"Prenatal Surgery May Be Preferable for Spina Bifida" (USN&WR Feb 10, 2011)

"The results also show that 42 percent of children who had undergone surgery in the womb were able to walk unassisted at age 3 compared with 21 percent of those who received the surgery postnatally. The two groups didn’t show marked differences in mental development. The in utero surgery was done between 19 and 26 weeks of gestation."

I. Maturation of the Vertebrate Brain

- The nervous system in human & non-human animal species develop in quite similar manner. We share similar neurotransmitters, ionic channels, & larger structures. Hence we often study non-human animals in order to understand what happens to humans.

- **Human Embryology**: The study of the development of the human embryo from Day 1 through Day 60 of gestation (the first 8 weeks of life). From Day 61 through Day 252 (roughly weeks 9 to 36), the developing organism is a fetus.

  **Week 1**: Conception -> migration of emerging organism to uterus

  **Week 2**: Implantation of organism (termed a "blastocyst" [III] into the uterine endometrium (wall of uterus; IV)
Week 3: Differentiation of embryonic nervous system begins (see below)

- Stages of Development of the Embryo

**Early Embryonic Development**

- CNS begins to develop at the beginning of Week 3. The **ectoderm** thickens to form the **neural plate** which in turn folds and forms the **neural tube** around a fluid-filled cavity. The upper portion of the neural tube becomes the brain while the lower portion becomes the spinal cord. The cavity becomes the central canal of the spinal cord and the ventricles of the brain. In diagram above on the right note how the folds of the neural tube at Day 22 begin closing like a zipper (on Day 23 and following).

- At birth, the human brain weighs ca. 350 grams (vs. 1000 grams at the end of year 1 and 1200-1400 grams for the adult brain)

**A. Growth and Development of Neurons**

1. **Proliferation = production of new cells**

   - **Stem cells** divide & redivide. Some become primitive neurons & some glia (see images on right) and migrate to other locations. Some stem cells remain in place and continue to divide.

2. **Migration (Movement)**

   - Neurons move (migrate) toward eventual destinations in the brain. They are guided by factors noted below (chemicals in families of **immunoglobulins**)
& chemokines). Some move from the inside to the outside (or vice versa) while others move along the surface.

- Deficits (too little) of immunoglobulins & chemokines may lead to intellectual deficiency or decreased brain size while excesses (too much, e.g., immunoglobulins) may possibly lead to some cases of schizophrenia.

3. Differentiation = develops dendrites and an axon

- Neural cell precursors differentiate, i.e., they take on a definite shape & form with an axon and dendrites.
- The axon often grows first & may actually trail the neuron like a tail as it migrates into place.
- Dendrites begin to proliferate when the neuron reaches its final location.

4. Myelination = glial cells produce fatty sheaths to insulate (myelinate) axons

- Myelination occurs first in the spinal cord, then the brain, in a process that extends through adulthood.

5. Synaptogenesis = formation of synapses

- In the right chemical environment (see below), synapses will form between neurons and neurons & muscles/glands

B. New Neurons in Later Life?

- Do we develop new neurons in our brains as adults? The old answer used to be "no," but research has identified some new neurons
  - Olfactory (smell) receptors in the nose. Stem cells in nose dive with one remaining a stem cell and the other becoming a neuronal smell receptor. Olfactory receptors have half-life of 90 days.
  - Hippocampus of adult mammals including humans
    - Perhaps keeps us open to "new learning" as we get older.
    - Also, need to keep separate but similar memories from interfering with one another: "But scientists ... believe that the main purpose of these adult-born nerve cells is to encode a kind of memory called pattern separation, which is necessary for the accuracy of memories because it keeps similar experiences from overlapping." Science News 20110129 "Making Nuanced Memories"
    - ≤ 2% of hippocampal cells are replaced each year
  - No other regions in the human brain have been shown to produce new neurons (see next item)

- What about the cerebral cortex? NO new neurons probably develop. Use of carbon 14 (\(^{14}\text{C}\)) dating in the 1960s & 1970s (after the 1963 Nuclear Test Ban Treaty) found
  - Skin cells ≤ 1 year old
II. Pathfinding by Neurons

A. Chemical Pathfinding by Axons

How do axons know where to go in linking up to target organs? They use chemical trails or pathways.

- **Chemical gradients**: axons initially follow surface paths or directions marked by differing chemical gradients, i.e., densities and types of chemical molecules which either attract or repel the migrating axon. For example, in the brain of the newt (an amphibian described below), one protein is 30x more concentrated in one area of the tectum compared to another area.

- The role of chemical gradients was originally discovered by **Roger Sperry** in experiments on newts in the 1940s. After cutting the optic nerve of a newt (a kind of salamander) and rotating its eye, the newt formed new neural connections to the tectum (its visual processing center). But, the optic nerve axons re-connected to their original targets in the tectum and not new targets.

B. Competition Among Axons as a General Principle

- Axons tend to find their targets and create a range of many "trial" or temporary connections (that is, they overproduce too many synapses). What then happens? The connections are either strengthened or weakened by the postsynaptic cells which "choose" which connections to keep or "discard" others.

- Gerald Edelman (1987) proposes a theory of **neural darwinism**, i.e., random synaptic connections made in the brain during development are followed by a process of selection: some connections are kept for their utility and others are discarded. This theory indicates a general principle of competition among axons for which will be chosen or rejected.
III. Determinants of Neuronal Survival

1. Nerve Growth Factor (NGF)

The Nobel-winning Italian scientist, Rita Levi-Montalcini (d. 2012), discovered that muscles produce a chemical, nerve growth factor (NGF), which is released at the synapse with axons. NGF promotes the survival and growth of these axons which are part of the sympathetic nervous system.

All neurons are born with a "suicide" program, i.e., instructions to die automatically if they do not make the right synaptic connections. Programmed cell death is called apoptosis. Some neurons must receive NGF or they will die.

2. Neurotrophins = Chemicals like NGF or BDNF (brain-derived neurotrophic factor) that promote survival & activity of neurons. We do not entirely understand what controls the survival of neurons in the cortex and other places of the brain. But, research suggests that NGF and BDNF lead to:

- Prevention of apoptosis
- Increased axonal branches
- Increased regrowth of axons after brain damage

3. Surplus Neuron Production

- The developing brain of the fetus produces more neurons than it will eventually need. For example, between Weeks 10 and 25 of gestation, the number of motor neurons in the ventral spinal cord decreases from 175,000 to about 120,000.

- The brain produces 2 to 3 times as many neurons as needed in adulthood
  - Adolescent brain shows decrease in number of neurons but growth of white matter in parietal & temporal cortex, i.e., more connections & myelination

IV. The Vulnerable Developing Brain

The pattern of brain development in most animal species is directed by a set of genes known as homeobox genes. These control how other genes express themselves and, thus, how anatomical development unfolds.

"Homeobox genes are a large family of similar genes that direct the formation of many body structures during early embryonic development. A homeobox is a DNA sequence found within genes
that are involved in the regulation of patterns of anatomical development morphogenesis in animals, fungi, and plants. In humans, the homeobox gene family contains an estimated 235 functional genes and 65 pseudogenes, which are structurally similar genes that do not provide instructions for making proteins. Homeobox genes are present on every human chromosome, and they often appear in clusters.\(^{(2)}\) (Structural Biochemistry, Wikibooks)

**During prenatal development, the nervous system is highly vulnerable to a variety of threats** (compared to what would happen later in life). These include

- malnutrition
- toxic chemicals (alcohol, cigarette smoke, others)
- infections

**Toxic Chemicals**

**Alcohol Use in Pregnancy → Fetal Alcohol Syndrome (FAS)**

- How does alcohol damage the developing brain?
  - interferes with neuron proliferation, migration, & differentiation
  - by inhibiting signals (alcohol increases GABA & dampens glutamate), neurons do not receive signals and, thus, die by apoptosis.
  - But, remaining neurons up the release of glutamate, become overstimulated, and die because of excess sodium & calcium ions (which damage mitochondria).

- Physical & psychological difficulties in FAS: decreased alertness, hyperactivity, intellectual/cognitive impairment, motor problems, heart defects, and facial abnormalities.

- No safe level for alcohol consumption in pregnant women has been found

**Cigarette Smoking**: prenatal exposure to maternal cigarette smoking may lead to a variety of disorders

- low birth weight & early life illness
- skull deformities (craniosynostosis) [from CDC.gov]
- Down syndrome (esp. with oral contraceptive use) [from CDC.gov]
- Sudden Infant Death Syndrome (SIDS)
- long-term intellectual deficits
- Attention Deficit Hyperactivity Disorder (ADHD)
- immune system impairment (more sickness in infancy & childhood)
- delinquency & criminal behavior in later life (esp. for males)

(Omit: Differentiation of the Cortex)

V. Fine-Tuning by Experience

Our nervous system can be "fine-tuned" or altered (within limits) by the effects of experience

1. Experience & Dendritic Branching

- In rats, environmental "enrichment" leads to more dendritic branches, thicker cortex, and better performance on new learning tasks.
- Much of this effect is due to exercise which causes the release of neurotrophins.
- Enrichment in environments appears to enhance sprouting of axons and dendrites for humans and other species.
- Exercise also appears to be helpful for older people in maintaining brain's functioning.
- Note that most studies of computer-guided "mental exercise" programs have found NO benefit for children, adolescents, or adults.
  - Studies of adult brain are usually never replicated or test so many alternative hypotheses that some positive results are found merely by chance.
  - However, physical exercise has been shown to positively affect the brain, especially, the hippocampus.

2. Effects of Special Experiences

**Blindness**

- Blind persons since infancy are more sensitive to tactile sensation (touch). The occipital lobe (usually dedicated to visual sensation) is activated by task such as reading Braille lettering.
- Blind persons also excel at verbal processing tasks.
- The occipital lobe seems to be "invaded" by connections related to these skills. Use of transcranial magnetic stimulation to inactivate the occipital lobe interferes with these abilities.

**Musical Training**

- Practice makes a person more capable of a skill. Some brain changes have
Musicians: auditory cortex responds more forcefully to pure tones than among non-musicians. Part of the temporal cortex is 30% larger in professional musicians.

Musicians who must listen for key sounds are able to recognize differences in tonal languages such as Chinese: **nián** (rising tone = year) vs. **niàn** (falling tone = study)

Postcentral gyrus (somatosensory strip): larger area devoted to left fingers among violin players vs. non-musicians.

**Focal hand dystonia:** fingers of musicians become clumsy & have difficulty playing correctly. Appears to be related to reorganization of the thalamus and somatosentory cortex devoted to the fingers: areas for individual fingers begin to overlap.

### VI. Brain Development and Behavioral Development

#### 1. Adolescence

- **Antisaccade Task:** Requiring someone to look in the opposite direction to a visual stimulation. Inhibiting impulse to look in the same direction before the age of 7 is almost non-existent. Ability to do so rises sharply between 7 and 11 years old and gradually during teenage years as prefrontal cortex matures. The myelination of prefrontal tissue is still continuing in adolescence.

- Adolescents more frequently choose immediate rewards than later larger rewards compared to adults, e.g., $100 now rather than $150 in a year. Research by Laurence Steinberg and colleagues at Temple University suggest that, in the brains of adolescent, the **reward system** ("incentive processing" system including the ventral striatum and orbitofrontal cortex) competes with the **cognitive control** system which "[keeps] impulses in check and...[provides] the mental machinery needed for deliberation regarding alternative choices" (Chein et al., 2011).

- Prefrontal cortex of adolescent brains (the "cognitive control" system) tend to be less responsive in situations requiring inhibiting behaviors. HOWEVER, **higher levels of impulsivity** occur mostly in **social settings** where **impressing peers** becomes the dominating influence. Note: "In addition to a puberty-related spike in interest in opposite-sex relationships, adolescents spend more time than children or adults interacting with peers, report the
highest degree of happiness when in peer contexts, and assign greatest priority to peer norms for behavior” (Albert et al, 2013).

- In the presence of adolescent peers, fMRI studies show that the reward system of adolescent brains becomes much more sensitive and active. (Chein et al., 2011)
  - For example, adolescents who drive cars with similar-aged peers present have a greater rate of traffic accidents than when driving alone or with adults present.

2. Old Age

- Memory and reasoning begin to weaken after age 60. Very gradual loss of brain tissue in temporal cortex and hippocampus. (Frontal lobe starts declining after age 30!)
  - Older people are very vulnerable to brain decline after illness or injury because of inflammatory processes.
  - However, the majority of individuals in positions of executive authority (CEOs, college presidents, political leaders) are over 60 years old.
- Yet, losses are relatively small, knowledge and experience base of older people is usually larger, and there are multiple compensation mechanisms that make up for many losses.

References
