and that will be discussed shortly.

There are also data showing that an intensive, case management approach works very well in preventing women from having additional children with drug and/or alcohol exposure.

Slide 23



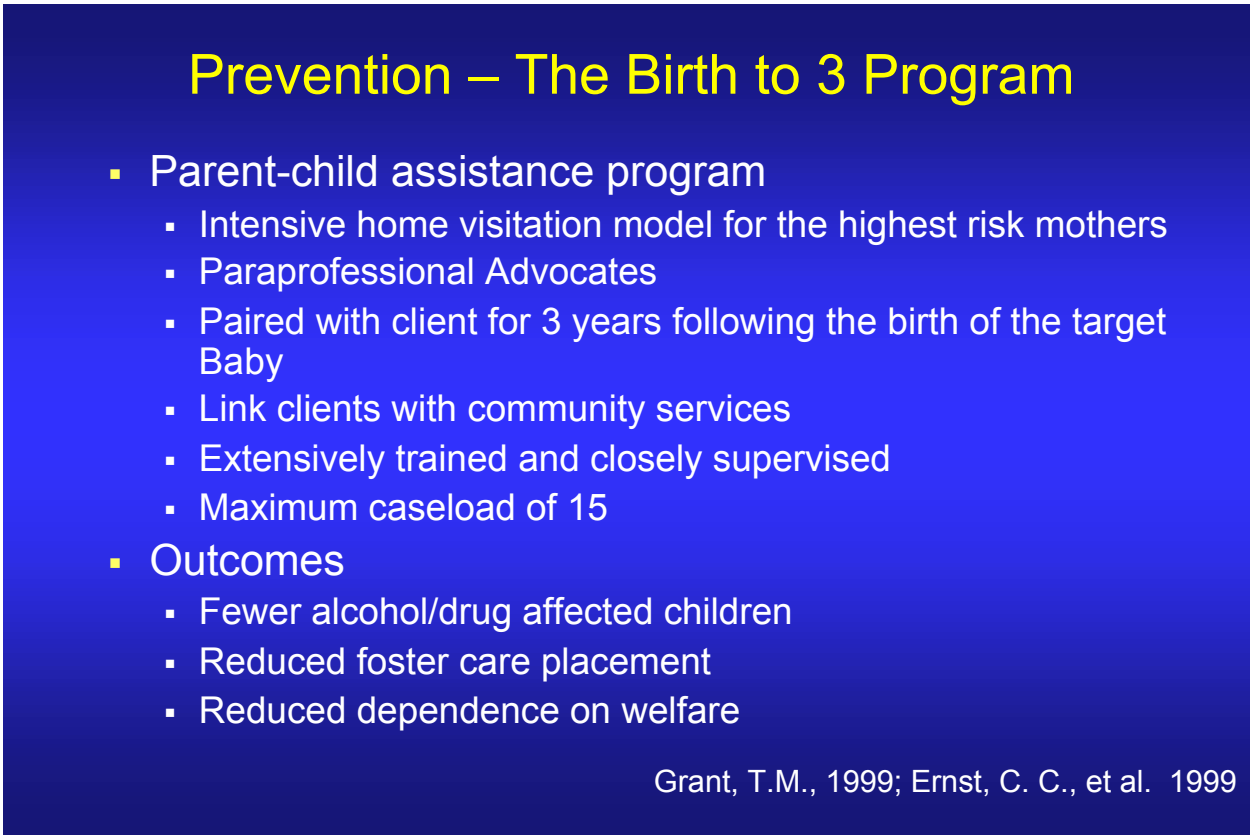
Background

One important area of treatment is using motor training to compensate for some of the deficits resulting from prenatal alcohol. Motor deficits, balance problems, and gait anomalies are common in children with FAS. Complex motor training can mitigate the effects of developmental alcohol exposure on motor coordination and on cerebellar structure. Shown here is the parallel bar motor task, which measures the rat's balance and fine motor coordination. The graphs illustrate the number of slips or falls on the parallel bars, an indicator of motor dysfunction. Subjects in the inactive condition (IC) did not receive motor training, subjects in the motor control (MC) group (not shown on graph) were exercised on a runway, and subjects in the rehabilitative condition (RC) were trained on a complex motor skill task for 20 days. As you can see, ethanol-exposed subjects (AE) that did not receive motor training were impaired on this task, slipping with greater frequency compared to controls (GC and SC). In contrast, complex motor training significantly improved motor performance in all groups on this task, including the performance of ethanol-treated subjects. In fact, there was no difference in performance among the ethanol-exposed and control groups following this rehabilitative conditioning. Consistent with this behavioral change, complex motor training increases the number of synapses per cerebellar Purkinje cell in both ethanol-treated and control subjects, a finding that indicates that the brain is still plastic and amenable to behavioral interventions even after the alcohol insult is complete. Also, these data provide evidence that behavioral interventions may successfully reduce the severity of fetal alcohol effects.

References

Klintsova AY. Cowell RM. Swain RA. Napper RM. Goodlett CR. Greenough WT. Therapeutic effects of complex motor training on motor performance deficits induced by neonatal binge-like alcohol exposure in rats. I. Behavioral results. *Brain Research. 800(1):48-61, 1998*

Slide 24



Background

This is a program ongoing in Seattle and which has been replicated in other communities. It began in 1991 to test the efficacy of an intensive, long term paraprofessional advocacy with high risk mothers who abused alcohol or drugs during pregnancy. Women became involved when they give birth to a child who was exposed to alcohol or drugs prenatally. They received intensive interaction with a case worker who acts as an advocate, getting them in touch with appropriate services. The results are impressive, with fewer subsequent children born exposed to alcohol or drugs, reduced foster care placement and a reduction in the dependence of welfare. Other positive outcomes are an increase in family planning and child well-being.

References

Grant, T.M., Ernst, C. C., and Streissguth, A.P. Intervention with high-risk alcohol and drug–abusing mothers: I. Administrative strategies of the Seattle model of paraprofessional advocacy. Journal of Community Psychology, 27, 1, 1-18, 1999

Ernst, C. C. Grant, T.M., Streissguth, A.P. and Sampson, P.D. Intervention with high-risk alcohol and drug–abusing mothers: II. Three-year finds from the Seattle model of paraprofessional advocacy. Journal of Community Psychology, 27, 1, 19-38, 1999

Slide 25

Summary

- Fetal Alcohol Syndrome is a devastating developmental disorder that affects children born to women who abuse alcohol during pregnancy.
- Although FAS is entirely preventable, and in spite of our increasing knowledge about the effects of prenatal alcohol exposure, children continue to be born exposed to high amounts of alcohol.
- It's consequences affect the individual, the family, and society.
- Its costs are tremendous, both personally and financially.
- Effective treatment and prevention strategies must be developed and made available.