Pharmaceuticals and Endocrine Disruptors
What is the Endocrine System?

- A complex network of glands and hormones that regulates many of the body’s functions, including growth, development, and maturation, as well as the way various organs operate.

- Endocrine glands (pituitary, thyroid, thymus, pancreas, ovaries, testes, etc.) release hormones into the bloodstream that act as chemical messengers in order to control and regulate various functions.
THE ENDOCRINE SYSTEM

HYPOTHALAMUS
Regulates hunger, thirst, sleep and wakefulness plus most of your involuntary mechanisms including body temperature.

PITUITARY GLAND
Controls all other endocrine glands; influences growth, metabolism and regeneration.

THYROID GLANDS
Regulates your energy and your metabolism.

PARATHYROID
Secretes the hormones necessary for calcium absorption.

THYMUS
Helps build resistance to disease.

ADRENAL GLANDS
Secretes hundreds of compounds including cortisone & adrenaline which helps you react to emergencies. Regulates your metabolic processes in the cells, water balance, blood pressure, etc.

OVARIES
Influences how your blood circulates and determines your mental vigor and your sex drive. (Testes in males.)

METABOLISM - The conversion of nutrients into energy and building materials to meet your body's needs.
Hormones can be proteins, polypeptides, amino acids, or steroids.

The best known hormones are the sex steroids estrogen (ovaries) and testosterone (testes).

Other hormones include thyroxin, and insulin (pancreas)

Hormones levels released into the bloodstream are very specific, highly regulated, and vital for human development and proper functioning.
Hormones are released by glands and travel throughout the body, acting as chemical messengers. They interact with cells that contain matching receptors to which the hormones will bind (Imagine a key fitting a lock).

Timing of hormone release is critical for normal function, particularly during fetal development.

Hormone imbalance can result in disease and disorders.
### What is an Endocrine Disruptor?

- An endocrine disruptor, or endocrine disrupting compound (EDC), is a synthetic chemical that when absorbed into the body either mimics or blocks hormones and disrupts the body’s normal functions. They can disrupt the production or release of hormones by glands.

- Since hormones are typically present in the body in relatively tiny concentrations, exposure to relatively small amounts of hormonally active substances can disrupt the proper functioning of the body’s endocrine system.
<table>
<thead>
<tr>
<th>Steroids</th>
<th>Pollutants</th>
<th>Plant Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>17(\beta)-Estradiol</td>
<td></td>
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<tr>
<td>17(\beta)-Estradiol</td>
<td>DDT</td>
<td></td>
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<tr>
<td>Genistein (isoflavone)</td>
<td></td>
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<tr>
<td>Diethylstilbestrol</td>
<td>PCB</td>
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<tr>
<td>Luteolin (flavone)</td>
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<tr>
<td>Ethynyl Estradiol</td>
<td>Bisphenol A</td>
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<td>Resveratrol (stilbene)</td>
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<td>Nonylphenol</td>
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<td>Coumestrol (coumarin)</td>
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</tr>
<tr>
<td>Zearalenone</td>
<td>Kepone</td>
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</tr>
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</table>
The Theory of Endocrine Disruption

There are studies of cell cultures, laboratory animals, wildlife, and accidentally exposed humans that show that environmental chemicals cause a wide range of reproductive, developmental, growth, and behavior problems, and so while “endocrine disruption in humans by pollutant chemicals remains largely undemonstrated, the underlying science is sound and the potential for such effects is real.”
While compounds that produce estrogenic, androgenic, and androandrogenic, and antithyroid actions have been studied, less is known about interactions with other hormones. Could some interactions be synergistic?

It is difficult to definitively link a particular chemical with a specific health effect, and exposed adults may not show any ill effects; however, fetuses and embryos, whose growth and development are highly controlled by the endocrine system, are more vulnerable to exposure and may suffer lifelong health and/or reproductive abnormalities.
"Really?"

Yes...

desPLEX®
to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR

recommended for routine prophylaxis in ALL pregnancies...

96 per cent live delivery with desPLEX in one series of 1200 patients—
—bigger and stronger babies, too.1,2

No gastric or other side effects with desPLEX
—in either high or low dosage3,4,5
DES: Direct evidence that humans are susceptible to endocrine disruption.

- In the 1950s and 1960s, as many as 5 million pregnant women were prescribed diethylstilbestrol (DES), a synthetic estrogen, to prevent miscarriages. Not only did DES fail to prevent miscarriages, but it also caused health problems for many of these women’s children. It was discovered that after the children went through puberty that DES affected the development of the reproductive system and caused vaginal cancer.

- Though not an environmental pollutant, DES shows that EDCs can have the most detrimental effects on a developing human.
Likely routes of exposure to endocrine disruptors:

- Exposure can occur through direct contact with pesticides and other chemicals or through ingestion of contaminated water, food, or air.
- Chemicals suspected of acting as endocrine disruptors are found in insecticides, herbicides, fumigants, fungicides, and Pharmaceuticals and personal care products (PPCPs) that are used in agriculture as well as in the home.
- Further studies have found endocrine disruptors to leach out of plastics, including the type used to make IV bags.
Endocrine disruptors enter the air or water as a byproduct of many chemical and manufacturing processes and when plastics and other materials are burned.

Many people assume that medicines will be fully metabolized as they progress through the human body. This simply is not the case.

Estrogenic compounds are probably the largest contributor to endocrine disruption by domestic wastewater because estrogens are routinely excreted to household sewage.

Synthetic estrogens are commonly detected in wastewater effluent and in surface waters affected by effluent discharge.
What’s in our Water?

- In a study carried out in 1999-2000 by the USGS, up to 95 trace chemicals frequently present in municipal wastewater were measured at 139 sites across the country.

- 80% of the waters tested contained at least one of the 95 trace contaminants, and 82 of the 95 were present at one or more of the 139 sites.

- Among the most frequently encountered contaminants were coprostanol, a fecal steroid (86% of samples), cholesterol, a plant and animal steroid (84%), N-diethyltoluamide, an insect repellant (74%), caffeine (71%), 4-nonylphenol, a detergent metabolite and estrogen mimic (51%), and triclosan, a disinfectant (58%).
It is difficult to assign health significance to the previous measurements, and this is a source for objection, as critics argue that does-response relationship data suggest that the amounts of the chemicals actually in the environment are too low to cause an effect.

Example #1: The daily consumption of 2L of water containing the highest caffeine level encountered in any U.S. stream for 30 years would lead to ingestion of the mass of caffeine in two Excedrin tablets. When applied to ibuprofen, it would take 550 years to ingest the amount of two 400mg tablets.

Based on these types of comparisons, the compounds of primary concern are pharmaceuticals that play physiological roles at very low concentrations.
Example #2: The mass of 17alpha-ethinyl estradiol in some oral contraceptives is just 20 micrograms. The highest USGG measurement was .273 micrograms. Drinking 2L of that water for 37 days would provide the same mass of estradiol as one birth control pill.

What happens when these are ingested by developing humans, fish, and other species?

What if there is synergism when chemicals react with other chemicals inside the body?

The frequency of intersex characteristics among male roach, a freshwater fish that inhabits many streams in the UK, was significantly higher among animals taken downstream from wastewater tx plant outfalls than from corresponding upstream locations.
How do we know that endocrine disruptors are dangerous?

- Many plant and animal species are showing signs of ill health due to exposure to endocrine disrupting chemicals.
- Fish in the Great Lakes, which are contaminated with PCBs and other man-made chemicals, have numerous reproductive problems. Fish-eating birds in this area have shown similar dysfunctions.
- Endocrine disruptors are believed to be causing a declining alligator population in Lake Apopka, FL, the site of a large pesticide spill several years earlier. These gators have diminished reproductive organs that prevent successful reproduction.
Fish Studies
Sequential hermaphrodites are organisms born as one sex that may later change into the other sex, and can only function as one sex at one time. A few species in this group can change gender multiple times. Their DNA does not change during these processes.

- **Protandry**: When the organism starts as a male, and changes gender to a female later in life.

- **Example**: Clownfish are colorful reef fish found living in symbiosis with anenomes. One anemone contains a 'harem', consisting of a large female, a smaller reproductive male, and even smaller non-reproductive males. If the female is removed, the reproductive male will change sex and the largest of the non-reproductive males will mature and become reproductive.
Protogyny: When the organism starts as a female, and changes gender to a male later in life.

Example: Wrasses are reef fish that are all Protogynous

For some species, they all start out as females, and when they get large enough they will change their gender to males.

Other species start out as females or males, and either may shift to become a supermale. The supermale is larger and usually brightly colored, and there is only one in a given area of the reef. This supermale dominates the other wrasses of the species, and pair spawns (one male, one female) repeatedly. The other males will group spawn, with many males and females participating.
The order of sequential hermaphroditism within a species is often driven by resource demands.

In a population where resources are scarce and can support limited bearing of young, it is advantageous to have a larger population of males supporting one female.

Where resources are abundant and can support bearing of many young, on the other hand, it is advantageous to have many females mating with a limited number of males, so that more young are produced.
Deformities in fish cause concern

Research on Boulder Creek and the South Platte has uncovered a disturbing problem: Some white sucker fish downstream from Denver and Boulder sewage plants have both male and female reproductive tissue. Researchers also found something else: Females far outnumber males. Now they want to know if chemicals that mimic the female hormone estrogen are to blame. Utilities that provide water to more than 2 dozen communities from the South Platte don't test for the chemicals. Said biologist John Woodling, who discovered the gender-bending fish: "This is the only thing that has ever really scared me."

The white sucker was used as a test fish because they tolerate a wide variety of conditions, including river stretches containing domestic sewage treatment plant effluents. They were the only fish at the effluent sites.

### Study results

<table>
<thead>
<tr>
<th>Downstream of sewage plant</th>
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<th>Total</th>
<th>Female</th>
<th>Male</th>
<th>Intersex</th>
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<td>20</td>
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<tr>
<td></td>
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<td>3</td>
<td>2</td>
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<tr>
<td></td>
<td>June 18, 2004</td>
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<td>32</td>
<td>4</td>
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<tr>
<td></td>
<td><strong>Total</strong></td>
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<td><strong>101</strong></td>
<td><strong>12</strong></td>
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<tr>
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<td><strong>Total for both</strong></td>
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<td><strong>117</strong></td>
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</table>

### Upstream of sewage plant

<table>
<thead>
<tr>
<th>Date</th>
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<th>Male</th>
<th>Intersex</th>
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</thead>
<tbody>
<tr>
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<tr>
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<td>Sept. 24, 2003</td>
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<td>12</td>
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<tr>
<td>June 18, 2004</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>May 7, 2002</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>85</strong></td>
<td><strong>46</strong></td>
<td><strong>39</strong></td>
<td><strong>0</strong></td>
</tr>
</tbody>
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Sources: University of Colorado; Colorado Division of Wildlife.

Theo Stein, Andrew Lucas | The Denver Post
### Smallmouth bass

Percentage of male fish found to be intersex in Potomac tributaries:

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
</table>
| South Fork of the Shenandoah River | 80%  
| North Fork of the Shenandoah River | 100%  
| Shenandoah River | 100%  

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
</table>
| Upper Conococheague Creek | 100%  
| Lower Conococheague Creek | 90%  
| Upper Monocacy River | 80%  
| Lower Monocacy River | 100%  

### Largemouth bass

Findings from 13 male fish found in the Potomac River near the District's Blue Plains Wastewater Treatment Plant.

- **6 were normal** (46 percent)
- **7 had female characteristics** (54 percent)
- **3 were also intersex** (23 percent)
Other Adverse Effects of EDCs on Wildlife:

- Eggshell thinning and subsequent reproductive failure of waterfowl
- Reduced populations of Baltic seals
- Development of male sex organs in female marine animals, such as whelks and snails
- Reduced or malformed frog populations
- Disruption of normal sex ratios among exposed populations of fish.
Should humans be concerned about their health based on evidence that fish, birds, and alligators have been effected?

- Yes because all vertebrates (fish, amphibians, reptiles, birds, and mammals) are fundamentally similar during early embryonic development.
- Because endocrine disruptors affect the development of the body’s vital organs and hormonal systems, developing fetuses, infants, and children are more vulnerable to exposure, as is the case with DES.
Types of Endocrine Disruptors

- Chemicals commonly detected in people include: Bisphenol A, Polybrominated diphenyl ethers (PBDEs), and a variety of Pthalates.

- Bisphenol A – found in plastics, dental materials, and the lining of food containers. Potential concern is linked to reduced sperm counts. There is an unproven belief of miscarriages, obesity, and cancer. It is under a great deal of scrutiny because it is a common component of plastic baby bottles (there is a class action lawsuit regarding a failure to warn customer of the contents).
Polybrominated diphenyl ethers – found in fire retardants used in plastic cases of TVs and computers, electronics, carpets, lighting, bedding, cars, and cushions. The potential health concern is that these are structurally similar to PCBs and have similar neurotoxic effects. These were banned in the European Union in 2006.

Phthalates – found in soft toys, flooring, medical supplies, cosmetics, and air fresheners. They are known to disrupt the endocrine system of animals, and some research has implicated them in the rise of birth defects of the male reproductive system. CA and Europe have banned them from toys. In 2002, the FDA released a public report which cautioned against exposing male babies to DEHP, a type of Phthalate.
How can you risk exposure to EDCs?

- Buy organic foods whenever possible.
- Avoid using pesticides in your home or yard, or on your pet – use baits or traps instead and keep your home clean to prevent ant and roach infestations.
- Avoid fatty foods, such as cheese and meat (EDC’s accumulate in fat)
- If you eat fish from rivers, lakes, or bays, check with your state to see if they are contaminated.
- Avoid heating food in plastic containers, or storing fatty foods in plastic containers or plastic wrap.
- Do not give young children plastic teether's or toys, since these leach potential endocrine disrupting chemicals.
- Support efforts for more research and government regulation with regards to EDCs.