

Putting it into Practice: Pediatric Environmental Health Training Resource

A Developmental Approach to Pediatric Environmental Health

User Guide



Children's
Environmental
Health
Network

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I. Slide Presentation

- **Slide 3:** As children progress through developmental stages, their exposure and susceptibility to environmental toxins changes. Sources of exposure, routes of absorption, metabolism, sensitive target tissues, and health effects are different at each stage of development. The developmental stages that will be addressed in this module include:
 - Preconception
 - Fetus
 - Newborn (Birth to 2 months)
 - Infant/toddler (2 months-2 years)
 - Preschool age child (2-6 years) and school age child (6-12 years)
 - Adolescent (12-18 years)
- **Slide 4:** The objective of this module is to understand sources of exposure, route of absorption, metabolism, distribution to target tissues, and health effects of environmental toxicants at each developmental stage. Environmental tobacco smoke (ETS) exposure will be used as an example at each stage of development.
- **Slide 5:** Infants and children may manifest adverse responses to their environment that may not be noted in the adult population. Several factors may contribute. First, the physical location can be experienced differently by children and has the potential to be more hazardous. For example, certain toxicants accumulate closer to the ground, where infants and toddlers may spend more time. Secondly, pre-ambulatory children cannot remove themselves from a dangerous environment, such as direct sunlight, thus are at risk for sustained exposure.
- **Slide 6:** Exposure to toxicants is impacted by the physical, biological, and social environment in which children interact, at each developmental stage. The physical environment consists of anything that we make contact with: food, air pollutants, radiation, etc. The biologic environment is determined by each child's genotypic response to exposure, at the various developmental stages. The social environment is determined by societal regulation of what can be controlled in the environment.
- **Slide 7:** This slide is the first to introduce environmental tobacco smoke (ETS). ETS is comprised of the smoke that comes from the end of a burning cigarette (called sidestream smoke) and the smoke that is exhaled (called mainstream smoke). ETS is also called secondhand smoke. ETS contains at least 250 chemicals, which vary with each cigarette.



There are at least 69 known carcinogens and no level of exposure is safe! Examples of some of the chemicals found in ETS are listed. Cotinine is a nicotine metabolite that can be used as a biologic marker of exposure. It has a long half life.

- **Slide 8:** This slide shows that an experimental chamber can mimic concentrations of the chemicals in ETS that can be found in indoor spaces.
- **Slide 9:** Metabolism of ETS differs between individuals, and at various developmental stages. Metabolism is impacted by the biologic environment of each individual. Chemicals found in ETS may be either metabolized to a form that can be excreted, or activated to a more potent toxicant (potential carcinogen) that cannot be excreted. The metabolic pathway is determined by both the developmental and genetic expression of metabolic enzymes. The developmental expression changes, conferring more or less susceptibility. For example, benzo(a)pyrene is one of the carcinogens in ETS. Benzo(a)pyrene first undergoes epoxidation to benzo(a)pyrene epoxide. However, there are two possible pathways for further metabolism. One leads to the “ultimate carcinogen,” a metabolite which is carcinogenic, cannot be further metabolized and is not excreted from the body. The other pathway involves glutathione transferase which allows the chemical to be excreted by the body. The relative amount of benzo(a)pyrene which is metabolized and excreted is determined by two factors: 1) the developmental expression of glutathione transferase and the other enzymes and 2) the genetic expression of these enzymes. The developmental expression of these enzymes changes as a child grows, thus conferring more or less susceptibility to the carcinogen. Genetic differences in the expression of glutathione transferase are known to confer greater risk of lung cancer in smokers who lack this enzyme.
- **Slide 10 and 11:** The toxicokinetic diagram illustrates how an environmental toxin enters the body, distributes in the various organs of the body including where it is excreted, the metabolism of the chemical, its interaction with target molecules, the repair process of any damage caused, or the resultant toxic effects of the chemical. Each of these processes is dependent on the developmental stage of the individual.
- **Slide 12 and 13:** The first developmental stage presented in this module is preconception. Slide 13 introduces the important concept of the epigenome. The epigenome describes certain interactions with the genome, which may regulate how genes are expressed. The epigenome is passed on during cell division, and is heritable between generations. The epigenome is a potential target for environmental toxicants, which can be inherited by subsequent offspring.
- **Slide 14:** Even before conception, environmental toxicants may affect pregnancy outcome. Future pregnancy can be impacted by direct effects on maternal or paternal reproductive organs. In addition, certain chemicals (such as lipid-soluble toxicants and heavy metals) bioaccumulate, and are mobilized during pregnancy. More women are entering the workforce annually, which increases occupational and environmental pregnancy risks.



- **Slide 15:** This slide describes maternal exposures that may affect subsequent pregnancies. Cells that are actively dividing are most susceptible to environmental toxicants. Ova are an example of actively dividing cells. Ova begin to develop during early fetal life, and the oocyte completes prophase of their first meiotic division before birth. Oocytes can remain in this state until puberty, and potentially until menopause. Ova are vulnerable to toxicants that may impact future generations. An example is the effect of maternal smoking on fertility. In addition, the transgenerational effects of diethylstilbestrol (DES) taken during pregnancy have been documented. Documented effects include hypospadias in DES grandsons, prematurity in DES grandchildren, and ovarian cancer in DES granddaughters.
- **Slide 16:** This slide describes paternal exposures that may impact subsequent pregnancies. Sperm are produced hours to days prior to conception. Therefore, environmental toxicant exposure during the peri-conceptual period may impact the fetus. Sperm have a short life span, which limits the period of vulnerability. However, rapid differentiation increases their susceptibility to harm. Sperm have no DNA repair mechanism, so in their mature form are vulnerable to mutagens.
- **Slide 17:** The table on slide 17 contains examples of environmental toxicants that may potentially impact future pregnancies. Organohalogenes, such as polychlorinated biphenols (PCB's), are an example of lipid-soluble chemicals that are stored in adipose tissue and mobilized during pregnancy. Similarly, lead is a heavy metal that is stored in bone and may also be mobilized during pregnancy due to calcium turnover from bone. Both exposure to PCB's and lead during pregnancy have been associated with neurodevelopmental delay. Paternal exposure to hydrocarbons and dietary exposure to nitrosamines have been potentially linked to development of leukemia later in childhood.
- **Slide 18:** This slide characterizes the impact of exposure to ETS and active smoking during the preconception period. Maternal active smoking has been associated with reduced fertility and decreased motility in the female reproductive tract. Active paternal smoking has been linked to altered sperm morphology, motility and concentration. There is inadequate evidence to link ETS and male fertility.
- **Slide 19:** The second developmental stage presented in this module is the fetus.
- **Slide 20:** The fetus is highly susceptible to environmental toxicants due to very rapid cell division and growth, allowing for enhanced opportunity for toxicants to interact with DNA and lead to mutation. In the fetus, the immune, neurologic, and endocrine systems are highly vulnerable as they undergo critical stages of development. In addition, the developing blood-brain barrier makes fetus highly susceptible to neurotoxicants



- **Slide 21:** The fetal stage is critical for brain development. During the fetal stage, neurons differentiate, proliferate, and migrate; Synaptogenesis occurs. Myelination begins and continues during the newborn period.
- **Slide 22:** There is a “critical window” during fetal development when the fetus is more vulnerable to certain toxicants. Organogenesis occurs during the embryonic period (week 3-8 of gestation); during this period major malformations are likely to develop in response to toxicants. Week 10-17 are more critical for brain development; exposure to ionizing radiation during weeks 10-17 of gestation is associated with a high risk of microcephaly.
- **Slide 23:** Certain maternal exposures during pregnancy have been associated with spontaneous abortion, miscarriage, and congenital anomalies. The chart depicted on this slide lists exposures during pregnancy that have been shown to impact pregnancy outcome.
- **Slide 24:** Fetal exposure to environmental toxicants can be measured at birth via cord blood samples and meconium. In 2007-2008, The Environmental Working Group (EWG) assessed cord blood and found ~200 of 413 toxins that were tested. Most were lipid soluble and bioaccumulative. Meconium samples from newborns can also be assessed to determine fetal exposure.
- **Slide 25-27:** The table found on slides 25-27 depicts examples of environmental toxicants that are associated with adverse birth outcome.
- **Slide 28-29:** The site of absorption of environmental toxicants from mother to fetus is the placenta. The placenta acts as a barrier to some substances, and allows other compounds to reach fetus. The placenta performs metabolic and detoxification functions similar to liver. Placental structure, gene expression, and metabolism of toxicants changes based on the gestational age of the fetus, leading variability in the level of exposure to toxicants. Slide 29 depicts the two possible pathways of fetal exposure to environmental toxicants: placenta-dependent and placenta-independent. Placenta-dependent pathways rely on the maternal bloodstream to deliver the chemical to the fetus. Properties that allow chemicals to readily cross the placenta include low molecular weight, lipid solubility, and the ability to utilize active transport mechanisms. Examples of chemicals that meet these criteria are provided. Carbon monoxide is an example of a low molecular weight compound that can cross the placenta and displace oxygen from hemoglobin. Exposures that occur via placenta-independent pathways include ionizing radiation, electromagnetic fields, heat, and noise. For example, heat has been associated with neural tube defects.
- **Slide 30-31:** Slides 30-31 describe maternal and fetal distribution of environmental toxicants to the fetus. Physiologic changes during pregnancy can impact distribution. During pregnancy, there is an 85% increase in plasma flow to the kidney which facilitates maternal excretion of toxicants before reaching the fetus. Hypoalbuminemia during pregnancy changes the ratio of bound chemicals, thus it may alter transport of toxicants to



the fetus. Certain chemicals have an affinity to accumulate in the fetal compartment, such as heavy metals, DDT, and polyhalogenated biphenyls. Fetal hypoproteinemia leads to decreased protein binding, and distribution to fetal tissues and organs. Lipid-soluble toxicants accumulate in the adipose-containing organs, including the brain. The immature blood-brain barrier may contribute to bioaccumulation in the fetal brain; this is somewhat controversial.

- **Slide 32:** This slide describes fetal metabolism of environmental toxicants. Expression of enzymes that metabolize environmental toxicants is developmentally regulated. The fetus may be protected against a toxicant if the active form is a metabolite for which the enzyme is not functional; an example is Acetaminophen toxicity from which fetus is protected by this mechanism. However, the fetus may be at increased risk from a toxicant if the active form cannot be metabolized to an inactive form. In addition, if the fetus metabolizes a compound to a less polar metabolite, the metabolite may not readily cross back to maternal circulation for elimination.
- **Slide 33-35:** These slides return to the example of ETS exposure during the fetal stage of development. Active maternal smoking or ETS leads to “passive smoking” across the placenta that directly affects fetus. Cotinine levels in cord blood are elevated in infants of mothers who smoke or are passively exposed to ETS. Intrauterine growth restriction (IUGR) a known outcome. As we learned earlier, carbon monoxide readily crosses the placenta due to its low molecular weight. Carbon monoxide has a higher affinity for fetal hemoglobin than adult hemoglobin, and the formation of carboxyhemoglobin is thought to lead to fetal hypoxia and IUGR. Slide 34 depicts the effects associated with active maternal smoking on pregnancy outcome. Spontaneous abortion, IUGR, low Apgar scores, preterm delivery, and cleft lip and palate are associated. It is important to note that impaired lung function present during fetal life can persist into childhood from this exposure. In addition, evidence is suggestive that there may be a link between maternal smoking and childhood cancers. Exposure to ETS may also impact the outcome of pregnancy. IUGR, low birth weight, and impaired lung function in the newborn and child are associated with exposure to ETS. Evidence is suggestive that there may be a link between ETS exposure and childhood cancers, preterm delivery, and congenital malformations such as neural tube defect.
- **Slide 36:** The third developmental stage presented in this module is the newborn (birth-2 months).
- **Slide 37:** There are several unique exposures during the newborn stage. The first is breast milk. The newborn is at the top of the food chain. This means that any chemical that bioaccumulates is concentrated in breast milk, especially lipid-soluble compounds. Exposure to drinking water is also a unique property of the newborn. If a baby is fed powdered formula made up with tap water, that infant is exposed to a significant amount of tap water and the contaminants that enter the water supply.



- **Slide 38:** This slide depicts target organ susceptibility in the newborn. During the newborn period, organs in which rapid cell division and growth continue are highly susceptible to toxicants. Neuronal cell division is complete by 6 months; migration, differentiation and myelination continue into adolescence. Pulmonary alveolar development continues with cell division and differentiation in this period. Although the brain and lungs are the most vulnerable organ systems, rapid turnover continues in the hematopoietic system and the skin epithelium. Somatic growth continues over the first year of life.
- **Slide 39-40:** The newborn also has differences in pathways of absorption. The skin is highly permeable, has a large surface to volume ratio, and is an important site of absorption of lipophilic compounds. Keratinization occurs over 3-5 days following birth, but the skin remains highly absorptive for first 2-3 weeks of life. There have been toxic exposures related to underestimation of the absorptive properties of newborn skin. In one case, cloth diapers were used in a newborn nursery. They had been stamped with the name of the laundry using an aniline containing dye. The babies suffered an epidemic of methemoglobinemia from the absorption of the aniline dye. The GI tract is also unusual in its absorptive properties during this period of time. The GI tract is highly permeable, and vulnerable to ingested toxicants in breast milk and formula. Gastric pH remains high allowing an overgrowth of intestinal bacteria. Hence, any nitrates contaminating well water from fertilizer residues and consumed in large amounts by the infants, results in high nitrite levels in the gut leading to high absorption of nitrites and subsequent methemoglobinemia. Immunoglobulin active transport mechanisms across GI epithelium are vulnerable to toxicants such as PCB's and other dioxin-like compounds. During the newborn period, the respiratory tract becomes a large absorptive area. The pulmonary lymphatic system is vulnerable to absorption of airborne pollutants. Hence, chemicals in ETS can be directly absorbed through the epithelial surface.
- **Slide 41:** Distribution of chemicals in a newborn's body is also affected by body composition as well as the presence of barriers to diffusion. A newborn's body is 75% water and 25% fat compared to an adult with 14% of body mass in fat. The higher fat content means that babies will have differences in distribution of fat soluble chemicals, such as the carcinogens in ETS. The formation of the blood brain barrier also occurs during this time, so that early in this period, there is no barrier to diffusion. This lack of a blood brain barrier is why pediatricians worry about jaundice in the newborn. Bilirubin has direct access to the brain and can lead to kernicterus.
- **Slide 42:** Complicated changes are occurring in the expression of the metabolizing enzymes during the newborn period. Phase I Enzymes (Cytochrome P450) and Phase II Enzymes that lead to excretion of toxicants are not well expressed in the newborn. In addition, genetic polymorphisms play a role in the level of activity of these enzyme systems at all developmental stages. Renal function is also developmentally regulated. At birth, glomerular filtration is a fraction of adult values, and gradually increases by 1 year of age. This can impact the excretion of both drugs and toxicants.



- **Slide 43:** The table found on this slide provides examples toxicants that have been reported to impact newborn infants, the route of absorption, and effects of exposure. As depicted in the table the GI and dermal routes of absorption are important in this developmental stage, and neurodevelopmental adverse outcome is common following significant exposure.
- **Slide 44:** This slides returns to the example of ETS exposure and outcome during the newborn stage of development. Outcomes that have been associated with ETS exposure in this stage include reduced lung volume and impaired pulmonary function, increased incidence of upper and lower respiratory infections, decreased somatic growth, neurodevelopmental delays, increased incidence of SIDS, and greater infant mortality.
- **Slide 45:** The fourth developmental stage presented in this module is the infant and toddler (2 months-2 years).
- **Slide 46:** Exposures to environmental toxicants unique to the infant and toddler stage are related to changes in diet, increasing ability to interact with the environment, and time spent in a particular environment such as the breathing zone nearest to the ground.
- **Slide 47-48:** During the infant and toddler period, oral exploratory behavior is a normal stage of development. However, oral exploration places the infant and toddler at risk for exposure to environmental toxicants such as lead and pesticides. In addition, dietary exposures increase as solid foods are introduced into the diet. It is important to note that approved food additive levels are based on the lifetime exposure of an adult, and that processed infant foods have been shown to have higher concentrations of additives and residues such as pesticides. Certain contaminants are unintentionally added to our food supply. Pesticide residues are released into air, soil water and make their way into the food chain Examples include reports of Alar contamination of apples, and Aldicarb contamination of bananas and potatoes. PCB's and Dioxin are bioaccumulative lipophilic chemicals found in our food supply, and nitrates and nitrites have been reported to contaminate the water supply. Other chemical additives are added purposefully to our food supply, such as coloring, flavoring, and preservatives. There are also chemicals found in plastic, paper and adhesive that indirectly may contaminate food (examples are BPA and phthalates).
- **Slide 49:** This slide describes the Food Quality Protection Act of 1996. The Food Quality Protection Act provides age appropriate estimates of dietary consumption based on children's dietary patterns for allowable pesticide levels on food. It accounts for exposures to pesticides via other routes such as drinking water and residential application and the cumulative effect for pesticides with a common mechanism of action. The Food Quality Protection Act requires the EPA to use a 10-fold margin of safety when setting standards for pesticide exposure when there is limited data on infants and children.
- **Slide 50-51:** One must consider the physical environment around the home when thinking about exposure during the infant and toddler period. The floor inside the home is an



important micro-environment for pre-ambulatory and ambulatory infants and toddlers when crawling, cruising, and walking. Surface contaminants are in higher concentration near the floor, such as cleaning solutions, pesticide residue and formaldehyde from new synthetic carpet. Certain contaminants layer in highest concentration in the lowest elevations, such as heavier particles in ETS, mercury vapor from latex paint, or radon. Oral, respiratory, or percutaneous exposure may occur while crawling or playing. Examples of common toxicants include lead paint, cleaning supplies, and pesticides or herbicides inside or on the grounds of the home.

- **Slide 52:** During the infant and toddler period the lungs, skin and GI tract remain common sites of absorption. The lungs have a large absorptive surface area. Infants have higher respiratory rate than older children and adults, and inhale more air/kg due to higher metabolic rate and oxygen needs. This correlates with a proportionally higher inhaled toxicant exposure and absorption per kg as compared to an older child or adult. Higher calorie/ kg/day leads to greater quantitative exposure to food and potential toxicants via the GI tract. Qualitative differences in diet increase exposure: greater consumption of fruit, vegetables, and milk products in this stage impacts relative ingestion of toxicants. During infancy, the ratio of skin surface area to body weight is double that of adults. Therefore, the skin remains an important site of absorption.
- **Slide 53-54:** The metabolic capability of the liver (sulfation, acetylation, etc) is developmentally regulated, and does not mature until 3 to 6 months of age. Also, important properties of the kidneys leading to excretion in urine do not mature until 6 months of age. Slide 52 describes the developmental regulation of the metabolic capability of the liver and excretion capacity of the kidneys by age.
- **Slide 55-56:** These slides return to the example of ETS exposure and outcome during the infant and toddler stage of development. Exposure to ETS continues to have detrimental effects on children in this stage. These effects include increased incidence of lower respiratory illness, upper respiratory infections, increased SIDS and infant mortality, increased morbidity of RSV infection, reduced lung volume and impaired pulmonary function, decreased somatic growth, and neurodevelopmental delay. In addition, evidence suggestive of a causal relationship with childhood cancers, and there are reports of increased adult-onset cancers with lifelong exposure
- **Slide 57:** The fifth developmental stage presented in this module is the preschool (2 months-6 years) and school aged child (6-12 years).
- **Slide 58:** This slide describes respiratory exposures unique to this developmental stage. It is important to think about how the same physical environment may be different for adults as compared to children at various stages of development. Breathing zones are a good example of this concept. For adults, the breathing zone is approximately 4-6 feet above the floor. However, for a child, their breathing zone is dependent on both height and mobility. Large respirable particulate matter settles closer to the floor, hence chemicals from carpet



or flooring have a higher concentration near the floor. In addition, oxygen consumption is greater in children than adults. Children have a higher metabolic rate, leading to increased oxygen consumption and CO₂ production per kg of body weight. This necessitates higher minute ventilation, and contributes to greater exposure to air pollutants compared to adults when adjusted for body mass.

- **Slide 59-61:** During this developmental stage, food remains a source of exposure to environmental toxicants. Children consume more food per kg of body weight and require higher calories/ kg/day for growth, as compared to adults. In addition, new environmental exposures come into play during the preschool and school age years. During this stage, the physical and social environments begin to change as children spend more time away from the home and parentally-controlled environment. Potential sources of exposure to environmental toxicants in this stage include home, play areas such as playgrounds and schoolyards, and the day care and school environment. The chart on slide 58 depicts examples of sources of exposure during this stage. The table on slide 59 gives examples of common environmental toxicants and potential indoor and outdoor sources of exposure.
- **Slide 62:** As children reach school age, they spend the majority of their day indoors. Thus the indoor environment at day care and school become important sources of environmental toxicant exposure. Examples of common indoor exposures, such as ETS, are given. Studies show that the increasing incidence of childhood asthma may be associated with increasing exposure to the indoor and outdoor air pollutants listed on slide 60.
- **Slide 63:** As described previously, the metabolic capability of the liver is developmentally regulated, and continues to mature and undergo change. As the metabolic activity of phase I enzymes changes, metabolism of environmental toxicants may impact their activation or excretion.
- **Slide 64:** This slides returns to the example of ETS exposure and outcome during the preschool and school age child stage of development. Chronic exposure to ETS has an additive and harmful effect on respiratory function. In this age group, increased incidence of asthma, chronic cough, phlegm production, wheezing, shortness of breath, and reduced lung function are sequelae of chronic exposure. Multiple studies have shown a relationship between prenatal exposure to both ETS and lead and the development of ADHD during childhood. Chronic exposure to ETS is associated with increased incidence of lung cancer later in life. There appears to be a relationship with the development of other cancers, such as brain tumors, but further research is needed. In addition, an important exposure that may impact neurodevelopment during this stage is chronic exposure to lead. Global intelligence, hearing, speech, and balance may be impacted by chronic lead exposure. Inattention and impulsivity have been reported. There is some evidence that a long-term sequelae that can present in adulthood is hypertension.
- **Slide 65:** The sixth developmental stage presented in this module is the adolescent (12-18 years).



- **Slide 66:** This slide describes how exposure to environmental toxicants may change during adolescence. During this stage, freedom from parental authority begins. The adolescent can begin to self-determine their physical environment. However, abstract thinking and reasoning skills remain immature leading to misjudging and ignoring risks of certain behaviors such as substance use and abuse. Adolescents may actively choose to expose themselves to toxicants such as smoking and drugs. Therefore, communication about potential toxicities is essential for educators, parents, and health care providers. Occupational exposures also begin at this stage of development.
- **Slide 67:** The chart on this slide reviews routes of absorption and common occupational environmental toxicants that an adolescent may be exposed to. The skin and respiratory tract remain common routes of absorption. Examples of toxicants that may be absorbed through the skin include pesticides, nicotine, solvents, and UV radiation. Examples of common environmental toxicants absorbed via the respiratory tract include ETS, lead fumes, pesticides, solvents, and asbestos.
- **Slide 68:** Metabolism of toxicants in the adolescent is typically similar to the adult. However, a decline metabolic rate and in hepatic phase I enzymes such as CP40 may be associated with hormonal changes associated with puberty.
- **Slide 69-70:** Growing, dividing, and differentiating tissues are most sensitive to environmental influences due to shortened time for DNA repair and changes within DNA during cell growth. During puberty, there is rapid accretionary and hypertrophic growth in the skeleton, viscera, and muscles. Development and differentiation occurs in the reproductive system. These tissues and organ systems become susceptible to environmental toxicants. This might explain why adolescent chimney sweeps in the 1800's were prone to scrotal cancer after exposure to soot. In addition, toxicants such as endocrine disruptors can mimic hormones (phthalates, BPA) and may impact reproductive organ differentiation
- **Slide 71:** This slides returns to the example of ETS exposure and outcome during the adolescent stage of development. Acute and chronic effects are described. Acute respiratory effects include cough and increased asthma exacerbations. Chronic exposure continues to have an impact on pulmonary function. Additionally, lipid profile may be impacted in the adolescent, and chronic exposure to ETS is associated with increased cancer risk. Adolescents who actively smoke are highly susceptible to nicotine addiction.
- **Slide 72:** As described throughout this module, the health risks of ETS exposure during all stages of development are significant, and potentially life threatening. The health care provider should provide anticipatory guidance to parents and children, appropriate to each developmental stage.



II. Discussion Questions

1. List examples of characteristics that would predispose to environmental exposures at each developmental stage
 - Exposure
 - Routes of absorption
 - Metabolism
 - Toxic Effects
2. For each developmental stage, identify an environmental health hazard to which the children in your community may be exposed
3. Give examples of the hazards of exposure to ETS at each developmental stage. How can you advocate for the children in your community?



KEY RESOURCES FOR FURTHER READING

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