Prenatal alcohol exposure and abnormal brain development: Insights from animal studies

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Studies of animal models allow:

✓ Identification of critical exposure periods and dose-response relationships

✓ Detailed analyses of affected areas of interest

✓ Correlation of structural and functional changes

✓ Verification and expansion of diagnostic criteria

Virtually all stages of prenatal development are vulnerable to alcohol-induced damage.

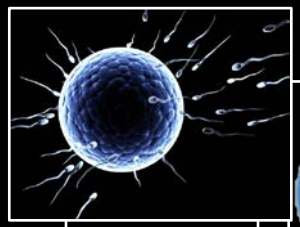
- First trimester exposures cause major malformations as well as functional changes
- Second and third trimester exposures typically yield functional changes in the absence of readily identifiable structural abnormalities

The most severe outcomes result from heavy prenatal (especially binge) alcohol exposure.

- Due in large part to individual variability in both people and animal models it appears impossible to determine a minimal alcohol exposure level that is safe for every individual.

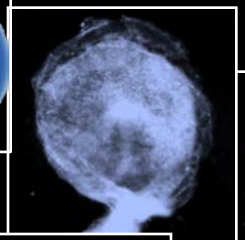
Much of embryogenesis occurs prior to the time that pregnancy is typically recognized

Embryo Age = Days After Fertilization

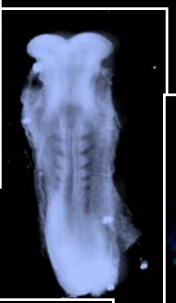


Day 1

Day 9



Day 17



Day 22

Day 26

Day 32

Day 42

Menses (Beginning of Last Normal Menstrual Period; LNMP)

14 Days/2 Weeks Post-LNMP

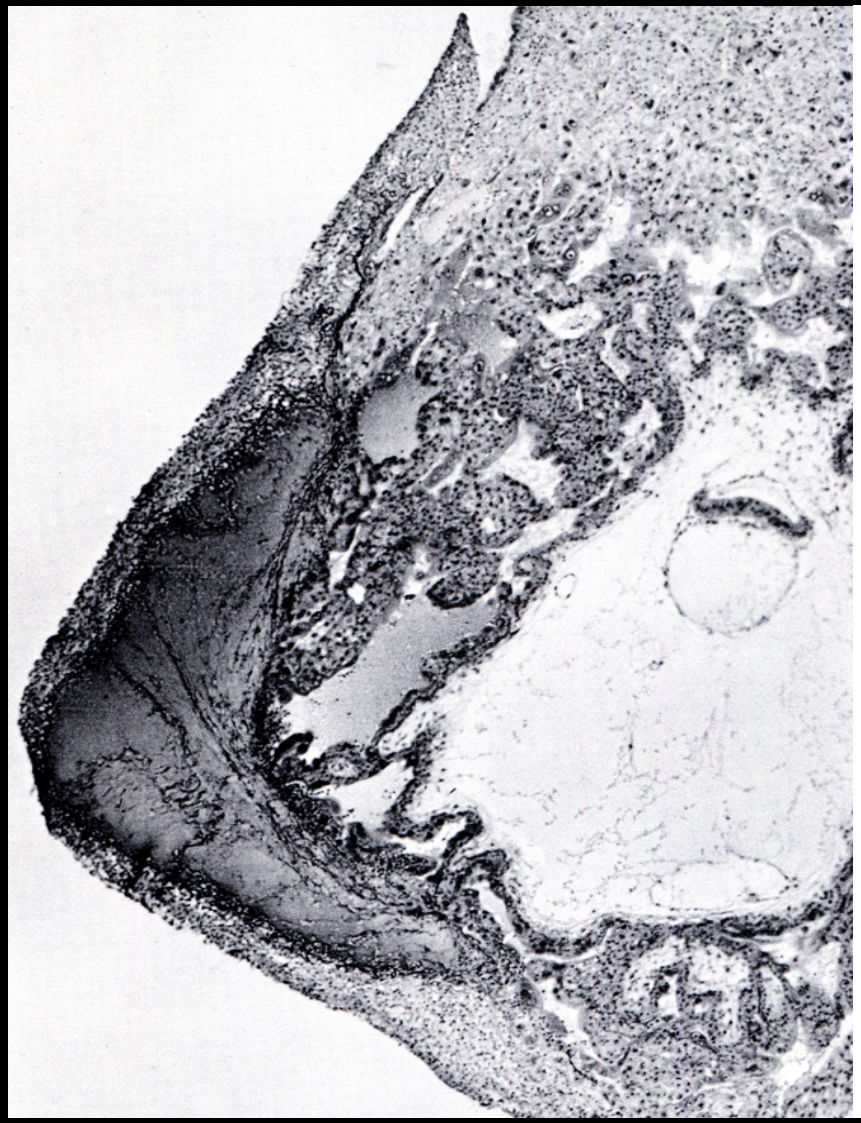
28 Days/4 Weeks Post- LNMP (First Missed Period)

6 Weeks Post- LNMP

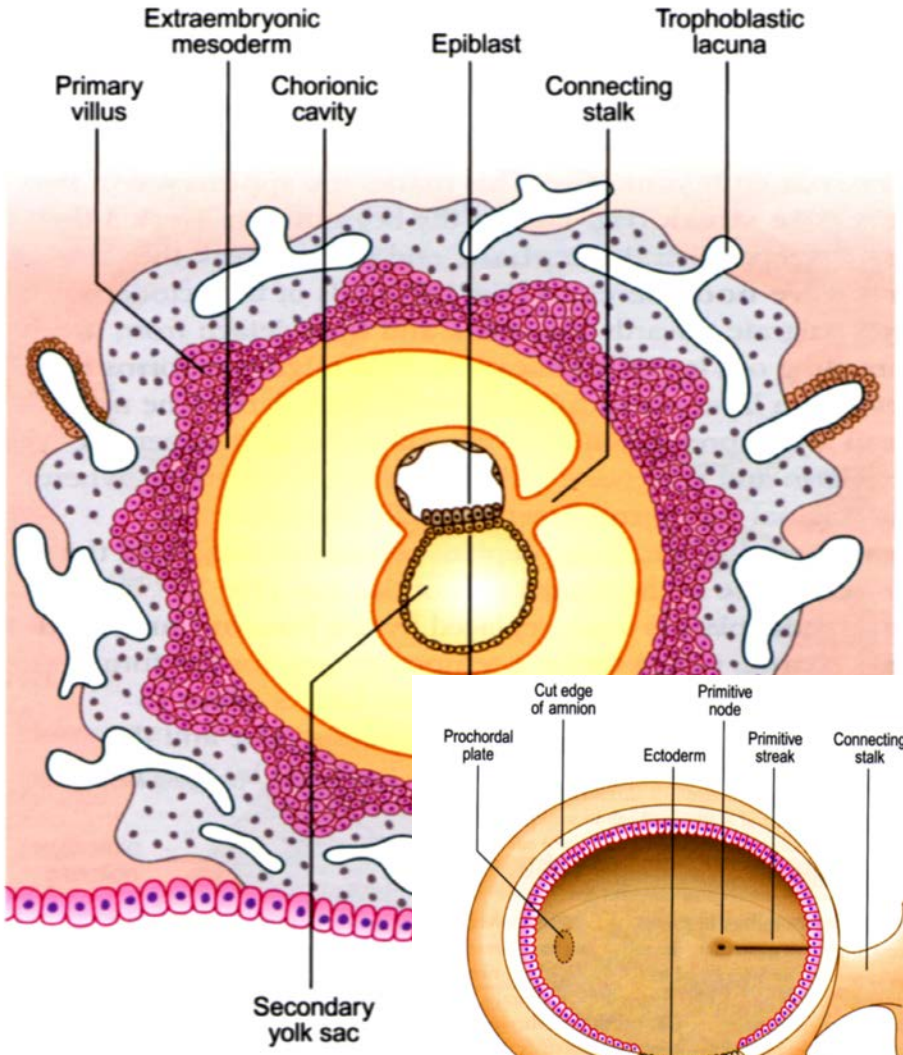
8 Weeks Post-LNMP (Second Missed Period)

Age Post LNMP = Embryo Age + 2 Weeks

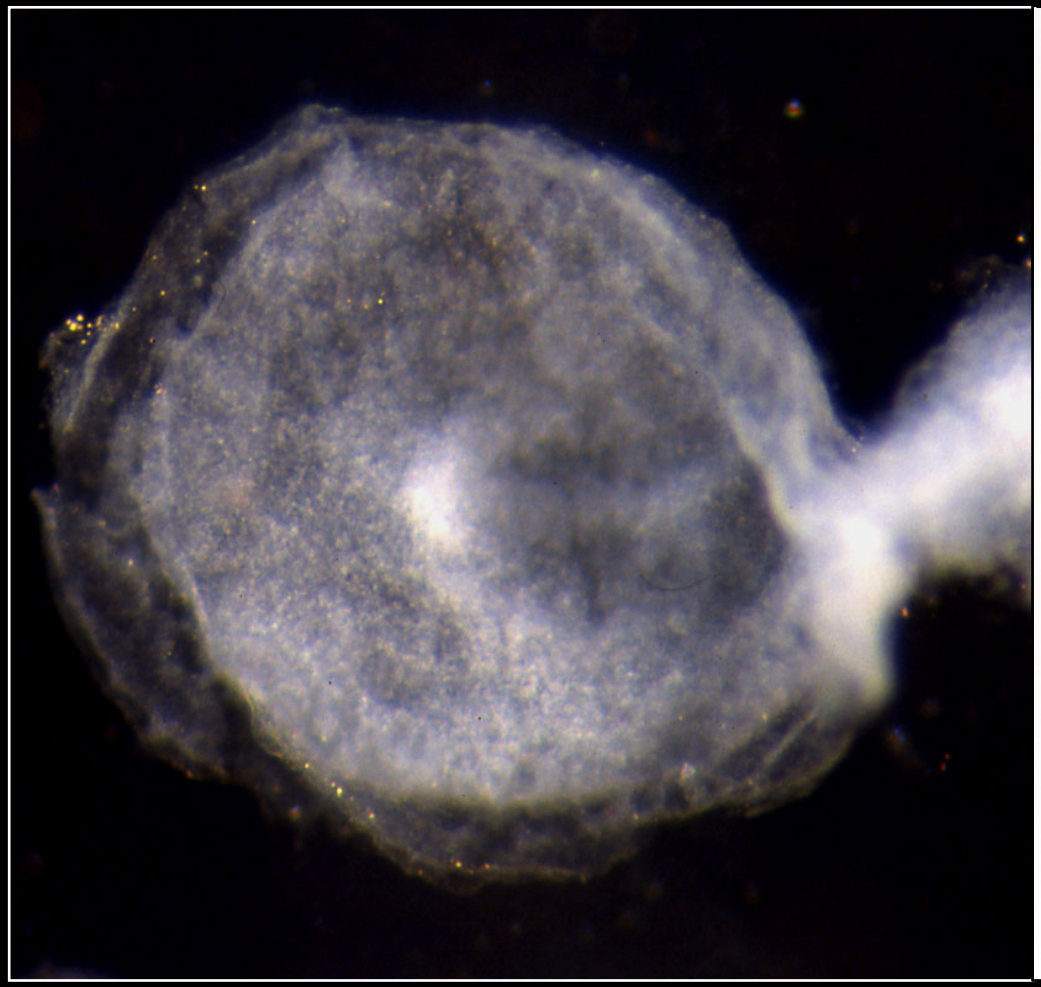
In the middle of the 3rd week of gestation, the human embryo has implanted in the uterine wall and is beginning to form a third (germ) cell layer



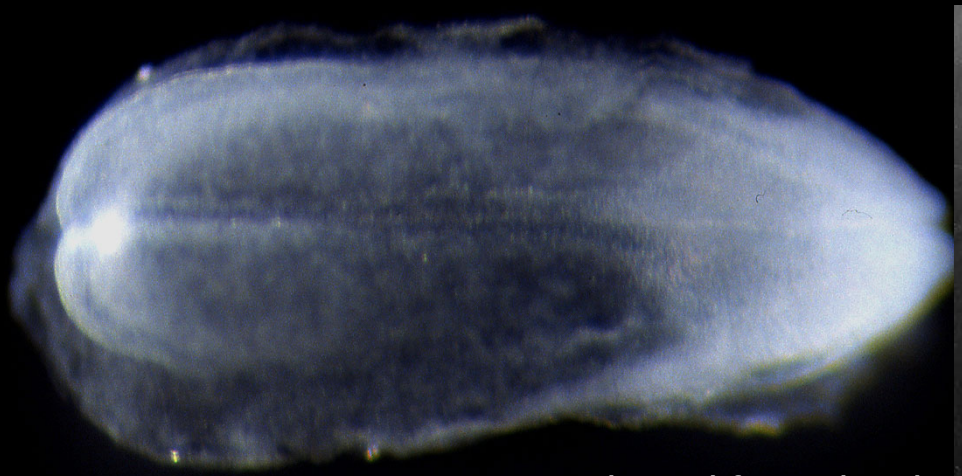
From Heuser, Rock and Hertig
Contributions to Embryology,1945

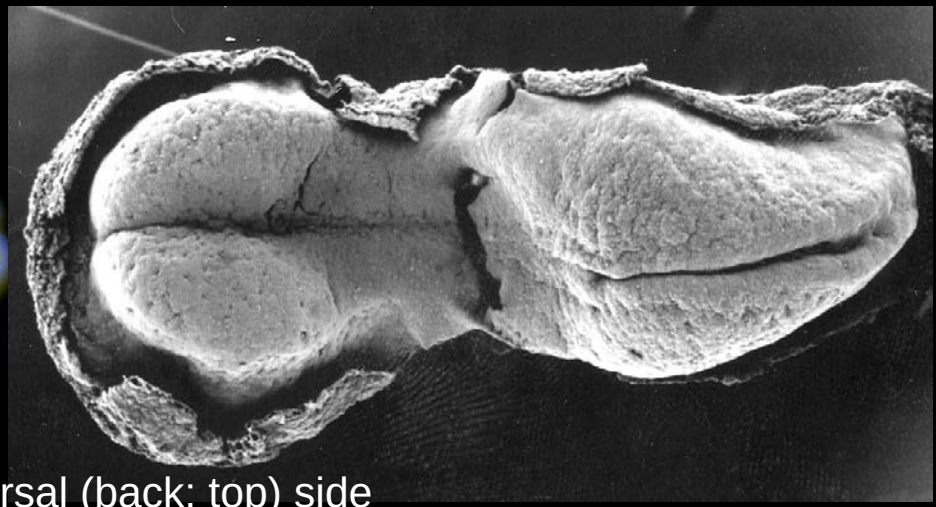


The 17 day old human embryo is less than 0.1 cm in diameter

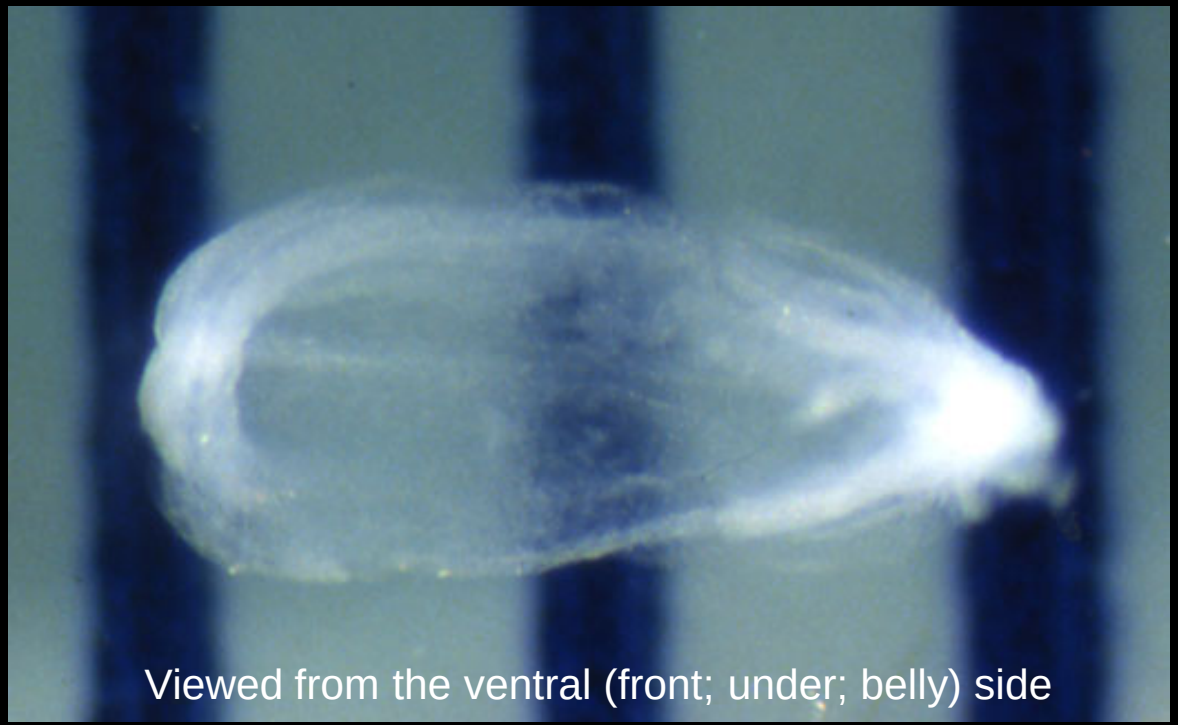


By 18 days after fertilization the human embryo is 0.2 cm long



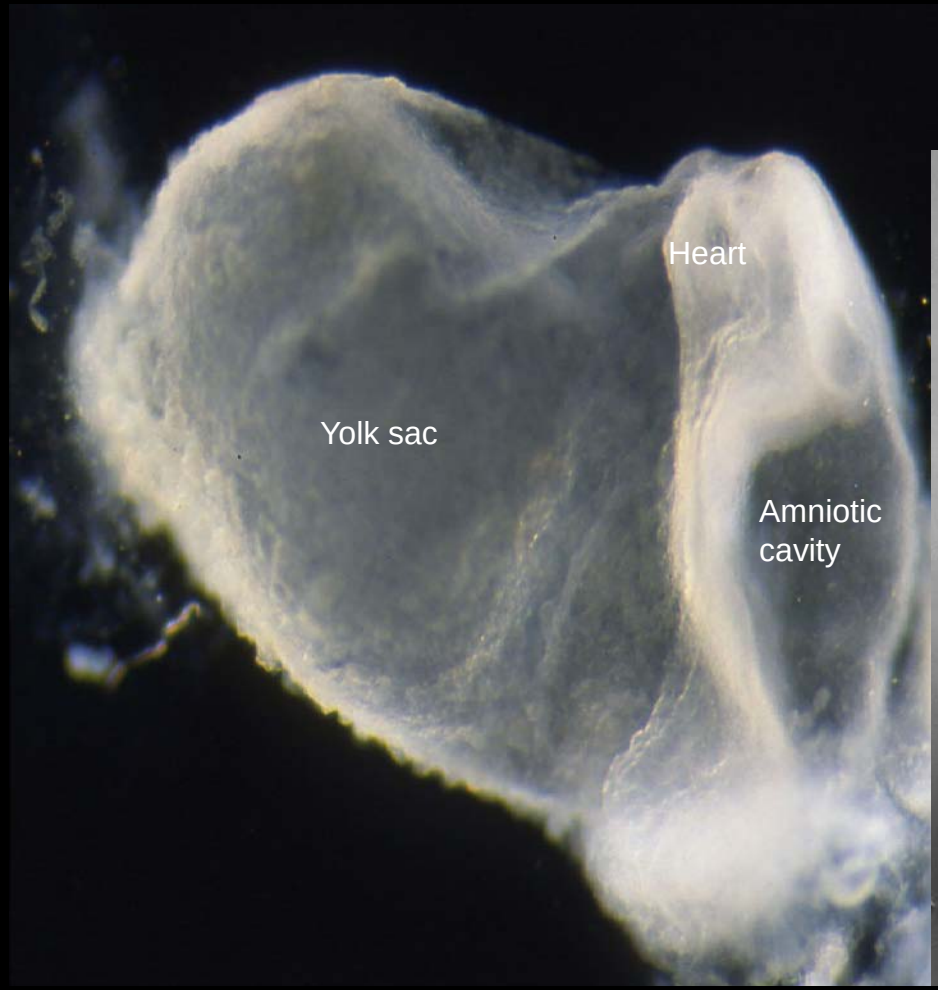


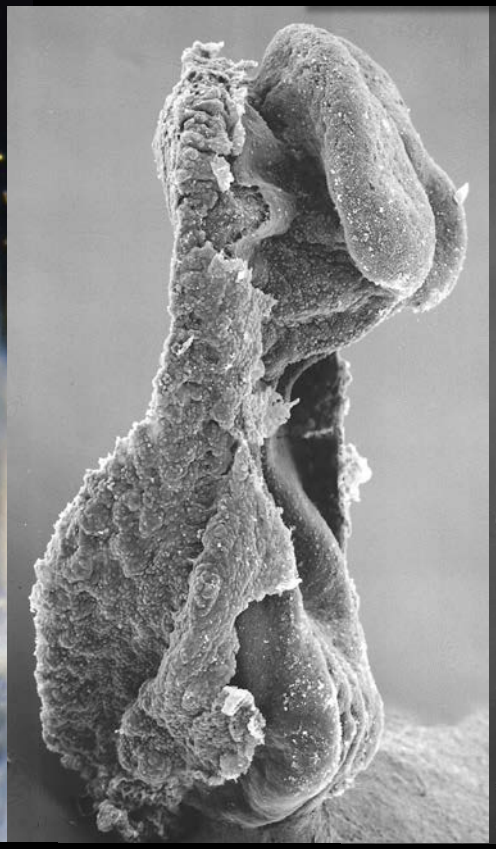
Viewed from the dorsal (back; top) side

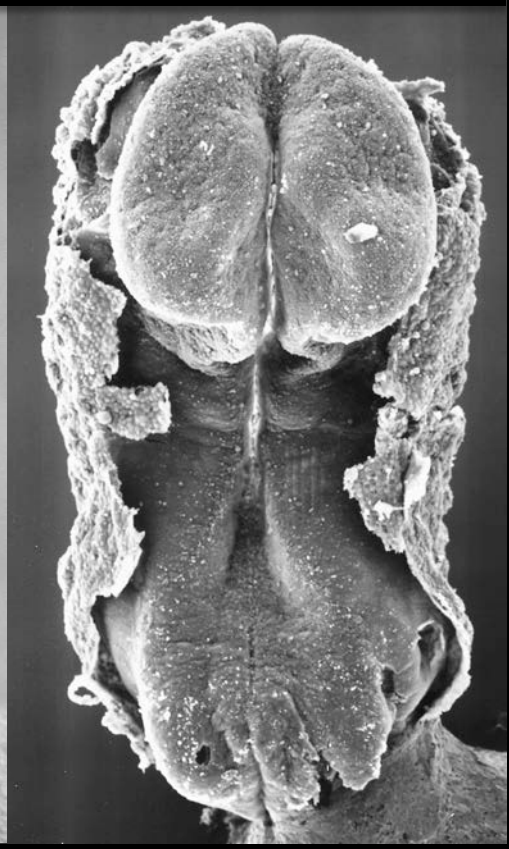


Viewed from the ventral (front; under; belly) side

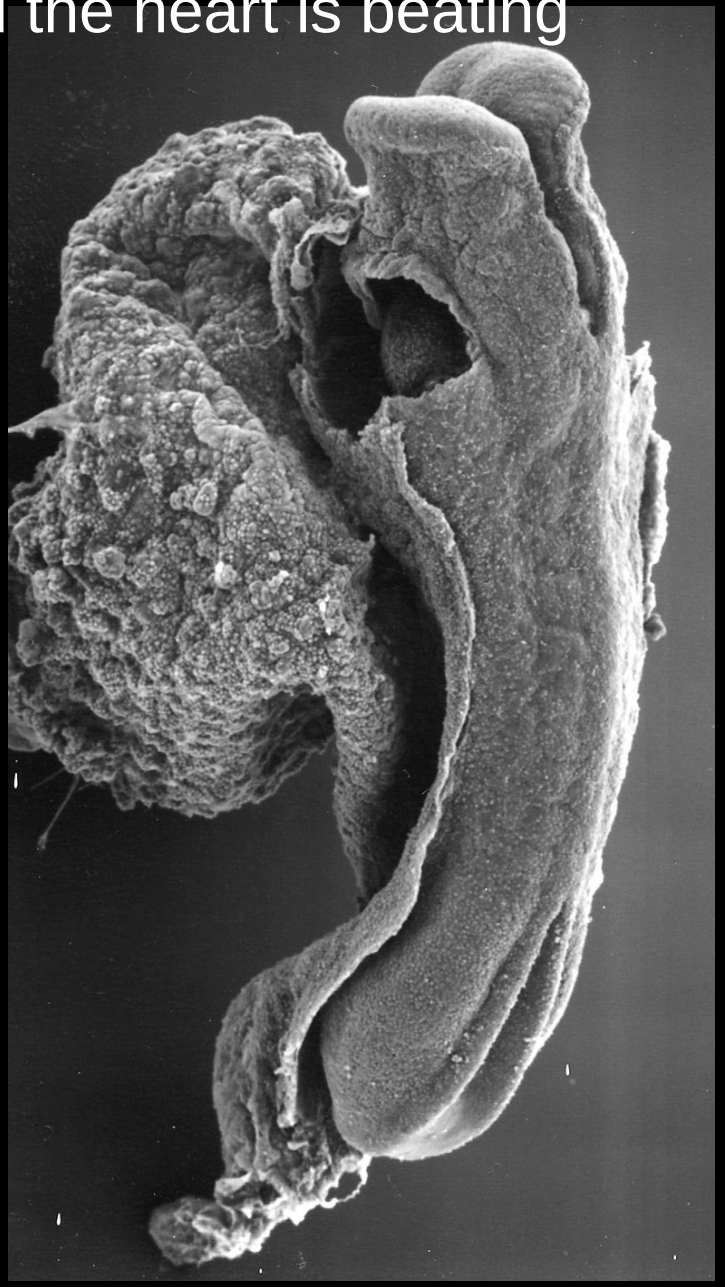
At 20 days after fertilization, the developing brain and spinal cord remain unfused



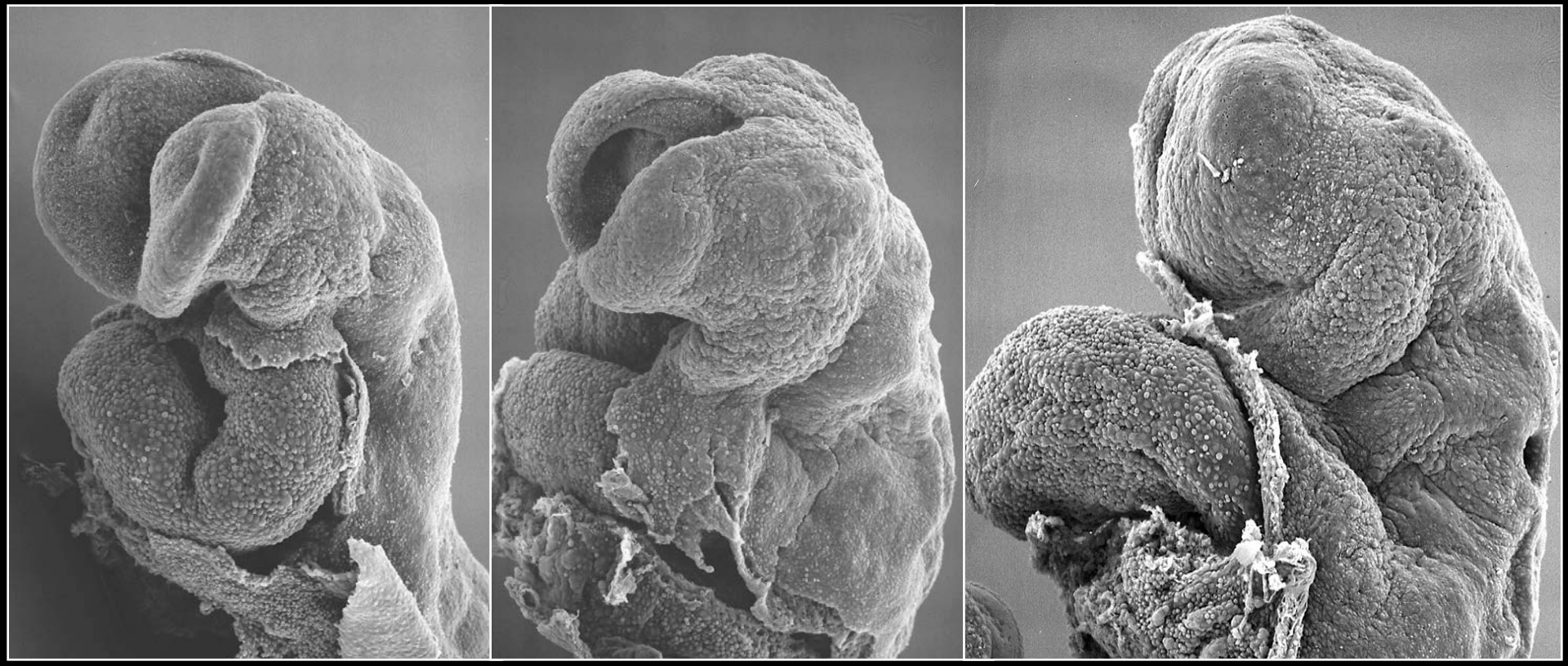




By 23 days, neural tube closure is progressing toward both the head and tail ends and the heart is beating



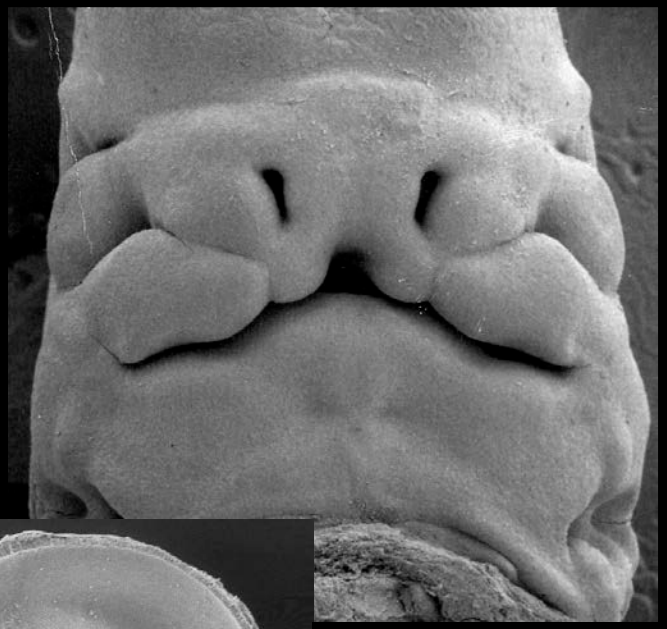
By 25 days after fertilization, the human anterior neural tube is closed



By 32 days after fertilization, the developing brain and face contribute to over 1/3 of the embryo's length

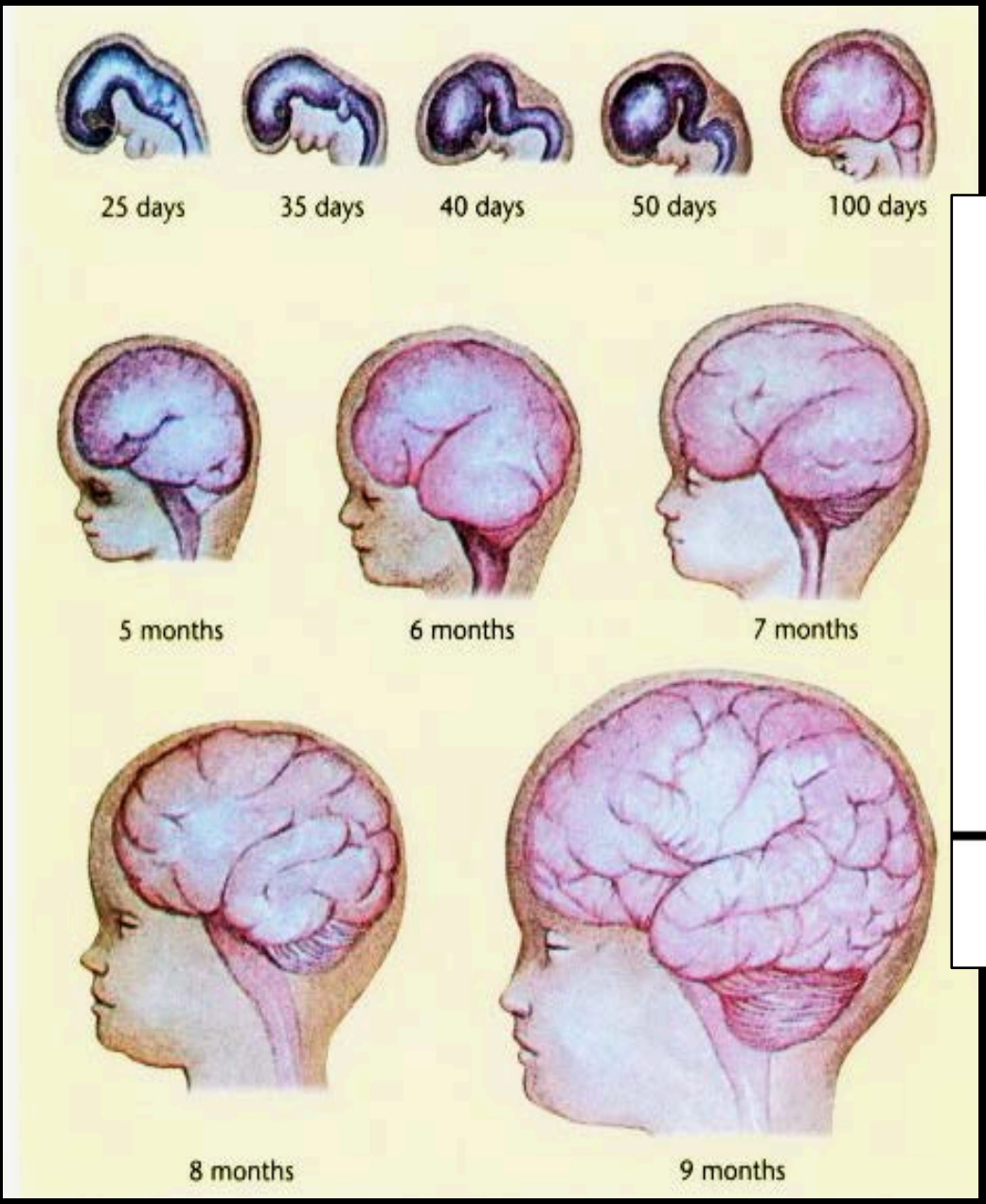
In the 5th week of gestation, the developing nostrils are widely separated, with the future cerebrum filling the space between them

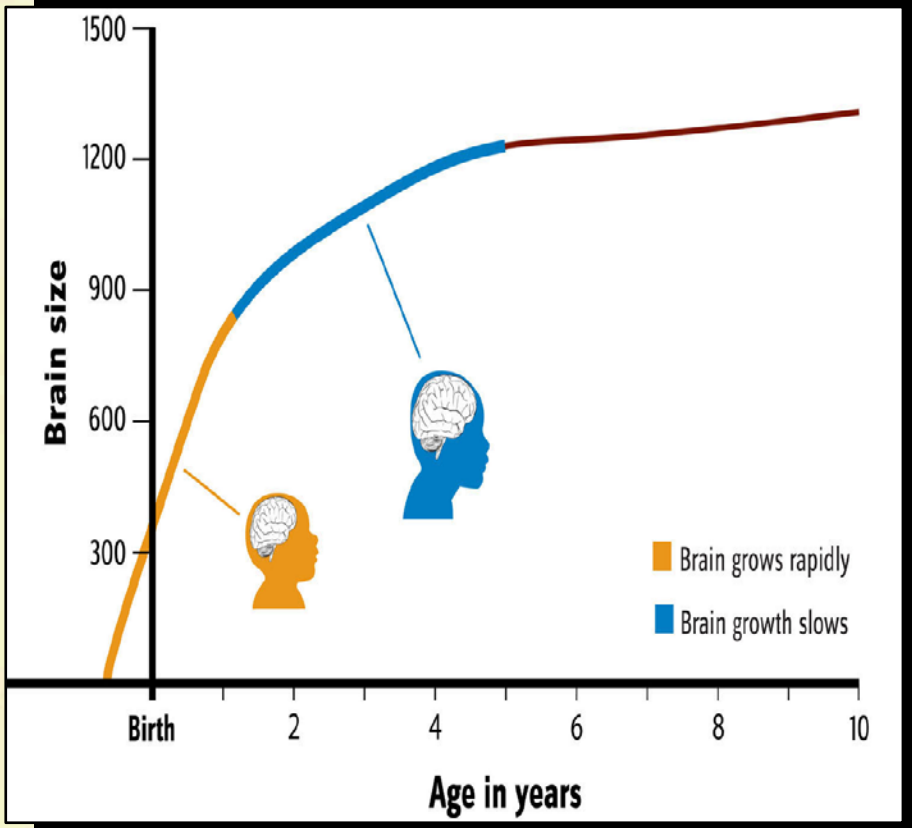
In the 6th week of development the face becomes more recognizably human



The developing brain is a hollow tube whose walls are only a few cell layers thick

While appearing quite adult-like at the time of birth, the brain continues to grow and develop postnatally, achieving 90% of its adult weight of 1300-1400 g. by age 10



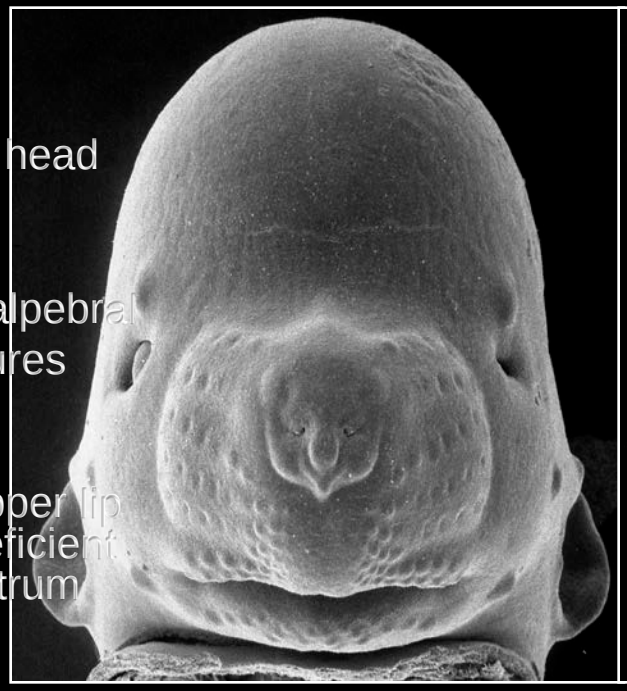


Early stages of mouse and human development are very similar

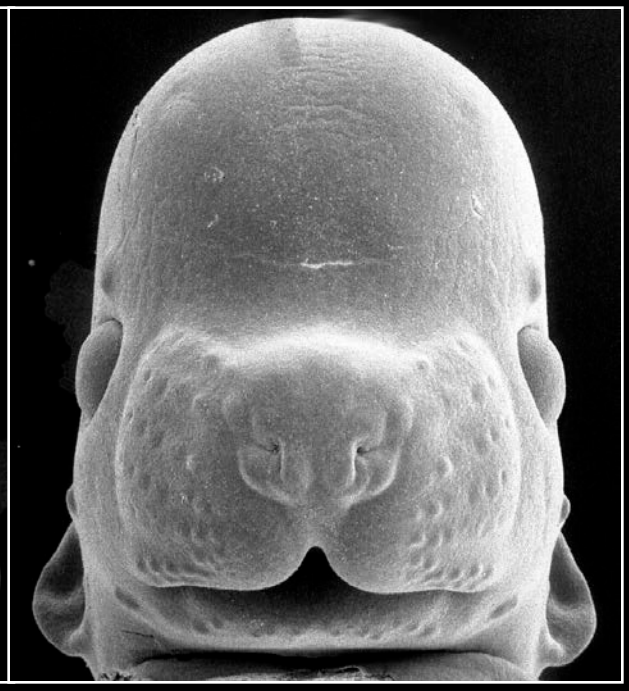
The characteristic facial features of Fetal Alcohol Syndrome can be seen in both a child and a mouse fetus that were exposed to alcohol during development.

Pregnant mice were given alcohol at a time corresponding to the middle of the 3rd week of human development.

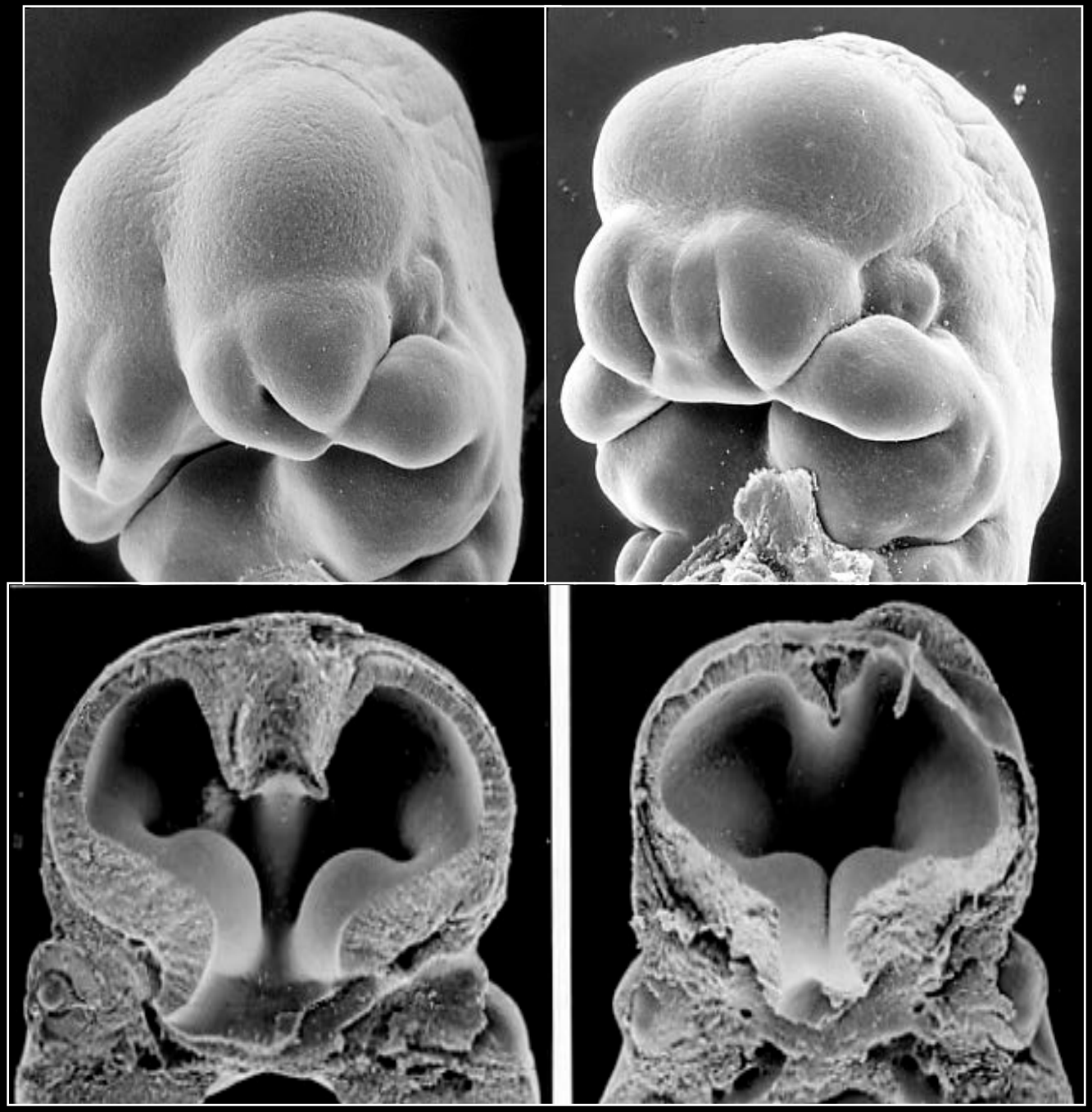
Child with FAS



Alcohol-exposed mouse fetus



Normal mouse fetus

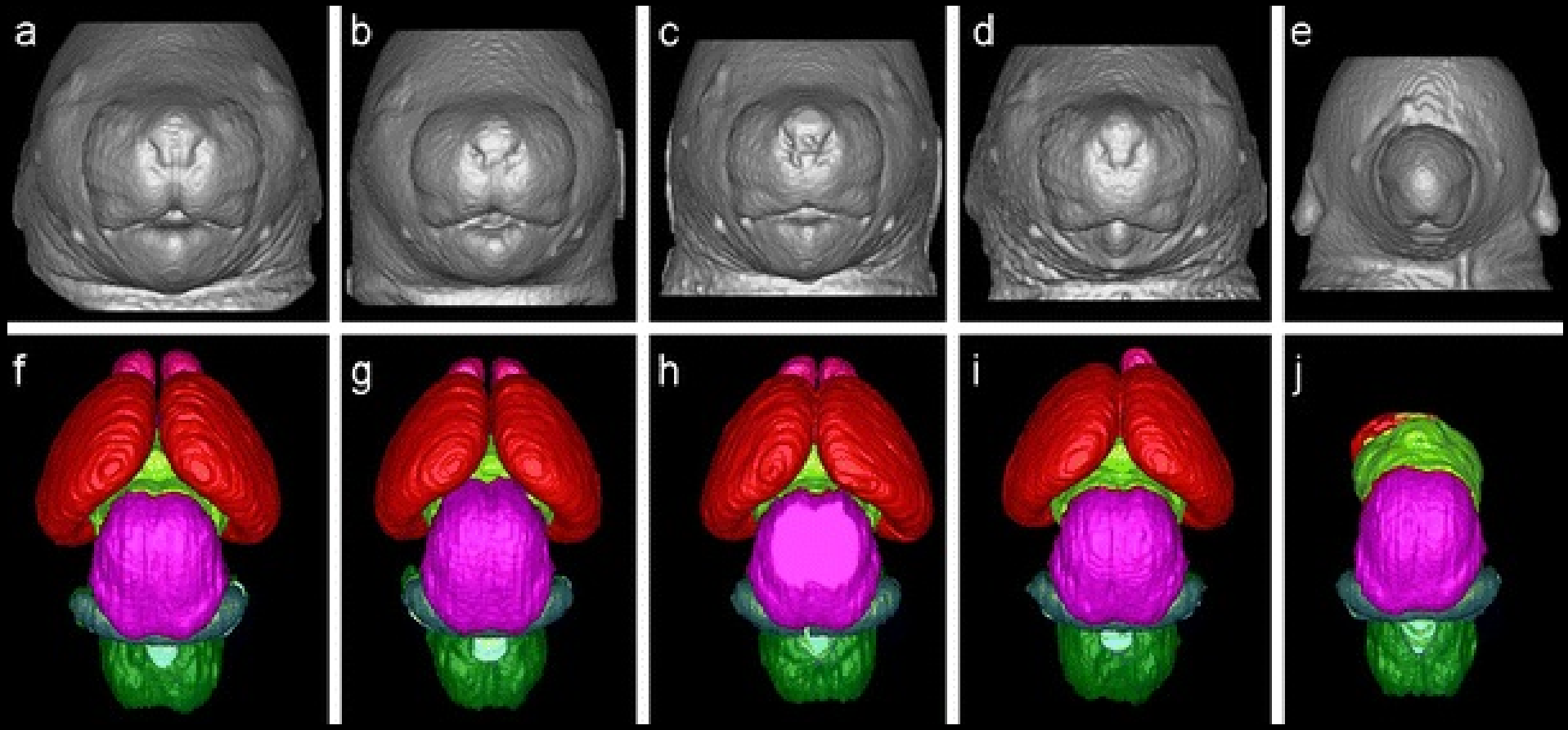


Normal

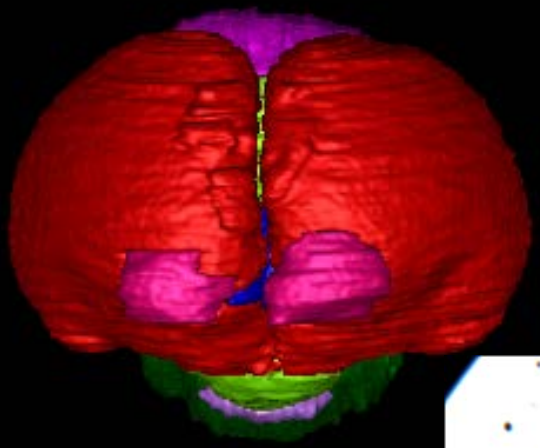
Alcohol-exposed

Alcohol-induced deficiencies in the tissues between the nostrils includes failure of the central portion of the cerebrum to form, along with an abnormal upper lip

Following early prenatal alcohol exposure the face and brain are affected to varying degrees

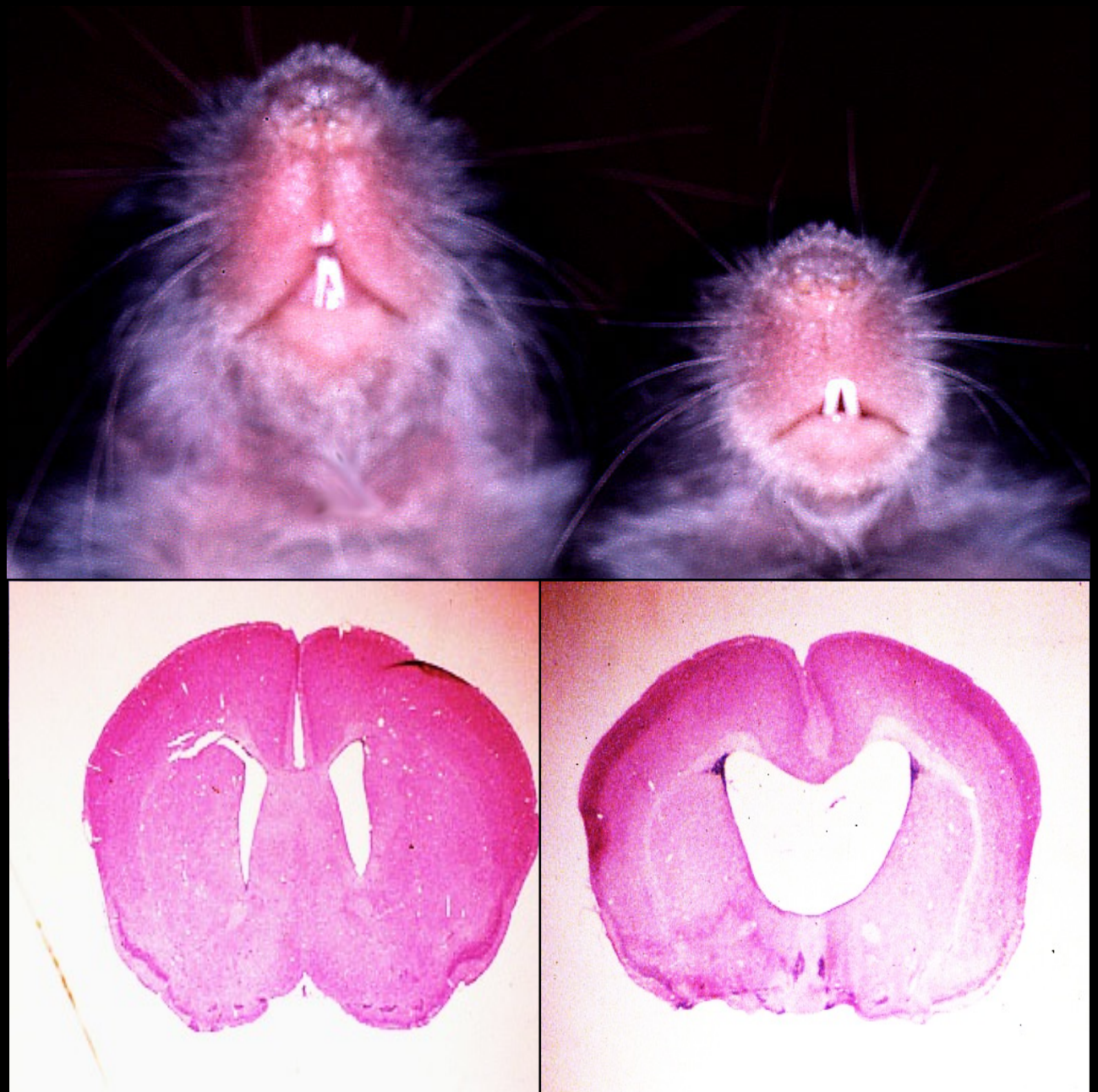


from O'Leary-Moore et al, 2011

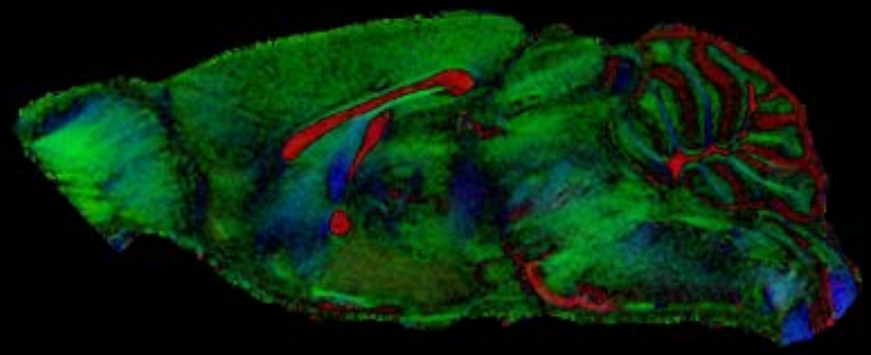


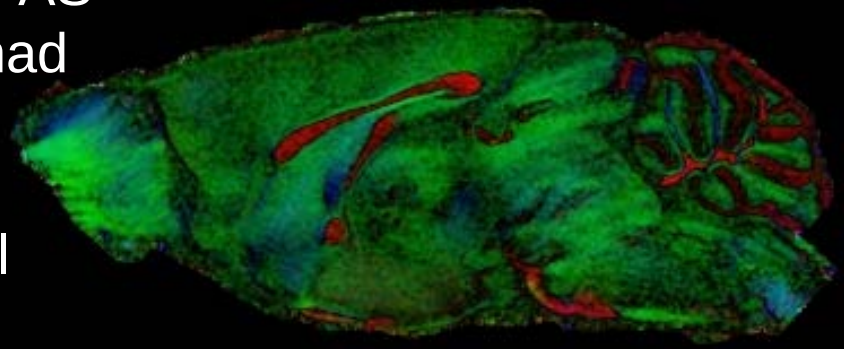
Remaining cortical tissues are abnormal

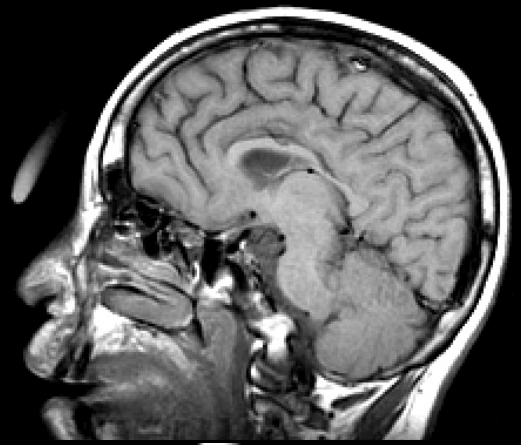
Midline defects of the face and brain persist postnatally

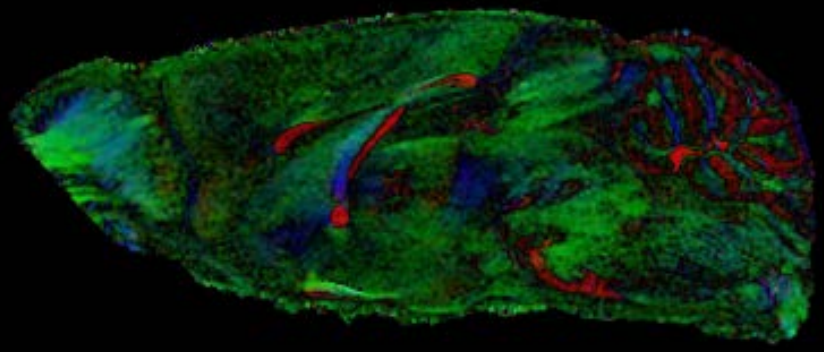


Corpus callosum abnormalities are similar in human FAS and in mice that had been exposed to alcohol at early stages of prenatal development



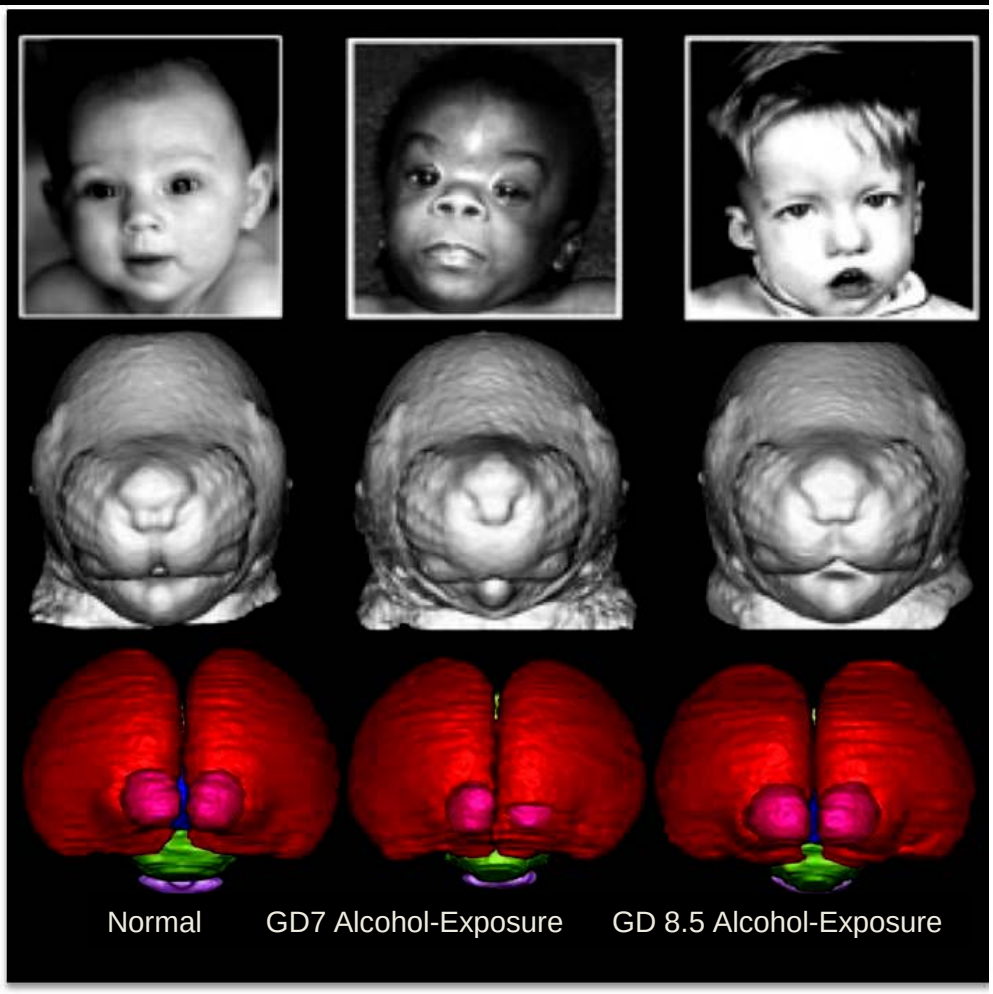


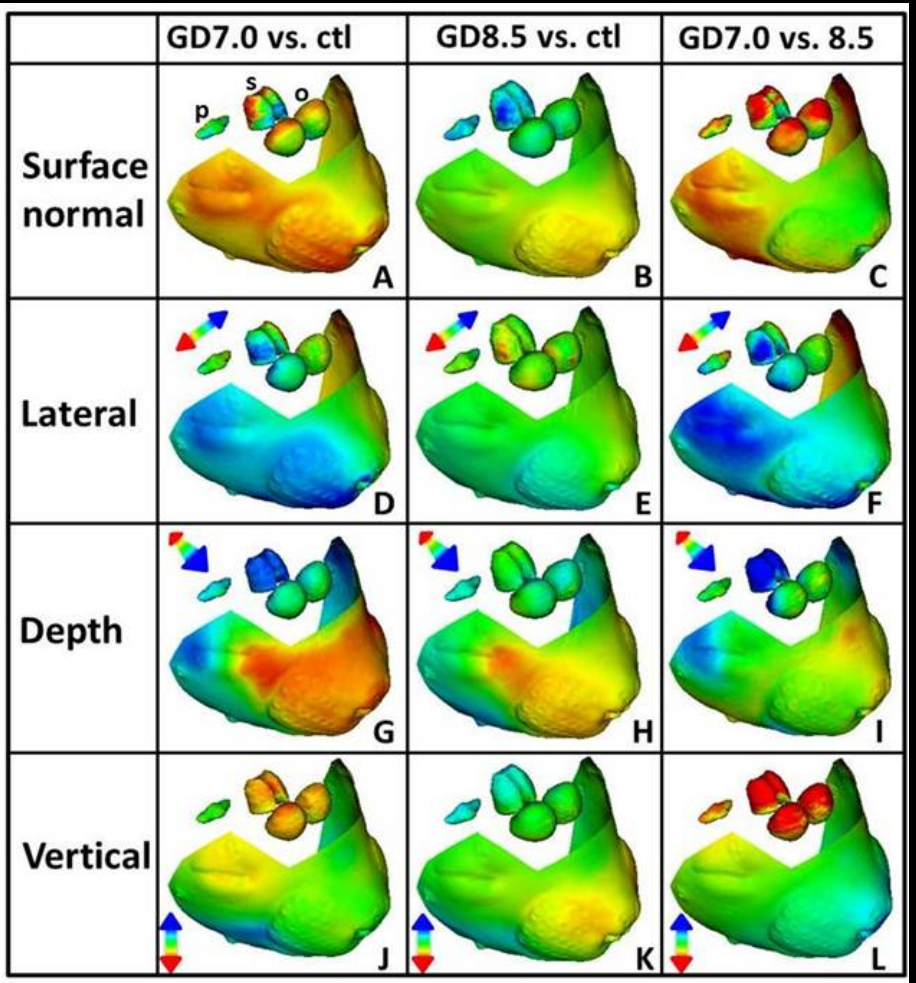




Human images courtesy of S. Mattson

Abnormalities of the face and brain vary depending on the developmental stage at the time of alcohol exposure





Lipinski et al, 2012; PLOS One

Mutation of genes in the sonic hedgehog pathway increases susceptibility to alcohol-induced birth defects

+/-

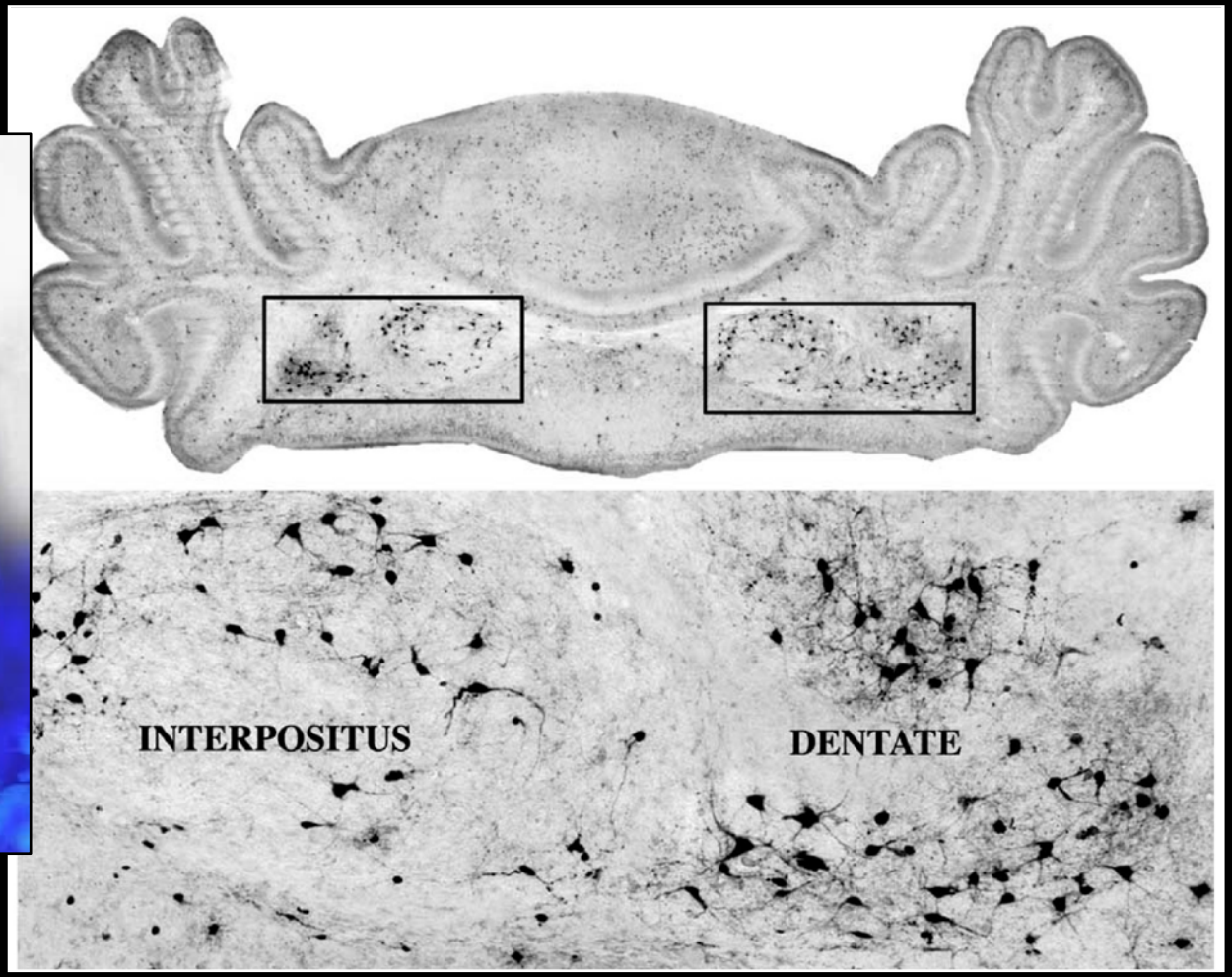
X

+/+

½ +/-

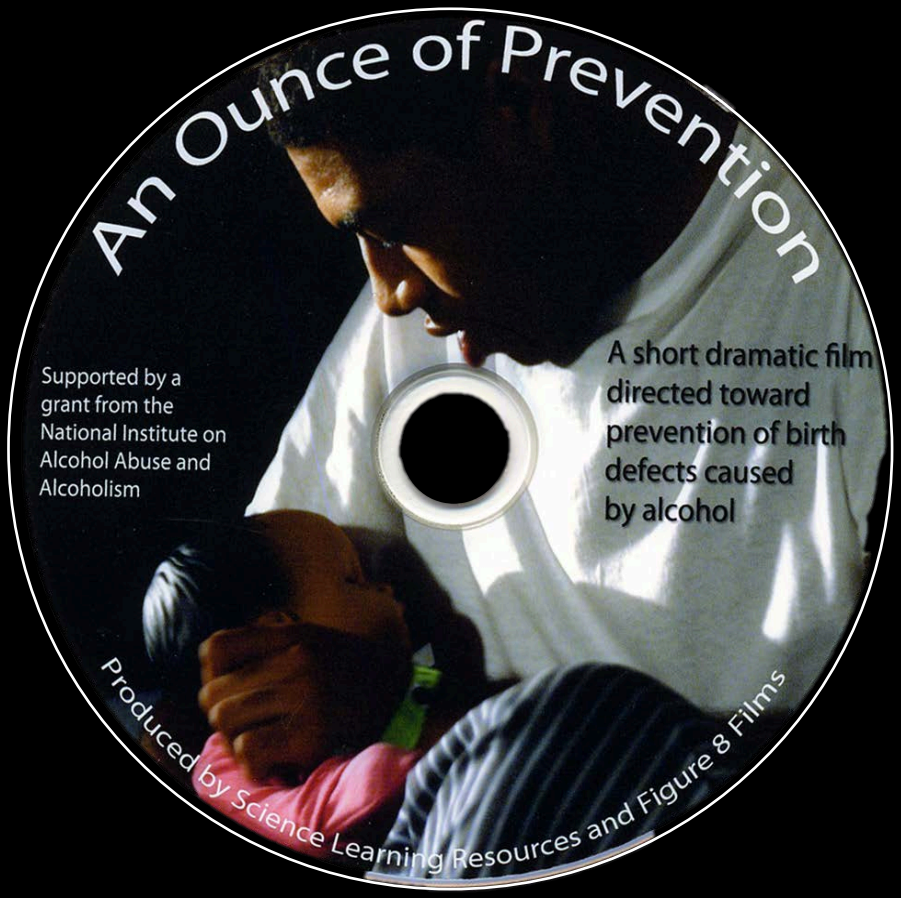
½ +/+

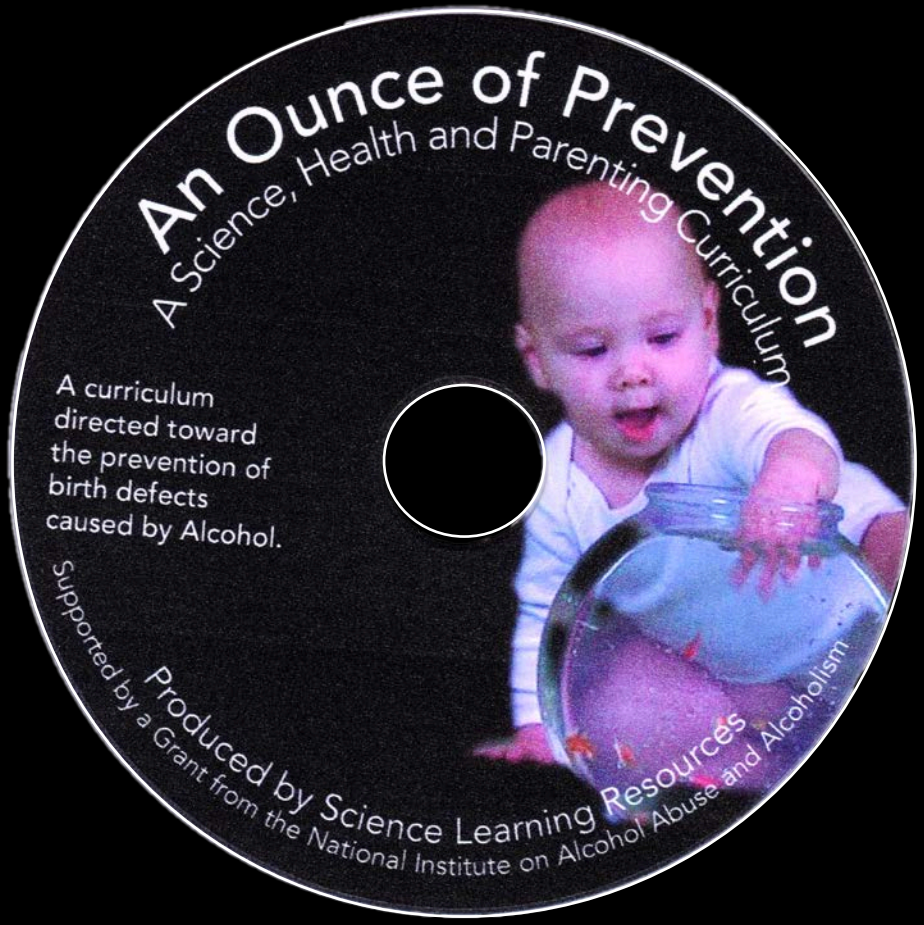
Alcohol causes cell death in the mouse cerebellum following 3rd trimester-equivalent exposure



From Dikranian et al 2005

NIH-supported school curricula emphasize prevention, the impact of early prenatal damage, and the biological basis for FASD
and may serve as a model for other (population-specific) education programs





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Thank you for your attention