TRANSSEXUALISM: AN UNACKNOWLEDGED ENDPOINT OF DEVELOPMENTAL ENDOCRINE DISRUPTION?

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ABSTRACT

Transsexualism: An Unacknowledged Endpoint of Developmental Endocrine Disruption?

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In recent years, evidence has accumulated demonstrating that endocrine disrupting chemicals (EDCs) have the potential to alter sexual development at the organizational and functional level in many species, including humans, indicating that this class of chemicals may play a role in the etiology of transsexualism. Although transsexualism has historically been attributed to social or psychological causes, little data exists to support these claims, thus requiring a closer examination of the evidence regarding changes in sexual development due to EDCs. Toward that end, this thesis considers data from studies examining hormonal signaling mechanisms and changes in sexual development observed in wildlife, laboratory animals, and humans exposed to EDCs, all providing a consistent picture that sex hormones and their receptors are highly conserved evolutionarily, finding similar effects of disruption in many species.

In order to place the data in context, a number of historical threads are examined, including: the use of chemicals in agriculture, the use of the pesticide DDT and the pharmaceutical drug diethylstilbestrol (DES), the intertwined relationship between chemical manufacturers and the military, and the history of transsexualism since 1950. The operation and function of the endocrine system is reviewed in order to provide the background to properly interpret findings from endocrine disruptor studies, focusing particularly on the hypothalamic-pituitary-gonadal (HPG) axis. Recent physiological data regarding the vomeronasal organ (VNO) is reviewed, demonstrating that the VNO is the organ responsible for detecting pheromones, or sexually-relevant chemically-based cues, and that exposure of the VNO to extremely low levels of putative sex hormones causes numerous autonomic system responses, including alterations in endocrine function in males. It is therefore suggested that the VNO plays a central role in the circuitry involving sexual development, and a hypothetical framework for testing this concept is provided.

Using this framework, a mechanism for the development of gender identity is proposed, suggesting that gender identity is determined via pheromones by comparing the self with others at an unconscious level. One consequence of this mechanism is that messages conveyed by pheromones can be regarded as signals that can be in contradiction from messages from society, leading to a paradoxical double bind, or a logical contradiction between messages that exist on different logical levels. Another consequence is that there may exist a class of chemicals, pheromone disruptors, that could interfere with pheromones in a manner analogous to endocrine disruptors. Further research must be performed to test this hypothesis since little data exists on pheromones in humans, but early data suggests chemicals may be found that interfere with normal pheromone function.

The prevalence of transsexualism is examined, finding that prevalence differences reported in various countries are not well explained by social factors. Also, it is observed

that existing studies have reported the prevalence of transsexuals seeking treatment over a specific time period, but this reporting method is not a measure of the number of transsexuals for each country, which is what the term implies to most people. Several recent epidemiological studies that address sexual changes from endocrine disruption are critiqued, finding that they are plagued with methodological weaknesses and contain a number of errors in interpretation. It is argued that instead of using epidemiological techniques, a more useful approach would be to perform demographic studies that map the birthplace of transsexuals in space and time to determine any patterns that may be related to environmental conditions. The lack of detailed data on transsexual demographics, especially in the United States where such data are completely lacking, has left a void where a lack of data has been interpreted incorrectly as a lack of effect.

The fundamental assumptions used in risk analysis and toxicology are reviewed in the context of recent findings that the effects of a chemical may be larger at low doses than at high doses and that thresholds for the endocrine system must be determined empirically, rather than by assumption of a dose-response curve and extrapolation from an observed toxicological endpoint. The use of invalid techniques by toxicologists has thus invalidated claims of chemical safety, and indicates that public policy based on these techniques are insufficiently protective of public health. Because few things are more important to the continuity of cultures than sexuality and social relations, a number of areas requiring further research are identified, and the need for education of the public is emphasized. I conclude that the existing evidence points towards chemical causes of transsexuality rather than social or psychological causes, requiring a shift in research priorities away from psychosocial studies towards physiological studies of transsexuals.

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1) The Basic Problem: an Introduction

This thesis examines evidence implicating endocrine disrupting chemicals (EDCs) as a causal factor for the condition known as transsexualism – the internal sense or feeling of being a member of the opposite sex, compared to the anatomical sex in which one was born. In the last several decades, studies have increasingly identified changes in sexual development in wildlife and laboratory animals, elucidated fundamental biochemical signaling mechanisms underlying these changes, and have found similar effects in humans that may be due to early endocrine disruption. Because researchers have long suggested that transsexualism could be induced by changes in the hormonal milieu during development (Benjamin, 1966), endocrine disruptors appear to be plausible etiological candidates of transsexualism that warrant closer examination by the scientific community. Despite the fact that sex hormones partly guide sexual development, historical and political factors have played a significant role in keeping the study of most sexual changes in humans relegated to the psychosocial literature.

The major sections of this thesis include: a discussion of the terminology of sex and gender, a review of relevant history, an introduction to the endocrine system, a wide-ranging review of evidence from endocrine disruptor research, important studies related to sexual development and gender identity, analysis of major epistemological fallacies embedded in chemical risk assessments and public health policy, and identification of some research gaps and policy needs.

At the core, arguments over the possible causes of transsexualism have essentially revolved around disagreements over the relative importance of genetics, hormones, and socialization on the development of gender identity, resulting in a kind of nature/nurture

debate that has affected both theories as well as clinical approaches to treatment (Diamond, 1965). From a theoretical standpoint, transsexual etiology arguments generally fall into three classes: 1) biological predispositions of various sorts (Diamond, 1965; Asscheman, et. al., accessed February 20, 2004), 2) faulty gender identification formation due to improper parenting and socialization (Zucker, et. al. 2003), or 3) a form of mental psychopathology (Haraldsen and Dahl, 2000; Michel, et. al., 2001). Each view has had proponents historically, and a lack of agreement among the groups required the separation of treatment from etiology, for the entirely pragmatic reason that doctors were faced with patients whose drive to change sex hormonally and surgically was unrelenting (Benjamin, 1966; Pauly, 1968). Although ethical concerns over medical treatment of transsexuals were immediately raised, those treating transsexuals argued that reassignment was the only known effective treatment, and also suggested that the process they devised offered the opportunity for surgeons to learn advanced plastic surgery techniques as well as offering psychiatrists material in which they could formulate new theories of gender identification (Benjamin, 1966; Pauly, 1968). A Standard of Care was eventually devised for medical treatment of transsexualism; however, because treatment had been separated from etiology, it reflected an approach that was an *ad hoc* solution, not a systemic solution aimed at alleviating the cause.

Medical research in the emerging science of endocrine disruption is showing that the nature/nurture paradigm is overly simplistic, and that more complex processes are at work with respect to ontogeny of the various dimensions of human sexuality (Myers, et. al. 2003). This research is attempting to elucidate how endogenous hormones (hormones produced in the body) that guide sexual development and function can be mimicked,

blocked, modulated, or otherwise upset by many man-made and some natural chemicals widely used in virtually every aspect of modern life (National Research Council, p. 10-12, 1999). The fetus has been found to be incredibly sensitive to these hormonally active agents; research in mice shows that alterations in sexual development occur with exogenous estrogen concentrations as low as fractions of a part per trillion (vom Saal and Bronson, 1980; Colborn, et. al., p. 40, 1996). This research also shows that because risk assessments did not take into account low-dose effects and made a number of invalid assumptions regarding mechanisms and operation of the endocrine system, most chemicals currently in production cannot be deemed safe because the expected endpoints of endocrine disruption were never examined (Welshons et. al., 2003). Given that the historical production volumes of chemicals that act as hormonally active agents coincides with impacts on wildlife populations related to sexual development and function (Colborn 1993), it is a reasonable question to ask retrospectively if similar effects have occurred in humans.

Because EDCs can alter the expression of genes directly and indirectly, the development of the fetus may not follow the same path as it would have without the exposure, all other things being equal (Myers, 2003). It follows straightforward logic that because sexual development is mediated by sex hormones (which are closely related to other hormones), release of these chemicals into the general environment is likely to increase the variance of sexual gene expression across many species, including humans, since the endocrine system is highly conserved evolutionarily (Stoka, 1999, McLachlan, 2001). This increase in the variance of gene expression may therefore lead to increased variation in sexual expression. Some forms of transsexualism may be a special case of

endocrine disruption that likely has a genetic component, in that genetic differences can partly determine how sensitive an individual organism is to the effects of a particular exposure during a particular time (Dörner, 2001). Primary and secondary socialization may then constrain or encourage people to act in certain roles that may be contrary to their biological predispositions, but this does not change the predispositions themselves (Diamond, 1965, Udry, 2000).

In the past, theories that relied strictly on social factors or psychopathology were more tenable because very little empirical data on transsexual physiology and neuroanatomy existed. Some endocrinological studies have been performed, but in most cases, sex hormones levels were within normal ranges (Wålinder, 1968); whether these ranges are meaningful relative to the physiology of the individual is questionable, however, as normal ranges are quite wide and have been developed during the same period in which EDCs were used in large volumes, complicating the determination of normal ranges. But recently, compelling physiological data were identified in the hypothalamus of transsexuals, providing for the first time physical evidence of a morphological difference between the brains of transsexuals and non-transsexuals (Zhou, et. al., 1995, Kruijver, et. al., 2000, Chung, 2002). This data has led some researchers to conclude that transsexualism is a neurobiological condition that may be induced by a number of factors, including manipulation of the hormonal environment during development (Asscheman, et. al., accessed February 20, 2004).

Because gender identity development is widely thought to be at least partly dependent upon the hormonal environment during development, the endocrine disruptor hypothesis is highly relevant to the question of transsexualism, and a wide array of data

indicate a plausible linkage between the morphological changes observed in transsexual brains, differences in adult gender identity expression, and exposure to EDCs during development. The endocrine disruptor thesis thus necessitates a reconsideration of the role of these chemicals in the development of transsexualism.

Sex and Gender

For many people, sex and gender are synonymous terms with two possibilities: male and female. Often, the term sex has been associated with the type of genitalia, whereas gender has been associated with social sex or sex of rearing. However, not only can sex and gender be different, but each is composed of various dimensions that complicates the simple male/female dichotomy, requiring more precise definitions of sex and gender. The sexologist Benjamin (p. 2, 1966) enumerated the following dimensions of sexuality: "chromosomal, genetic, anatomical, legal, gonadal, germinal, endocrine (hormonal), psychological, and – also – the social sex, usually based on the sex of rearing." Under typical circumstances, all of these dimensions of sex are more or less in agreement, however, in cases such as transsexualism where the psychological dimension is contrary to other dimensions, the common definitions of sex and gender begin to break down. One recent study estimated that 2 percent of people in the U.S. have one or more dimension of sex/gender at variance with the others (Blackless, et. al., 2000), thus a more precise and comprehensive taxonomy of sex and gender are required to capture the full range of human expression. In this text, whenever possible, the term sex or gender will be qualified with the appropriate adjective when used in a dichotomous sense in order to reduce the ambiguities that invariably arise when terminology is used inconsistently. The terms sex and gender are retained as general umbrella terms, but every attempt will be

made to avoid their use in the traditional dichotomous manner. Transsexuals are defined as people whose gender identity is contrary to the other dimensions of sexuality; male to female transsexuals (MTF) identify as female and female to male transsexuals (FTM) identify as male.

Shown below are the various dimensions of sexuality enumerated by Benjamin and notes on some important features of the different compartments across which sex is distributed (Figure 1). It can be seen from this figure that the unqualified terms "sex" or "gender" are meaningless in cases where all the dimensions of sex are not in agreement; they may only be used in the dichotomous sense without qualification with reference to persons for whom all the dimensions are in agreement.

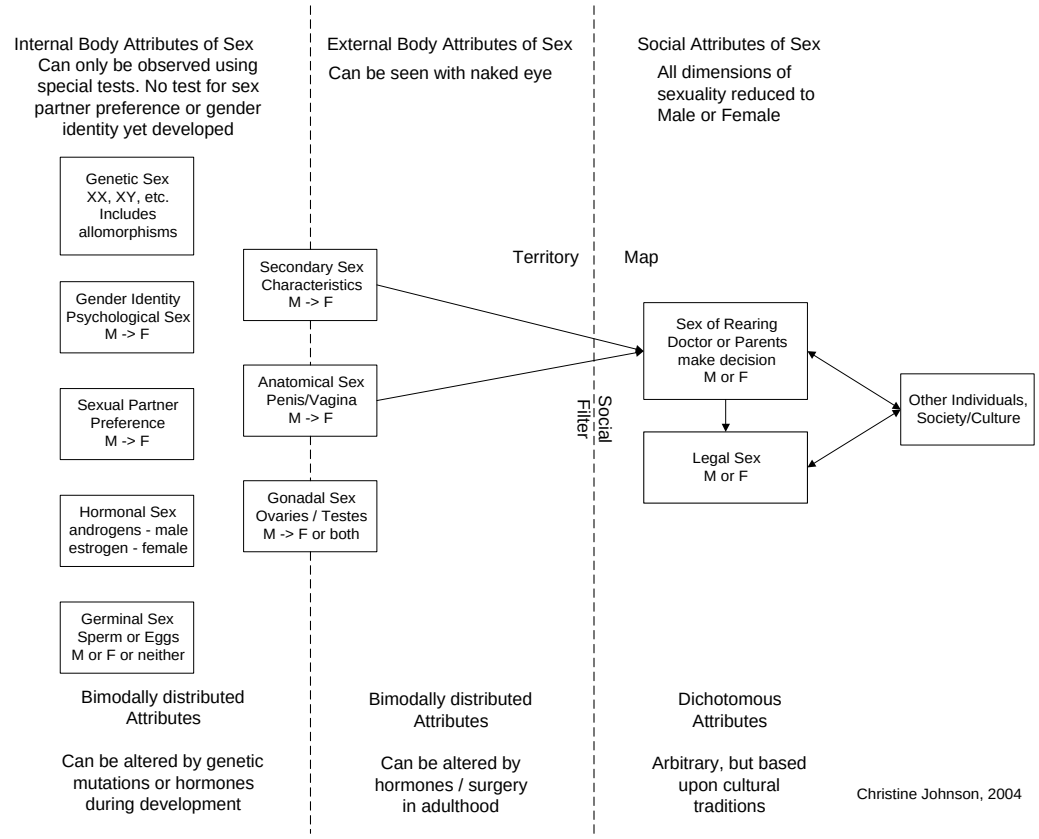

Figure 1: Attributes of Sex/Gender located within the body (Left), visible attributes (Middle), and attributes outside and apart from the body (Right). The differences in the dimensions of sex/gender require qualifying terms to specify which dimension of sex is being discussed. See text below for further explanation.

The internal attributes of sex are those not visible to the naked eye; these attributes can only be determined by special tests and no such test yet exists for sexual partner preference or gender identity. The secondary sex characteristics, anatomy, and genitalia can be determined in most cases by visual inspection. Gonads must be imaged or studied using standard histological techniques (after removal), although reduced size of the testicles in males is a diagnostic marker for hypogonadism (undersized gonads) that can be estimated visually in cases where they have descended. The sum total of all these attributes are what I am calling the territory; it is the set of attributes that defines an individuals' unique sex/gender, regardless of whether they are expressed outwardly. The

social attributes of sex, on the other hand, are initially based on a decision made by doctors or parents at the time of birth, typically a cursory examination of the genitals. In cases where ambiguity of genitals exists, other tests are now conducted to determine genetic sex and possible hormonal changes, for example, enzyme deficiencies (White & Speiser, 2000). However, because there is currently no known method of determining at birth if a person will identify psychologically as male or female in adulthood, it is possible for the wrong decision to be made regarding sex of rearing (Reiner, 2004), often leading to surgical reassignment of the neonate to the female anatomical sex because it is technically simpler to surgically construct a vagina than a penis. (Diamond & Sigmundson, 1997). This social aspect of gender has been termed gender expression (Currah and Minter, 2000).

This distinction between the map and the territory is important to make explicit, so that it is remembered that the name is not the thing named (Bateson, pp. 30-31, 1979); many difficulties have arisen from this epistemological error, and so by making this distinction explicit it becomes clear that there is a mapping process that occurs and further, that it is performed by people embedded in a cultural context that defines meaning (Bateson, p. 429, 1972; Ruesch and Bateson, p. 4, 1951[1968]). No person can truly understand that which they have not experienced directly; communication of internal states of perception across linguistic channels necessarily reduces experience to words, which are limiting by nature and varying in meaning depending upon context.

This difference between the map and the territory is explained by Bateson (p. 481, 1972), observing that we live in two worlds; one world is the physical universe in which things are related by forces and impacts, what Jung has called the pleroma, and the other

is the world of communication of information, encoded in differences, what Jung called the creatura. The two worlds have different rules; in the world of the pleroma, the body is a unique physical entity that more or less coincides with the boundaries of the skin; in the world of creatura, the system boundaries do not coincide with the body of the individual, but instead comprise the pathways in circuits of causation, including interactions with other people in society. In these pathways, what is passed is information, or news of a difference. Creatura corresponds with logic; pleroma with analogic. This gives us two ways of describing anything in the world – by describing the similarities among them (pleroma), or the differences between them (creatura). Both descriptions are also necessary components of any organism possessing "mind."

We also share this feature of two levels of description. In essence, we have messages from our bodies in the form of hormones, pheromones, and messages from our central nervous system based on past experiences. Other people can comment about us, and alter our perceptions of ourselves. When there are discrepancies between the messages received on different logical levels, the conditions of a double bind are created, in that there are two simultaneous messages that can be in contradiction – a paradox is created.

It is also important to note that many of the attributes that comprise the territory of sexuality are continuous in nature (a range from male to female corresponding to the Pleroma), whereas the map is dichotomous, permitting only two possible values for people living in society (male or female, corresponding to the Creatura). Thus, in the mapping process, the entire constellation of sex-related attributes is reduced to a single dimension and a line is drawn between the two serving as the demarcation; one half is

called male and the other half is called female; this process is indicated by the dashed vertical line that shows the mapping process as a type of social filter. The filtration function is introduced because although there are potentially an infinite number of differences between people, only some differences are considered important (Bateson, p. 481, 1972), in this case with regard to sex.

This concept is shown diagrammatically below for the gender identity dimension of sex, showing that gender identity may take on a range of values with a different mean value for the population of genetic males and females (Figure 2). Some people will fall into the region associated with the opposite gender, indicating a higher probability of cross-gender identification. The general shape of these distributions when added together is similar in shape to the figure drawn by Dr. Christian Hamburger, the physician that reported the sex reassignment surgery on Christine Jorgenson (Jorgenson, p. 160, 2000[1967]). It should be noted, however, that the actual shape of the curves is unknown, partly due to the fact that no single metric of gender identity has been identified which correlates to male or female identity. Conceivably the size of the bed nucleus of the stria terminalis (BTSc) region of the hypothalamus could serve as such a measure, but because it can only be measured by dissecting the brain, current technological limitations prohibit using the size of this region as a measure of gender identity. Additionally, factors other than the size of the BTSc region might also play an important role in perceived gender identity, hence the arbitrary units for the gender identity axis.

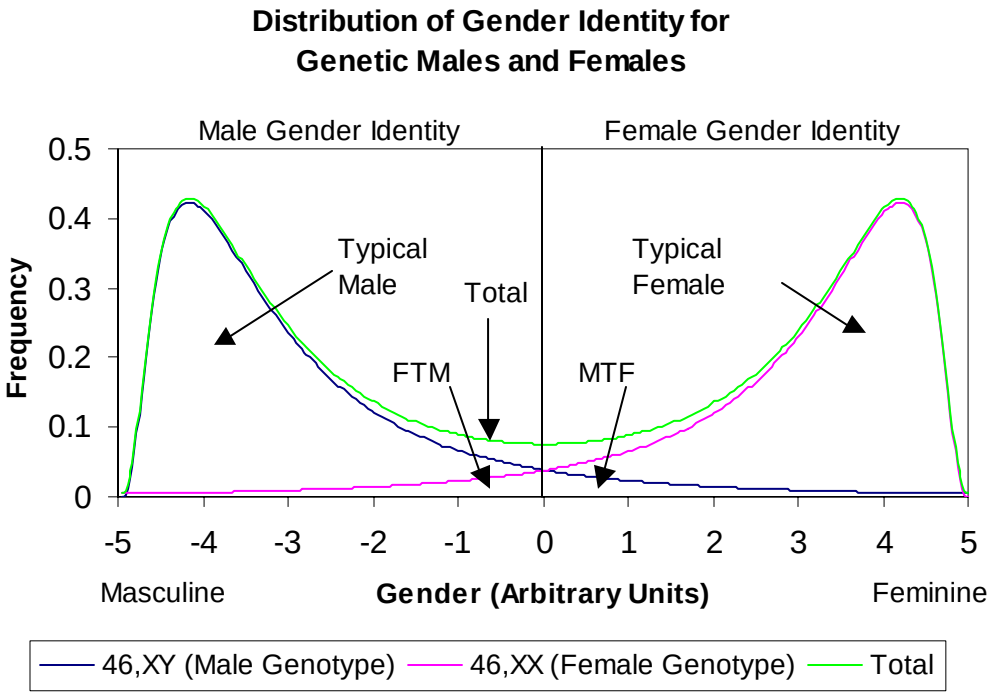

Figure 2: Plot of gender identity expressed as two continuous variables. A small fraction of genetic males have a gender identity in the range associated with genetic females, and vice versa.

Shown below are some formal dependencies in the development of gender identity and transsexualism, which is meant to serve as a heuristic tool (Figure 3). Represented are the primary predicates for each stage of gender identity development, providing a framework for enumerating the major events that determine how later events unfold. For example, gonadal sex is dependent upon the genetic sex – if there is no Y chromosome, no set of conditions can induce the development of testes, and so on. When a persons' gender identity is contrary to the other dimensions of sex, transsexualism is the result.

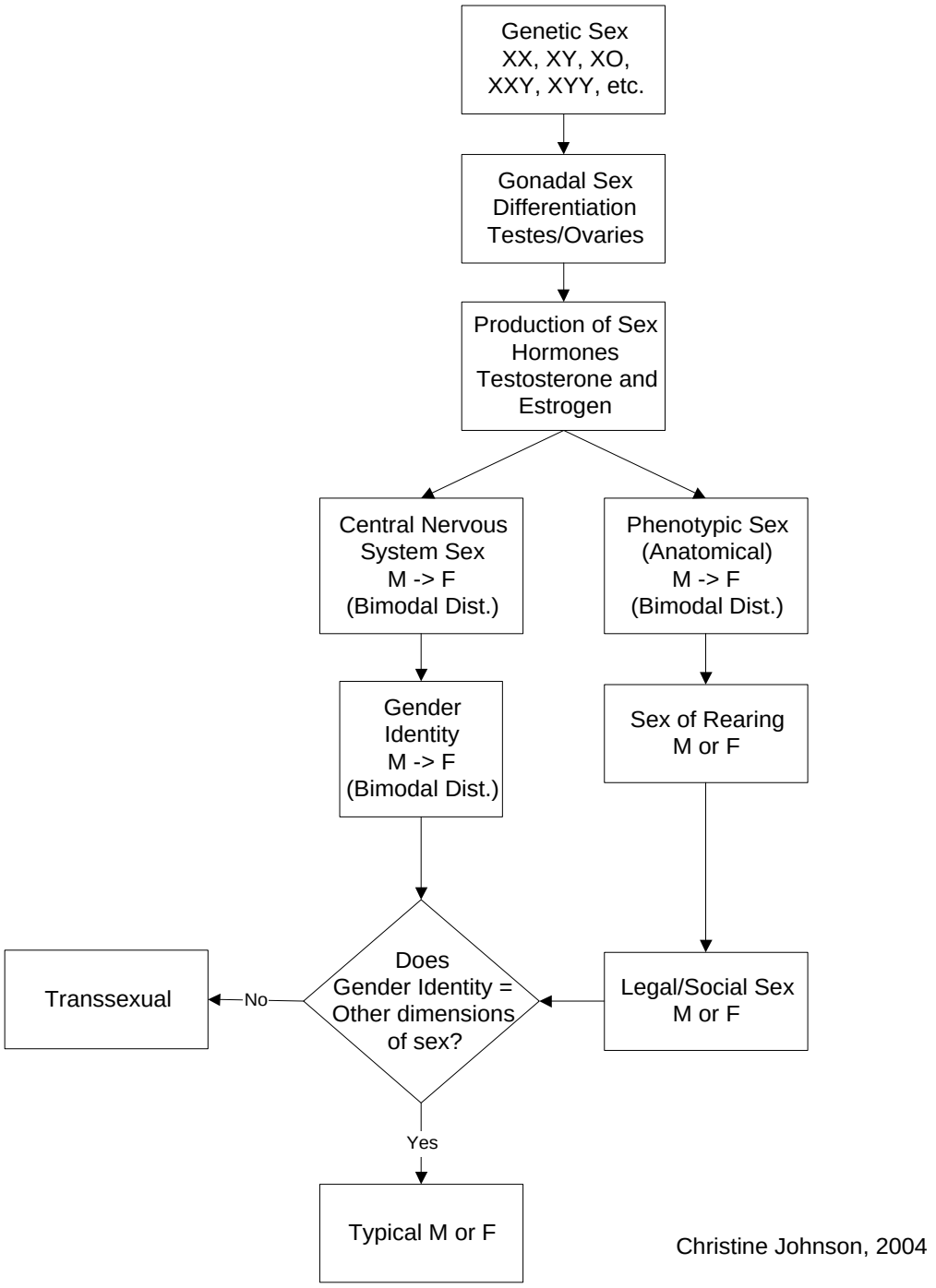

Figure 3: Formal dependencies in the development of the gender identity dimension of sex/gender. At each level, predecessors determine the possible outcomes. Other dimensions of sexuality are omitted from flowchart for simplicity. See text for further description

Some stages of sexual development are overlapping, and there are significant differences in the sequence and timing of developmental stages in chromosomal males and females (Figure 4). While there is uncertainty over the precise window when gender identity is established, it is known that gonadal hormones are responsible for programming brain structures and mechanisms during early development (McEwen & Alves, 1999). MacLusky and Naftolin (1981) suggested that for males, the critical period in central nervous system sexual development begins with Leydig cell development and the onset of testosterone synthesis. Leydig cells are located in the testes and produce the primary male sex hormone testosterone (Murray, et. al., p. 594, 2000).

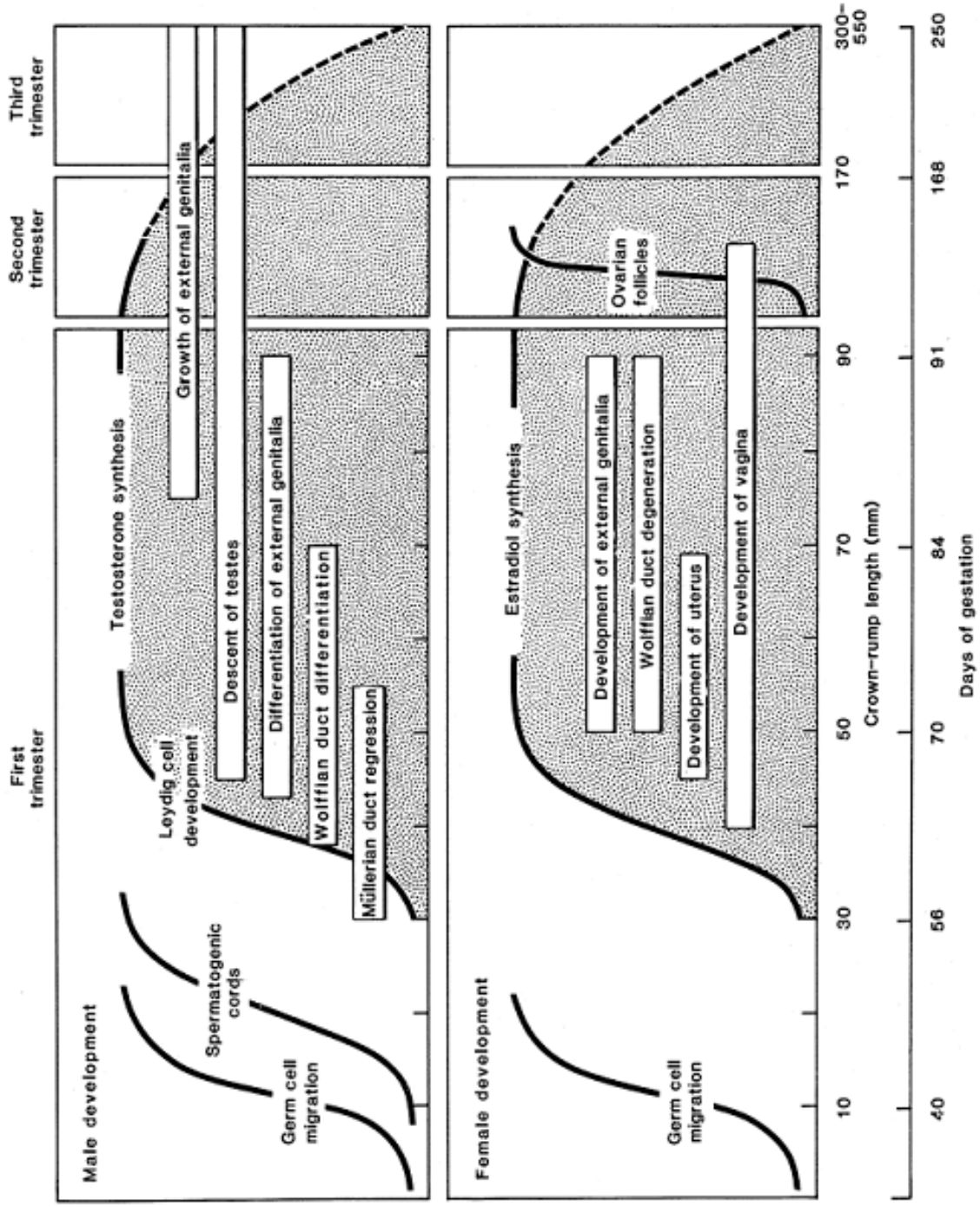

Figure 4: Milestones and important developmental windows in anatomical sexual development for human genetic males and females. Vertical axis is arbitrary scale. Source: Wilson, et. al., 1981.

The testosterone concentration of a normal genetic male over a lifetime is shown below (Figure 5). If gender identity is dependent on testosterone concentration during development, then gender identity must develop around the second trimester or in the first year after birth, as these are the periods when androgen receptors are expressed in the hypothalamus and a significant concentration of testosterone exists. Behavioral evidence in humans suggests that the second trimester may be the period during which sex-typed behaviors are determined, at least for females (Udry, 1994); gender identity may also be determined during this period.

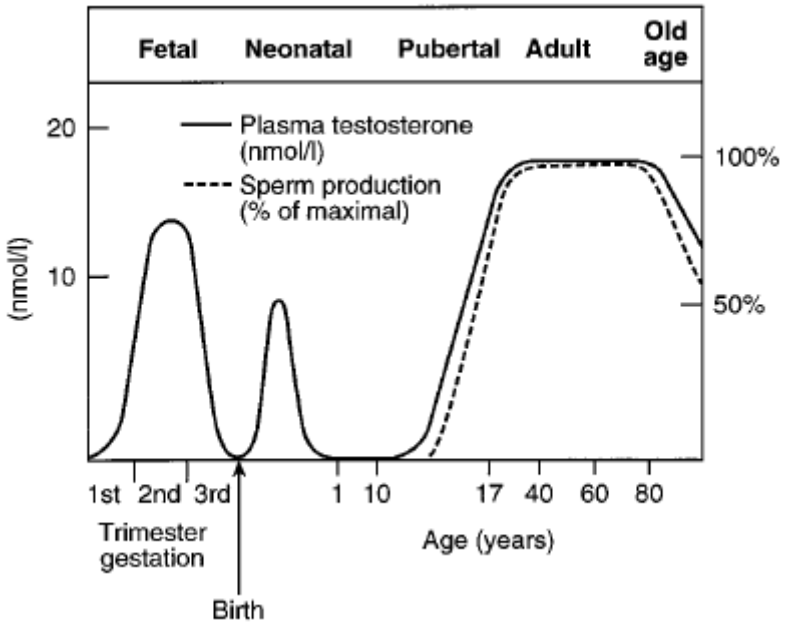

Figure 5: Testosterone concentration for normal genetic male throughout life. Source: Wilson J., 1999.

Now that the necessary terms and background of sexuality have been defined, the next section will examine various historical threads that have played a role either directly or indirectly in the problem of transsexualism.

Historical Background

In order to understand any etiology - the cause of some effect, it is necessary to have some historical perspective that provides a context for interpreting the data. This historical background will weave together several different historical trends and show how each has played a role. These trends include: the rising use of chemical controls in agriculture, the synergistic nature of the military and chemical industries, the use of propaganda in media, the persistent cultural mythology of transsexualism as a purely psychological or social construct, widespread use of the pesticide dichlorodiphenyltrichloroethane (DDT) and the pharmaceutical drug diethylstilbestrol (DES), the paradigm shift represented by the endocrine disruptor thesis, and recent scientific studies that point towards new understandings of the development of sex and sexuality.

Where one starts a history is necessarily an arbitrary selection; there are always earlier precedents that have set the course for a particular direction, but it appears that a radical departure in the way humans relate to the environment occurred with the introduction of chemical controls to kill "pests" on economically valuable crops. Originally, the use of chemicals for pest control came out of the desperation of farmers whose crops were being destroyed by insects, partly because monoculture agriculture is an invitation for insect infestation, and partly because increased population and settlement and commensurate increases in overseas trade increased the spread of non-native insects (Dunlap, p.19, 1981). In time, these factors would reinforce one another, resulting in a kind of systemic runaway.

Farmers tried various remedies seeking immediate solutions, and it was discovered that Paris green, or copper aceto-arsenite, an insecticide containing the heavy metal arsenic, was effective at controlling the Colorado potato beetle; this was the first widespread use of a pesticide, but by the turn of the 20th century, insecticide use had become an accepted practice in farming, increasingly promoted by newly instituted agricultural research stations at each college in the country, created by the Hatch Act of 1887 (Dunlap, p. 20, 1981). While most entomologists before 1900 were trained as naturalists and advocated methods such as physical or biological controls, entomologists who were trained through the new agricultural research centers were focused almost solely on pesticides; this focus was especially true after a variety of non-chemical methods failed to achieve eradication (Dunlap, p. 36, 1981). As Dunlap (p. 37, 1981) points out, the use of military metaphors framed the problems with infestations as a battle between humans and nature; a kind of Darwinian survival of the fittest.

This view was dramatically enhanced during the first World War, as chemical companies repeatedly reminded the public and politicians alike that chemicals were central to winning the war in Europe and on the home front. Speaking on the reasons why chemical companies may have found war attractive, James Withrow said in 1915 that: "'business is awakened to the value of chemistry as a source of power and wealth as business has never had occasion to be hitherto.' (Russell, p. 18, 2001)" In order to try to protect their profits after the war, chemical companies began lobbying politicians to enact a tariff on German dyestuffs, since before the war, German companies made about 80 percent of dyes worldwide, whereas American companies imported about 90 percent of needed chemical dye precursors from Germany (Russell, pp. 18-19, 2001). Although this

lobbying effort by chemical companies failed on the grounds of protecting profits, they were later able to achieve the same result by framing chemical production capability as a matter of national security, since military ammunition was also a product of the same class of chemicals (Russell, p. 19, 2001). Seventeen companies entered the dye field during 1917, including such names as Du Pont and National Aniline and Chemical (later bought by Allied Chemical); therefore, the end of World War I may be considered as the dawn of the organic chemical industry in the United States (Russell, p. 19, 2001).

Prior to World War I, the role of the press was central to efforts to rouse the American public into supporting a war on another continent and to encouraging the simultaneous co-evolution of the chemical industry and military operations; as an indication of the degree of entanglement of these three factors, Charles Herty of the American Chemical Society observed in 1916 that: the constant repetition in the press "'that modern war is largely a matter of chemistry and engineering,'" resulted in the welcome situation where the public recognizes the crucial role played by chemistry in the war effort. So, as Russell observes, "The European War shaped the rhetoric as well as the technology of pest control by encouraging use of military metaphors (p. 21, 2001)." The use of military metaphors is important to understanding the reasons why information about chemical effects are still very often concealed from the public, and consequently, why the public believes chemicals on the market are "safe." These metaphors would often be used in newspaper cartoons or advertisements, blurring the distinctions between war and insect control (Figure 6).

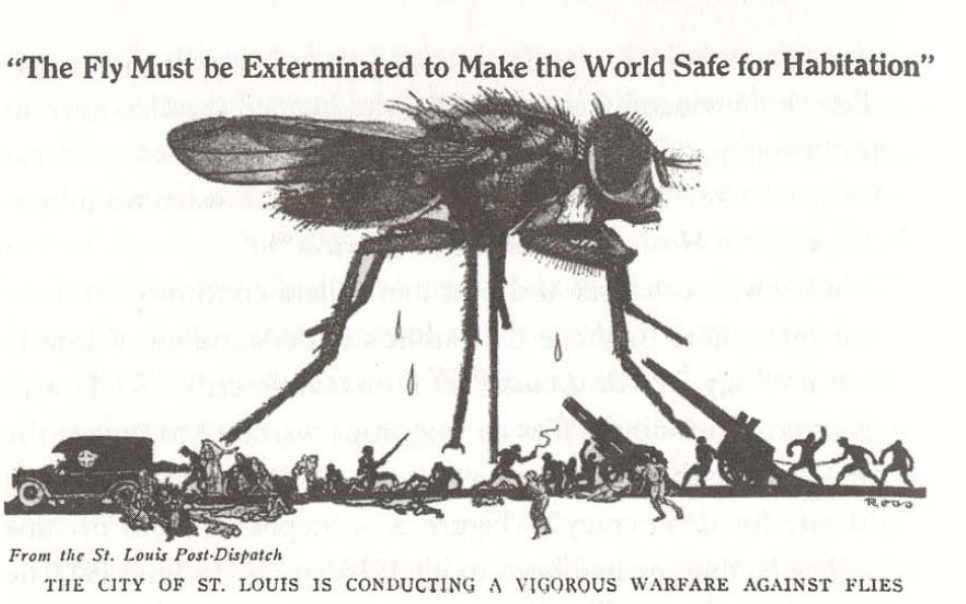

Figure 6: A 1918 advertisement suggesting that the fly is a menace to human society, requiring the use of military means to eradicate it. Source: Russell, p. 48, 2001.

Following World War I, a variety of arsenic-based pesticides were widely used on fruit and vegetable crops, and problems with insecticide residues became more serious as spraying became widespread (Russell, p. 81, 2001). In what would become a common approach, the Public Health Service limited its focus to acute poisoning and ignored chronic effects entirely; because there was little understanding of chronic effects and no adequate diagnostic tests, it was assumed that chronic effects from residues were insignificant (Dunlap, p. 53, 1981). And most importantly, the residue limits imposed on farmers by the U.S. Department of Agriculture in 1927 were based on what could be achieved with the best available technology for cleaning residues, not what was harmful to health (Dunlap, p. 46, 1981).

Pesticide residue problems did not disappear, however, and the response of the government was to permit more time for farmers to address the problem (Dunlap. p. 48, 1981). When the issue again arose, the Food, Drug, and Cosmetic Act of 1938 stipulated:

"'that no part of the funds appropriated by this act shall be used for laboratory investigations to determine the possible harmful effects on human beings of spray insecticides on fruits and vegetables' (Dunlap, p. 52, 1981)." This provision was inserted into FDA appropriations for 1938 by Rep. Clarence Cannon of Missouri, who was on the Subcommittee on Agricultural Appropriations of the House Appropriations Committee (Dunlap, p. 50, 1981). Cannon often remarked that: "[L]ead arsenate on apples never harmed a man, woman, or child," suggesting that his opposition to determining health effects of residues was ideological and not based on scientific data. His intent was clearly to eliminate funding for testing the health effects of residues that had been started in 1935 by the FDA. In other words, the approach was to permit the widespread use of chemicals, and at the same time, deliberately restrict research that would be used to demonstrate adverse effects; this data would obviously have political, social, and economic consequences. This same pattern has been repeatedly applied by the chemical industry with great success (Chemical Manufacturers Association, 1979; Chemical Manufacturers Association, 1996), and is a major source of the problems with regulation of the chemical industry.

The residue problem was further compounded by the lack of knowledge about the chronic effects of poisoning. As reported by the Hunt Commission, a congressional commission convened in January 1927 to investigate residue problems in agriculture, "'Though the evidence for widespread poisoning from spray residues was "scanty and unconvincing … the insidious character of accumulative poisoning by these substances is known to be easily overlooked [sic], and … the lack of evidence of prevalence of such poisoning must not be accepted as proof that such poisoning does not exist (Dunlap, pp.

45-46, 1981).'" However, the lack of evidence was taken as proof of pesticide safety; in February 1927, Secretary of Agriculture William Jardine set an arsenic tolerance of 0.025grams/lb, and no tolerance level was set for lead, nor was an explanation of the omission provided (Dunlap, p. 46, 1981). Again, the Department of Agriculture based these limits on the best available technology at the time for cleaning residues from fruits, but these limits were not based on health effects.

Continuing arsenical pesticide residues on foodstuffs encouraged chemical research to find replacements that would achieve the same insect killing power but without the risk of arsenic or lead poisoning – this motivation is an indication that there may have been more awareness of the risks of arsenicals than was acknowledged by public health officials at the time; it was well known that if the public knew there was a risk of poisoning, publicity would induce people to adjust their purchases accordingly, resulting in immediate economic consequences (Dunlap, p. 43, 1981). For instance, in 1925, an analytic chemist in England identified arsenic on sprayed American apples as the cause of two deaths. The reaction in England was significant, and after prodding by the British government, American apple growers quickly adopted pesticide residue limits as a cost of doing business in order to avoid further bad publicity, even though the American public was not aware of British action to enforce limits – growers simply saw limits as a method of protecting foreign markets (Dunlap, pp. 43-44, 1981). This setting of arbitrary limits was to become the accepted method of "managing" human risks from pesticides, a way of framing chemical risks that would later shape how Americans would view DDT.

Ultimately, desires to eliminate concerns deriving from pesticide residues drove chemical research during the period from World War I to World War II; in mid-1942, the U.S. Department of Agriculture first received samples from the Swiss chemist Paul Müller, who, while working for Geigy Chemical Corporation in the mid-1930's, discovered that the organic chemical dichlorodiphenyltrichloroethane (DDT) was effective at killing Colorado Potato beetles and the clothes moth (Dunlap, p. 60, 1981). DDT had first been synthesized in 1874 by Othmar Ziedler, a German chemist, but it had initially been found as part of an effort to understand substitution products generated from aromatic hydrocarbons (Dunlap, p. 60, 1981). But now, DDT – the newly identified insecticide, was indeed something new under the sun.

A few years earlier, in 1938, Sir Charles Dodds, an English chemist, was searching for synthetic chemicals that could mimic the function of estrogen, the primary female sex hormone in vertebrates. In order to test the different chemicals, Dodds removed the ovaries from rats and then treated the rats with the chemical. If the vaginal tissue responded in the same way as natural estrogen, this was taken as evidence of a chemicals' estrogenicity (Dodds, 1938). Dodds found that the chemical diethylstilbestrol (DES) was even more effective than estradiol, the sex hormone secreted from the ovary of females (Dodds, 1938). Physicians seized upon the new chemical for treating various hormonal problems of women and for prostate cancer in men; By 1939, the drug was available for prescription in the United Kingdom, France, Germany, Sweden and the United States, and would eventually be marketed under at least 400 different trade names (Krimsky, p. 9, 2000).

However, the real problems with DES began when the FDA approved the drug for uses associated with pregnancy, such as preventing stillbirth and spontaneous abortion in the early 1940's. This was the first time a chemical known to behave as a sex hormone had ever been prescribed to pregnant women. From the end of the 1940's to the early 1970's, up to 3 million pregnant women had been prescribed the drug in the U.S. alone (Krimsky, p. 9, 2000). Decades later, DES was found to be ineffective for its intended purpose, and by 1971, the first reports of an extremely rare cancer, vaginal clear cell adenocarcinoma, were reported in 8 women whose mothers were known to have taken the drug in 7 of the 8 cases (Krimsky, p. 10, 2000). These findings spurred a new line of research into the biochemical effects of DES that was pursued by John McLachlan, who began performing a number of studies on mice to elucidate the mechanisms and effects of transplacental DES exposure (Krimsky, pp. 12-13, 2000; McLachlan, 1975).

After World War I, defense spending was scaled back considerably, resulting in something of a panic for the federal government's Chemical Warfare Service (CWS), whose existence critically depended upon a wartime status. In order to avoid dissolution of the agency, for several years it campaigned with limited success to convince the public that gas was a humane method of waging war, but eventually, the CWS offered its services to the Department of Agriculture's eradication programs by suggesting that crop dusting would be a good way to teach the techniques of chemical warfare to new CWS recruits. Upon this premise, that the CWS would "beat their swords into plowshares, (Russell, pp. 61-2, 2001)" was the basis upon which Congress declined to abolish the agency.

During the period between world wars, when the demand for the products of the chemical industry were significantly reduced, it was believed among industry executives that the key to convincing the public of the safety of insecticides was in advertising (Russell, pp. 84-85, 2001). Public relations experts began using military metaphors, and the scope of their reach was immense; a speech given by Army Medical Corps Major M.A. Reasoner, framing insecticide use in terms of a war between humans and insects, was utilized by the Publicity Committee of the Insecticide and Disinfectant Manufacturers Association to increase sales of pesticides and disinfectants (Russell, p. 85, 2001). A summary of the speech was then sent to "44 trade journals, 8 trade associations, 144 medical journals and state health departments, 450 metropolitan newspapers, and 4,000 small-town weekly newspapers (Russell, p. 85, 2001)." This pattern of biased promotion where only benefits were articulated but no consequences mentioned is one that would be repeated often by the chemical industry and others in an effort to convince the public of their products' supposed safety (Chemical Manufacturers Association, 1979; Chemical Manufacturers Association, 1996). An example of the use of military metaphors in advertising is shown below (Figure 7).

Figure 7: A 1944 advertisement in the journal serving the National Association of Insecticide and Disinfectant Manufacturers, demonstrating the use of military metaphors in insecticide advertising. The equating of human and insect enemies is literal. Source: Russell, p. 121, 2001.

This approach of widely publicizing the immediate benefits, but completely ignoring the consequences, was clearly evident in the case of DDT. Initially utilized by the U.S. Army to protect troops in Italy from lice carrying the typhus bacterium and to protect against malaria carrying mosquitoes in the South Pacific, DDT was presented in the media as the perfect insecticide that was largely responsible for having won the war in Europe and in the South Pacific (Russell, pp.112, 127, 2001). The post-war propaganda of the army crediting DDT with helping to win the war was a boon to

chemical manufacturers, who never could have had as much sway with public opinion. One manager of a chemical product line said: "It is only within the past war years that the American people have become insecticide conscious and this has largely been due to insistence by the Army and Navy that our troops should not fall prey to typhus, malaria, and other insect-borne diseases (Russell, p. 155, 2001)." Advertisements of the period heralded the new chemical as a weapon against enemies human and insect alike (Figure 8 and Figure 9). And most germane, at one meeting of DDT producers, it was said that: "The general public has been led to believe that DDT will perform miracles under all circumstances (Russell, p. 155, 2001)." Thus, it is clear that the propaganda of the government during the war was biased against publicizing the risks of DDT; on the other hand, in its defense, the conditions under which the army used DDT were constrained, not used on pregnant women, and the period of exposure was comparatively brief. However, the wartime presentation of DDT would radically affect the degree of acceptance by the public – and this would be greatly enhanced through the use of the new technology of television.

Figure 8: A 1945 Advertisement from the Chicago Tribune using military metaphors to frame DDT as a new weapon in the war against insects. Source: Henkin, et. al, p. 128, 1971.

Figure 9: A 1946 United States government poster illustrating that the annihilation of malaria was equated with the eradication of the Japanese, shown in caricature to reduce them to the status of an insect. Source: Russell, p. 133, 2001.

The period from 1945 to the early 1970's could be described, in retrospect, as a period of wild abandon with regard to chemicals in general and pesticides in particular. In 1954, 300 million pounds of pesticides were produced, and by 1971 this had risen to over 1 billion pounds annually (Edwards, p. 2, 1973) (Figure 10). Applications for pesticides were primarily for use in agriculture, public health, or in the home. By 1962, enough evidence of problems existed that Rachel Carson sounded the alarm that there were unacknowledged problems with wildlife effects and possibly human effects from pesticides in her book Silent Spring (Carson, 1962). Already by 1946, early evidence showed that DDT was stored in body fat and present in milk, causing some to question the logic of widespread use of the chemical, particularly around dairy cows (Russell, p. 176, 2001).

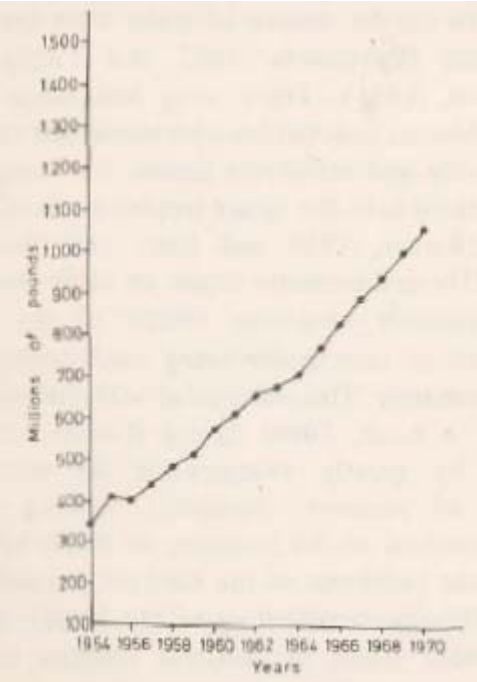

Figure 10: Annual Pesticide Production in the Unites States from 1954 to 1970. Source: Edwards, p. 2, 1973.

Because DDT had been framed in terms of its utility for protecting troops from infectious diseases carried by insects, the chemical took on great military significance. The short-term advantage of DDT was indisputable from a military standpoint, whereas long-term effects were relatively unimportant militarily. However, in the post-war context, the government began assuming a position of increased secrecy, as it took a radical departure from the period after World War I: this time there would be no reduction in efforts of the military to find new ways of destroying the enemy. Experience in the South Pacific especially reinforced this idea – if one side was able to protect themselves against insect-borne diseases and the other side was not, victory would be more likely assured to those protected by insecticides. This approach amounted to a qualitative change in the stance of the military from a temporary entity created to protect the country in a time of need to one permanently institutionalized to continually develop more effective killing methods. Coupled with the goals of the economic entomologists to eradicate certain insect pests, neither group wanted to seriously consider the possible long-term chronic effects, so assured they were that acute effects were the only effects worth considering. This led to the situation where scientific studies were not made freely available to the public, and instead circulated in professional circles, where members believed that they had the scientific authority for proclaiming pesticides safe.

DDT *was* proclaimed safe to the public, and television commercials showed people being sprayed with DDT while eating lunch at picnic tables, and children running behind trucks spraying for 'public health' reasons, leaving an indelible impression in the mind of the American public that would take a substantial amount of scientific evidence to undermine (Moyers, 2001). The chemical industry had since the end of World War I

regarded advertising as a key component of their business, but following World War II, television took on a critical role in shaping the consciousness of the public with respect to chemicals. Slogans such as "Better Living Through Chemistry" spoke to the benefits of chemicals while obscuring their risks, and though constant repetition instilled a definite idea of the American version of "better living" in the mind of the public (Moyers, 2001); by 1961, the Chemical Manufacturers Association (CMA) was spending $288 thousand dollars just on public relations out of a total budget of $1.02 million. Partly as a result of these aggressive public relations efforts, production volumes of DDT and other pesticides increased dramatically over this period (Figure 11).

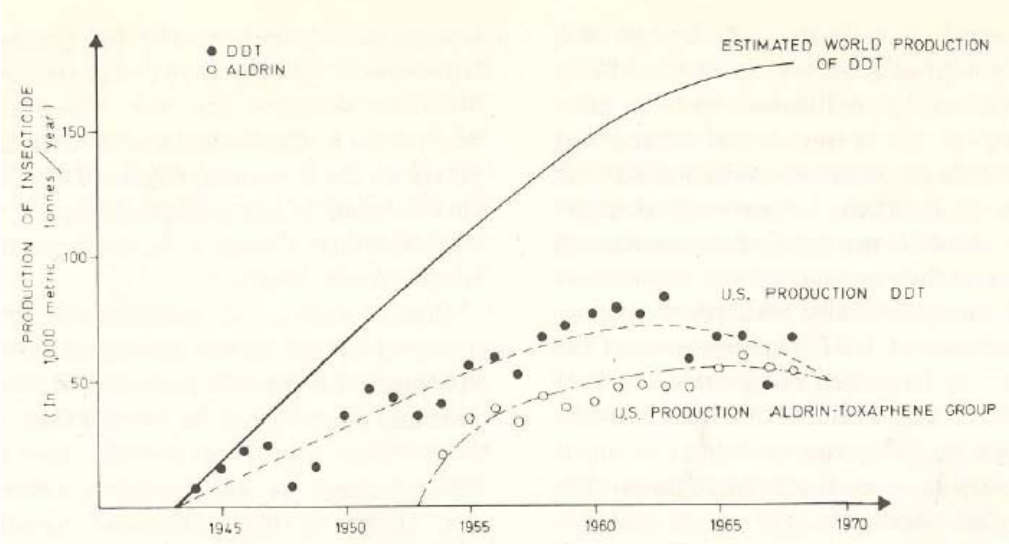

Figure 11: Persistent Pesticide Production from 1945-1970. Source: Edwards, p. 3, 1973

Meeting minutes of the CMA Board of Directors have recently been made available from the 1940's onward as the result of litigation related to adverse health effects from polyvinyl chloride (PVC) exposed workers. The meeting minutes detail the importance of public relations to the chemical industry, and their efforts to guide, limit,

and influence regulation of chemicals by the government. In 1979, a report was produced for the CMA board entitled: The Environmental Management Committee of The Chemical Manufacturers Association is "managing" The Environmental Regulatory Arena Affecting The Chemical Industry (Chemical Manufacturers Association, 1979). The report argued that increasing regulations translated directly into increased costs for companies, and thus reduced profits; the way to ensure profits was to control the regulatory process. The first sentence of the report is crucial in terms of understanding the actual intent of chemical companies: "The Environmental Management Committee of the Chemical Manufacturers Association has undertaken an aggressive role to moderate, change, or stop governmental regulations in the pollution control arena (Chemical Manufacturers Association, 1979)." The conclusions of the report analogize the struggle over government regulations using familiar military metaphors, saying: "This is war – not a battle" (Chemical Manufacturers Association, 1979). At the same time, the line between propaganda and education was blurred, as the CMA spent substantial amounts of money to provide "educational" materials extolling the virtues of chemicals to science teachers and students, and paid for chemical industry professionals to visit colleges around the country (Chemical Manufacturers Association, 1976). The efforts in academia were geared towards mobilizing the academic community to impede efforts at regulating their products. These efforts were largely successful; a report produced in 1990 by the U.S. General Accounting Office (GAO) found that the number of chemicals recommended for testing by the Environmental Protection Agency (EPA) dropped precipitously from over 100 in 1979 to a maximum of 20 during the entire 1980's (General Accounting Office,

1990) (Figure 12).

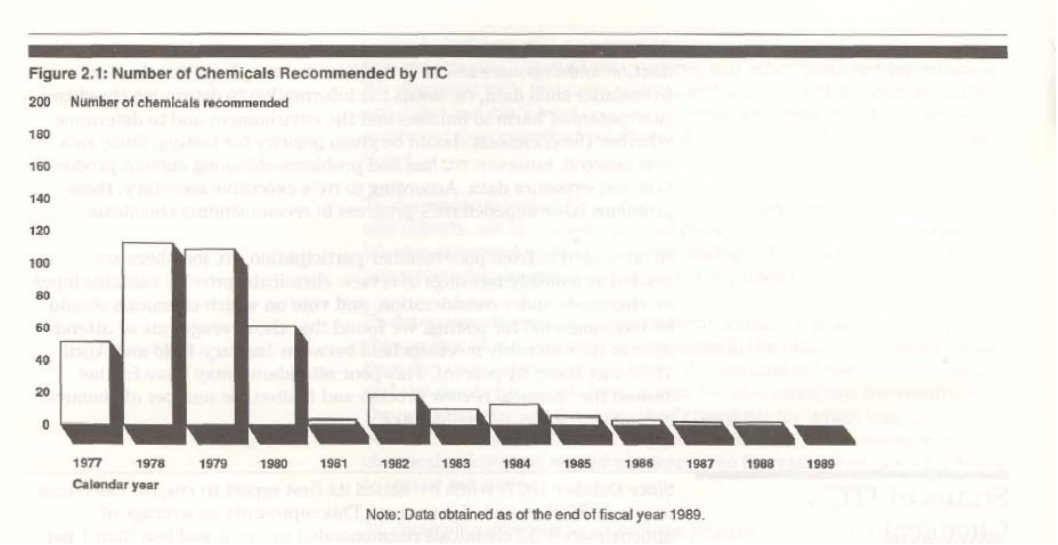

Figure 12: Number of chemicals recommended for EPA testing by the ITC. Source: GAO, 1990.

This reduction coincided with a new concept introduced by industry to implement their goals of reducing regulatory oversight, known as "regulatory relief." According to Fagin and Lavelle (pp. 139-140, 1999), regulatory relief became "an article of faith within the Reagan administration," and in order to impede, delay, or reverse regulatory decisions, the Reagan administration introduced legislation that would require that cost benefit analysis be applied to all new regulations. When the legislation did not pass in the House, the administration required the Office of Management and Budget to examine the costs and benefits of every existing regulation, thus slowing regulatory decision-making accordingly. Interestingly, this policy was continued by the Clinton administration, reflecting the fact that the decision to use cost benefit analysis as a tool for policy-making was not a partisan issue. This is an indication that the reductions in chemicals recommended for testing found in the GAO report were not strictly attributable to the Reagan administration, but were instead driven by demands of industry.

Modern Transsexual History

In 1952, the term 'transsexual' became a household word – or at least known to many, even if they didn't understand exactly what it meant. December 1st of that year, Christine Jorgensen's story hit the headlines: "Ex-GI Becomes Blonde Beauty: Operations Transform Bronx Youth (Jorgensen, 2000[1967])." When Jorgensen came back from Denmark in 1953, the press could not get enough coverage of her recent sex-reassignment surgery (SRS). Her revelation generated what was then called a scandal – it is estimated that over a million and a half words were written about her in the 18 months after her surgical reassignment, giving an indication of the amount of controversy she stirred-up (Jorgensen, introduction, 1967).

Several years later, in 1955, a new theory of the process of gender identity formation was proposed by Money, Hampson, and Hampson, which is sometimes referred to as the psychosexually-neutral-at-birth theory. They contended that children are born without any innate gender identity, and that they may only acquire one through the learning or imprinting processes that occur during early socialization (Diamond, 1965). This view was widely influential among researchers and clinicians alike, and it provided a framework for many of the arguments about etiology that would come later. By the mid 1960's, animal studies were indicating that hormones have a much more powerful effect on sexual development and adult behavior than the psychosexually-neutral-at-birth adherents had admitted (Diamond, 1965), but arguments disputing the importance of biological differences between men and women advanced by feminists would keep the focus on the primacy of socialization for several more decades (Haig, 2004). For feminists, this was a political argument, concerned with opposing those who claimed that biological differences between men and women justified the continuation of

social and institutional structures that oppress women (Sweeney, 2004). Male-to-female transsexuals would soon end up embroiled in this larger political struggle.

In the early 1970's, lesbian separatists fighting for women's rights began to attack MTF transsexuals, claiming that transsexual women brought male privilege, behaviors, and what was often referred to as "male energy" with them and therefore they were not welcome in women-only spaces. (Meyerowitz, p.259, 2002) Several MTF transsexuals were removed from prominent positions in women's groups, most notably the vice president of the San Francisco group Daughters of Bilitis (DOB), Beth Elliot. Elliot was also a guitarist and singer, and at the West Coast Lesbian Conference in 1973, Elliot's status as a woman was at issue, and some at the conference tried to shout her off stage while others tried to defend her. The issue was explosive in this context, and later in the conference, Robin Morgan, a radical feminist, described Elliot from the podium as: "an opportunist, an infiltrator, and a destroyer – with the mentality of a rapist" (Meyerowitz, p. 260, 2002).

This view of MTF transsexuals within feminist circles gained adherents and culminated in Janice Raymond's 1979 book The Transsexual Empire: The Making of a She-Male, which used the same 'rape' metaphor used by Morgan years earlier, taking a militant and uncompromising approach to MTF transsexuals. She claimed that transsexual women can never be women because they do not have the proper set of chromosomes and were not raised as females. This highly influential book destroyed many alliances between feminists and transsexuals, and eliminated places for feminist transsexuals – those who agreed with feminists that existing gender stereotypes are destructive and problematic. In the 1990's, the center stage of the debate over who

qualified as a woman was the Michigan Womyn's Music Festival (MWMF), a yearly gathering composed mostly of lesbian feminists. In 1991, Nancy Burkholder, a MTF transsexual, was ejected from the festival, and organizers justified the action, saying that the MWMF was only for "womyn-born-womyn (Meyerowitz, p. 261, 2002, van Gelder & Brandt, p 73, 1996)." By 1999, the position of the organizers was stated by Lisa Vogel as: "We also define that further as … a place for people who were born and have lived their entire life experience as female."

By defining a woman in this way, the definition also defines those lacking consistency of these features as 'not woman.' For instance, the policy does not explain what happens in cases where one or more dimensions of sexuality is not in agreement with the others, and which differences would disqualify a person from being considered a woman. Indeed, debates among organizers and attendees concerning the policies of MWMF grapple with the difficulties created by the existence of individuals who do not strictly adhere to one sex or the other.

Ultimately, this narrowed definition of 'woman' was applied specifically to exclude transsexual women from the festival, and a variety of arguments, both theoretical and practical, are still raised to support the exclusionary policy. The MWMF has a large attendance of FTM transsexuals, indicating that from the point of view of the organizers and the vocal majority of attendees, once female, always female. Because MWMF is attended by women from all over the country, many of whom are activists, the transsexual-exclusionary policies and attitudes of MWMF have tended to spread to local communities and this has deleteriously affected employment of transsexual women in

places such as rape-crisis centers, and other contexts traditionally considered women's only space (e.g. Sweeney, 2004; Heyes, 2003).

In 1979, the same year that Raymond's book was published and the Chemical Manufacturers Association claimed it was "managing" the regulatory arena, John McLachlan held the first symposium on estrogens in the environment. He brought together researchers interested in the problems of placental transport of hormonal mimics to the developing fetus and the effects of DES, DDT, and other synthetic estrogens on animals and humans (Krimsky, p.11, 2000). Few scientists were working in the field at the time, as it crossed several disciplinary boundaries that were usually considered separate entities: endocrinology, toxicology, and developmental biology. McLachlan learned that DES had been added to cattle feed, and that prior to 1977, 13 tons of DES had been used for this purpose (Krimsky, p.12, 2000); this had unknown consequences for the general population, since like DDT, DES had been proclaimed absolutely safe for practically all purposes.

DES was assumed safe, despite the fact that it is now known to be significantly more potent than 17β-estradiol, the most potent form of endogenous estrogen. Initial attempts at determining the reasons for the estrogenicity of hormonal mimics relied on structural analysis, which is used to predict the action of a chemical based upon its shape. However, many chemicals known to mimic estrogen were found to have radically different shapes, rendering structural analysis useless for this particular problem. This resulted directly in the need for animal testing in order to identify which chemicals had estrogenic properties (McLachlan, 2001).

Initially, funding and support for early work on endocrine disruptors came from the National Institute of Environmental Health Sciences (NIEHS), a branch of the National Institutes of Health, that publishes the journal Environmental Health Perspectives. Similarities among the effects of DES and polychlorinated biphenyls (PCBs), DDT, and others began to be noticed by researchers at NIEHS. As research advanced, new tools such as screening assays were developed, and methods of studying the effects of endocrine disruption began to increase the pace of discovery.

Starting in 1987, Theo Colborn, a research scientist working for the Conservation Foundation, was trying to determine if the Great Lakes ecosystem was recovering from decades of intense pollution (Colborn et. al., p. 12, 1996). Drawing on over 2000 papers and 500 government reports covering a wide array of evidence, she identified certain patterns in the wildlife that indicated that the Great Lakes system was not recovering as expected: unhatched eggs, missing eyes, crossed bills, and behavioral changes in parenting (Colborn et. al., p.14, 1996). The results of this research project were detailed in the 1990 book Great Lakes, Great Legacy, that chronicled the environmental changes in the region, the effects on wildlife, and policies for the future (Colborn, et. al., 1990). In July 1991, with the help of Pete Myers, she coordinated a conference in Racine, Wisconsin, that brought together 21 scientists from a variety of disciplines who had each studied a part of the larger problem. In attendance were experts from the fields of: anthropology, ecology, comparative endocrinology, histopathology, immunology, mammalogy, medicine, law, psychiatry, psychoneuroendocrinology, reproductive physiology, toxicology, wildlife management, tumor biology, and zoology (Colborn & Clement, p. 1, 1992). The attendees of this conference, known as the Wingspread

Conference, published a consensus statement that summarized the findings of the participants, and in 1992, published a compilation of papers from the conference (Colborn & Clement, 1992).

In order to gain a wider audience for this largely unrecognized problem, Colborn and Myers would team up with science writer Dianne Dumanowski to create the 1996 book Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival? A scientific Detective Story, which included a forward by then Vice President Al Gore. It received significant attention in the press, leading to Congressional Hearings on the topic, but the Congressional Representatives focused almost entirely on the possible links between endocrine disruptors and cancer, even though the scientists repeatedly mentioned endpoints other than cancer (United States. Cong. Committee on Energy and Commerce., 1993). Although these hearings resulted in new EPA directives to evaluate the chemicals at issue for their endocrine disrupting properties, EPA progress has been slow, partly due to the complexity of the scientific problems but mainly due to political forces that hamper regulation.

In 1995, during the same period Theo Colborn and her colleagues were learning more about endocrine disruptors, a group of research scientists at the Netherlands Institute for Brain Research identified for the first time a difference in the size of a region in the hypothalamus believed to be important in sexual behavior based upon similar studies in animals (Zhou, et. al., 1995). The group published a series of papers showing that this region, called the central subdivision of the bed nucleus of the stria terminalis (BTSc), a region in the preoptic area of the hypothalamus, is sexually dimorphic, or different between the sexes. The size of the BTSc in males is normally approximately

double the size in females. This morphological difference was also found in transsexuals, but the size of the region was found to be female-sized for MTF transsexuals, and in the only FTM brain available, the BTSc was found to be male-sized (Zhou, et. al., 1995, Kruijver, et. al., 2000). In other words, the size of the region is correlated with the persons' gender identity, but it is not dependent upon genotype, phenotype, hormonal status at the time of death, or sex of rearing. The authors conclude that the studies provide unequivocal evidence that this difference in size reflects a form of 'brain hermaphroditism,' where the brain is sexually differentiated contrary to the genetic and genital sex. They also believe that many other brain structures are probably affected and that this sexual dimorphism in the hypothalamus is just one example, important though it may be, because studies in animals show a similar relation between the size of certain hypothalamic nuclei and sexual behavior in adulthood (Kruijver, et. al., 2000). As brain imaging technology advances, *in vivo* evaluation of morphological brain differences may be feasible.

Most recently, researchers of transsexual etiology have compiled a document outlining the current thinking of professionals in the field, entitled: Definition and Synopsis of the Etiology of Adult Gender Identity Disorder and Transsexualism. The document has 24 signatories, including many of the most prominent researchers of transsexual etiology in the world (Asscheman, et. al., accessed February 20, 2004). Regarding contrary sexual differentiation of the human brain, the authors state: "Factors which may contribute to an altered hormone environment in the brain at the critical moments in its early development might include genetic influences (Landén,1999; Coolidge et. al, 2002) and/or medication, environmental influences (Diamond et. al.,

1996; Whitten et. al., 2002), stress or trauma to the mother during pregnancy (Ward et. al., 2002; Swaab et. al., 2002) (Asscheman, et. al., accessed February 20, 2004)."

In line with the thesis that interference with the hormonal system during development can result in transsexualism, the next chapter will introduce the basic operation of the endocrine system, examine the evidence generated by studies of endocrine disruptors, and argue that levels of some chemicals are known to be at levels that are physiologically relevant in animals and humans, and that viable mechanisms have been identified that could plausibly explain features of transsexuals identified in the literature.

2) Endocrine Disrupting Chemicals

In 1991, a new hypothesis concerning the biological significance of a class of chemicals on wildlife was formulated, now known as the endocrine disruptor hypothesis (Colborn & Clement, 1992). Based upon patterns observed in the wildlife of the Great Lakes region of the United States, Theo Colborn hypothesized that certain chemicals were accumulating in animals, behaving as the sex hormone estrogen, and causing behavioral, morphological, and reproductive problems in a large number of resident species, especially at the top of the food chain (Colborn, et. al., p. 16-20, 1990). In the last fifteen years, a significant number of studies have demonstrated that there are several classes of chemicals that can behave as biologically relevant signals, capable of altering the control of gene expression at the molecular level and interfering with homeostatic systems at the developmental and functional level (Myers, 2003). A generalized hypothesis of biological signaling in ecosystems has been advanced, suggesting that any process mediated by chemical signals is a potential target for disruption, whether it occurs inside the body of an organism, between organisms, among organisms, or ecosystem-wide (McLachlan, 2001). This approach is consistent with the thesis of Ruesch and Bateson, who suggested in their book Communication: The Social Matrix of Psychiatry, that communications theory is a unifying framework in which different organizational levels can be connected together, from level of the individual, to the community, to the ecosystem (Ruesch & Bateson, 1951 [1968]).

Almost all biological development unfolds as a sequence of events, orchestrated and controlled by biochemical signaling mechanisms that activate gene expression. Key among these signaling mechanisms are hormones; chemical messenger molecules that are

produced in one part of the body and transported to another where they enter a cell and in concert with other intracellular complexes, initiate gene expression. Interference with any step in these signaling processes during development can result in adverse effects ranging from obvious birth defects to subtle changes that only become manifest long after exposure has occurred (Myers, 2003). High doses of endocrine disrupting chemicals (EDCs) can result in overt toxicity, such as cell death, but at lower levels, they can alter the expression of genes, resulting in endocrine system changes during critical periods of development and thus becoming permanent (Welshons, et. al., 2003). In addition, different EDCs can interfere with different signaling pathways using different mechanisms, and when combined with other chemicals in mixtures, this can result in a wide variety of possible outcomes, most of which would be difficult to detect statistically (Myers, 2003, DeGuise et. al., 2001, Weiss, 1998; Weiss, 2002).

The vast majority of the 85,000+ chemicals registered with the EPA have never been evaluated for their potential for biological signal disruption, so it is not known how many chemicals in commerce might be implicated (Landrigan, et. al., 2003). Because estrogenic effects are the most prevalent in the environment and were identified first, there has been a focus on estrogenic chemicals, but it is now known that androgens, anti-estrogens, and anti-androgens exist, as well as others (National Research Council, 1999). A partial list of chemical classes demonstrating endocrine disrupting properties includes: halogenated dioxins and furans, organochlorine pesticides, polychlorinated biphenyls (PCBs), phthalates, Bisphenol A, polybrominated diphenyl ethers (PBDEs), heavy metals, and the breakdown products of alkylphenol polyethoxylates, surfactants used in detergents (Colborn, et. al., 1996). In addition to these chemicals, products intended for

consumers, including pharmaceuticals, which are pharmacologically active by-design, and personal care products, many of which contain EDCs and are used in great abundance, are increasingly found in the nation's waterways (Kolpin, et. al., 1996). Many of these chemicals have been found in people at levels where endocrine disrupting effects are observed in animals (Centers for Disease Control and Prevention, 2003, Houlihan, 2003).

Because these biologically relevant signals from outside the organism can enter the body and alter gene expression (Holliday, 1987; Jirtle, et. al., 2000), endocrine disruptors are a new source of evolutionary variation. This new form of chemically-induced variation involves many dimensions because it acts on evolutionarily conserved signaling molecules, receptors, and processes, some of which are believed to be nearly global in nature. Estrogen, for example, is believed to be the first, and most ancient signaling molecule; consequently the estrogen receptor is widely found in the animal kingdom, including many vertebrates and invertebrates (McLachlan, 2001). Importantly, different organisms may use the same signaling molecule for different functions, making prediction of effects at the ecosystem level difficult (Stoka, 1999, Daughton & Ternes, 1999). The fundamental nature of these processes indicates that changes will occur from the level of the individual, to the community, species, population, and ecosystem. There are also indirect and non-independent effects due to multiple chemicals acting on the same pathway (Rajapaske, et. al., 2002), individual chemicals acting on multiple pathways (Frigo, et. al. 2002, Adams, et. al., 2002), bioaccumulative effects as concentration increases up the food chain (Colborn, et. al., 1993), and multigenerational

effects, where the accumulated toxins are passed to offspring *in utero* and via lactation (Latini, et. al. 2003, Schönfelder, et. al., 2002, Foster, et. al., 2000, LaKind, et. al., 2001).

These rapid changes introduced into the environment were historically unprecedented prior to World War II. Many, including DDT and PCBs are volatile, persistent, and can travel long distances through atmospheric circulation and global distillation. Using tree bark to determine global transport of 22 organochlorine chemicals, a recent study found that all but 4 were ubiquitous globally (Simonich & Hites, 1995). The World Health Organization (WHO) recently reported that world-wide, levels of DDT and PCBs are decreasing, but PBDEs are increasing dramatically (World Health Organization, 2002).

The history of chemical production demonstrates that a large number of chemicals that behave as endocrine disruptors have been released into the environment, suggesting a possible role in altered sexual development, including gender identity. The next section examines some of the empirical evidence supporting a causal role of EDCs in a variety of adverse outcomes due to early exposure, focusing on studies observing sexual changes. Because knowledge of basic endocrine system operation is critical for interpreting outcomes to be expected from exposure to EDCs, the next chapter begins with an introduction to the human endocrine system.

The Endocrine System

The human body contains three major integrating systems that are responsible for coordinating development and function: the nervous, immune, and endocrine systems (Colborn, et. al., p. 32, 1996). Each system is related to the others, and together they coordinate all activity; importantly, they all utilize signaling to pass messages from place to place in the body. The endocrine system is generally responsible for regulating numerous metabolic processes through the production of hormones, chemical signaling messengers that instruct cellular development and function (Hadley, pp. 22-23, 1992). A number of ductless glands are dedicated to the production of hormones, and their cells are specialized accordingly (Figure 13). One of the most important of these glands is called the hypothalamus, which is a small gland located at the base of the brain that serves as an important connection between the nervous and endocrine systems, acting as the master controlling endocrine gland (Hadley, p. 5, 1992). The connection is achieved via nerves that terminate at hypothalamic cells; when the nerves fire, the cells secrete small amounts of specialized hormones (Hadley, p. 137, 1992) (Figure 14). These hormones then pass through a special direct blood connection, known as the hypophysial portal system, to the pituitary gland, where pituitary cells receive and amplify these signals and produce another hormone. These hormones are then released into general blood circulation, where they can then act on the appropriate target cells (Hadley, pp. 125-128, 1992).

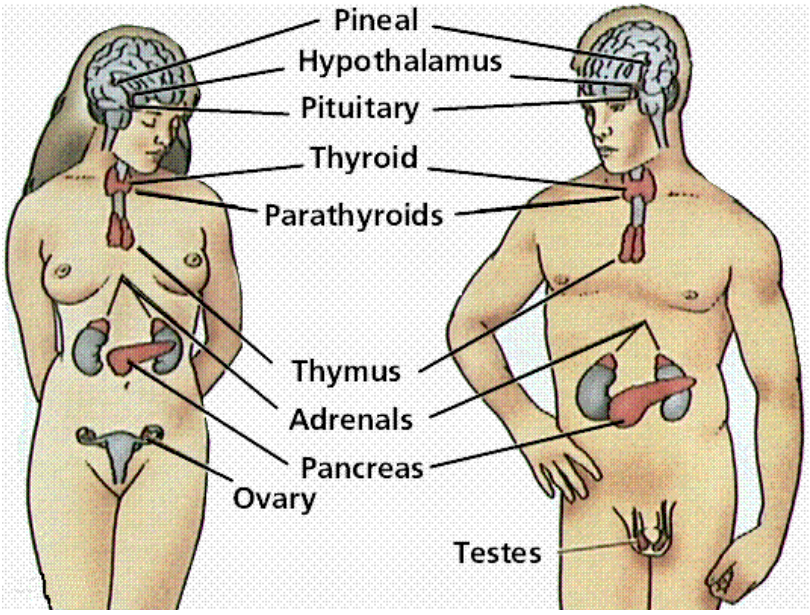

Figure 13: Glands of the Endocrine System. Source: Purves et. al. (2003)

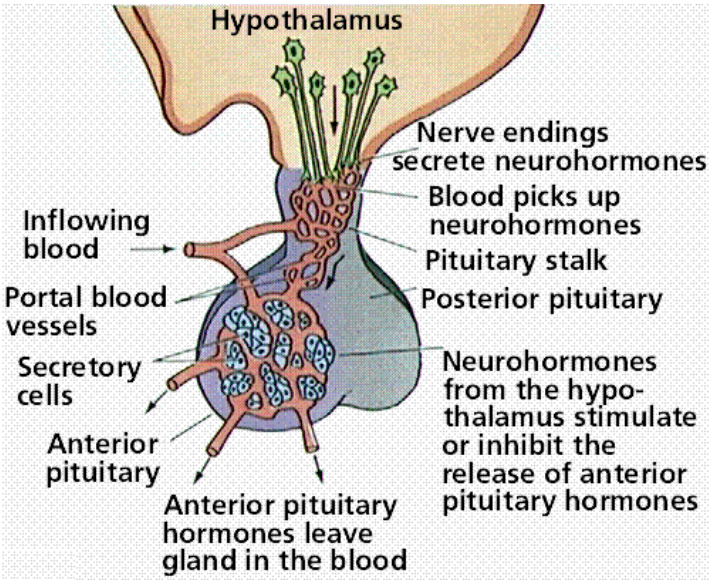

Figure 14: Detail of hypothalamus and pituitary glands. Source: Purves et. al. (2003)

Each hormone is specialized and there is a correspondence between the shape of the hormone and the corresponding cellular receptor (McLachlan, 2001). An analogy that is often used is that of a key fitting in a lock – the cellular receptor is able to discriminate between differently shaped molecules so that only those possessing the correct shape and charge are able to bind to the receptor and initiate the associated physiological response. However, as the field of endocrinology has advanced, it has become clear that additional processes are at work other than those described by the classical model of a hormone produced by a gland, released into general blood circulation, acting on distant cells. It is now known that other processes are at work, such as autocrine responses where cells modulate their own production of hormones, paracrine responses, where cells act through hormones to affect neighboring cells, and intracrinological responses, where the intracellular hormonal milieu is controlled within the cell (Labrie, et. al., 2000).

Although the endocrine system consists of many regulating feedback loops responsible for controlling the concentrations of a large number of chemicals in the body, one subsystem is primarily responsible for development of the reproductive system and sex: the hypothalamic-pituitary-gonadal axis (HPG) (World Health Organization, p. 11, 2002), which controls the production of the primary sex hormones: estradiol for females and testosterone for males. Most studies of the biology of sexual development have focused specifically on the HPG axis, but others have noted the importance of two related axes, known as the hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-thyroidal axis (HPT) (World Health Organization, pp. 18-19, 2002). This is because the axes are not strictly independent – a change in one axis can change the others in a variety of ways (World Health Organization, p. 20, 2002). The basic operating

principles for each axis is roughly the same; the HPG axis will be described, but the other two axes are similar.

The HPG axis comprises three glands: the hypothalamus, the pituitary gland, and the gonads: testes in males, and ovaries in females (Hadley, p. 141, 1992). The central nervous system (CNS) signals the hypothalamus through nerve cells that induce the release of Gonadotropin-Releasing Hormone (GnRH) (Figure 14). The hormone GnRH passes through the hypophysial portal system to the pituitary gland, where the gonadotropins Leutinizing Hormone (LH) and Follicular Stimulating Hormone (FSH) are produced and released into general circulation. The primary sex hormones for each sex are then produced: testes produce testosterone in males, and the ovaries produce estrogen in females. The amount of GnRH produced is adjusted in order to maintain a proper concentration of the sex hormones (World Health Organization, p. 13, 2002). In this manner, homeostatic control of the sex hormones is maintained.

This description is the first-order mathematical model of the HPG axis in genetic males developed by Smith (1980). The model was later modified by Cartwright and Husain (1986) to take into account several empirical findings that could not be explained by Smith's model, such as oscillating testosterone concentrations in genetic males after castration. A more recent paper expanded these earlier models by taking into account saturable responses and the direct effect of testosterone on the release of leutinizing hormone from the pituitary gland (Bing-Zheng & Gou-Min, 1991). While these models are useful for learning how the HPG axis may be altered in adults, they do not explain how the axis develops in the fetus and how temporary changes in the concentration of

hormones in this loop during development may change the operational behavior of the homeostatic circuit in adulthood.

While there have been many papers that have made associations between exposure to EDCs and changes in sexual development in animals, and a small number of papers describing anatomical and hormonal differences between transsexuals and non-transsexuals, there has been much less focus on mechanisms of action. The following will propose a novel mechanism for the development of gender identity, providing a framework for a new line of research that may be able to answer long-standing questions regarding the influence of chemical cues on sexuality and social behavior.

The Vomeronasal Organ

The vomeronasal organ (VNO) is a special sensory organ that is a subset of olfaction, responsible for the detection of pheromones – chemical messengers that are released from various parts of the body such as the skin and mouth (Kohl, et. al., 2001; Monti-Bloch, et. al., 1998) (Figure 15). Discovered in 1703 by Ruysch, the VNO was long assumed to be a non-functional vestigial organ whose function was lost during evolution. Recently, however, the organ was found to be fully functional in adults (Monti-Bloch, et. al., 1998) and, in animal experiments, during prenatal life (Pedersen, et. al., 1983). The function of the VNO appears to be centrally related to sexual and social behavior, and has recently been found to be sexually dimorphic; males respond to certain pheromones while females respond to others.

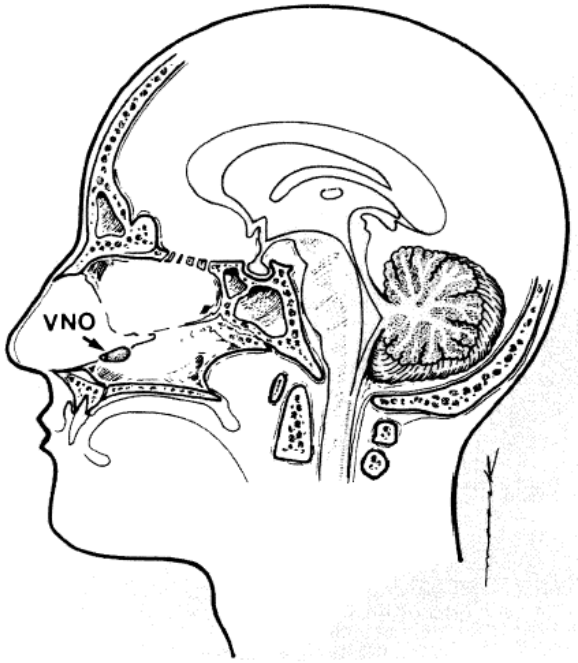

Figure 15: Anatomical location of the Vomeronasal Organ (VNO). Source: Monti-Bloch, et. al., 1998

During embryogenesis, gonadotropin-releasing hormone (GnRH) cells migrate from the VNO to the pre-optic area of the hypothalamus and the basal forebrain, forming the connection between the VNO and the controlling centers of the limbic system required for detection of chemically-based sex and social cues (Monti-Bloch, et. al., 1998). Researchers have found that the migration of GnRH cells from the VNO to the pre-optic area of the hypothalamus is incomplete in an X-linked condition known as Kallmann's syndrome, resulting in hypogonadotropic hypogonadism (reduced gonad size due to the lack of GnRH) (Monti-Bloch, et. al., 1998). Several cases of Kallmann's syndrome (Kallmann's syndrome incidence ranges from 1:10,000 to 1:60,000) with concurrent transsexualism have been reported in the literature (Meyenburg & Sigusch,

2001), a possible indication that the VNO-preoptic hypothalamus circuit is crucial for proper sexual development.

In a recent paper reviewing the VNO, Monti-Bloch and his colleagues note that the VNO is "essential for maintaining male and female sexual behavior in mammals, influencing the onset of puberty, the estrus cycle, gestation, maternal behavior, and social behavior (Monti-Bloch, et. al., 1998)." In humans, this organ has been found to be involved in the synchronization of menstrual cycles in females, again suggesting a direct role in sexual and social behavior that has only just begun to be explored in the fields of sexology, psychology, psychiatry, and sociology.

Monti-Bloch and his colleagues have devised a special measurement system that permits quantitative measurement of the response of the VNO to various chemical stimuli (Monti-Bloch, et. al., 1994). The apparatus consists of several small Teflon tubes and a probe; the tubes provide a means to deliver and quickly remove small bursts of pheromones to a specific location, and the probe provides a means of measuring the electrical response of the organ to the stimulus, what the authors have called a vomerogram, an analog to the electroencephalogram. Using this apparatus, the authors have been able to finely distinguish between the response of the VNO and that of other structures such as the olfactory bulb, due to the ability to precisely control the location of pheromone application.

The authors found that the psychological affective state can be significantly altered by exposing the VNO to 100 picograms (100×10^{-12} grams) of the pheromone androstadienone. Using the Derogatis psychometric test, which consists of 70 questions used to evaluate affective state, the authors found a significant decrease in negative affect

after stimulation with the pheromone using a parallel experimental design, which was randomized and double blind. The constellation of changes included: nervous, tense, ashamed, anxious, irritable, angry, and enraged, demonstrating that emotional effects can be directly induced by exposure to pheromonal chemicals (Monti-Bloch, et. al., 1998) (Figure 16).

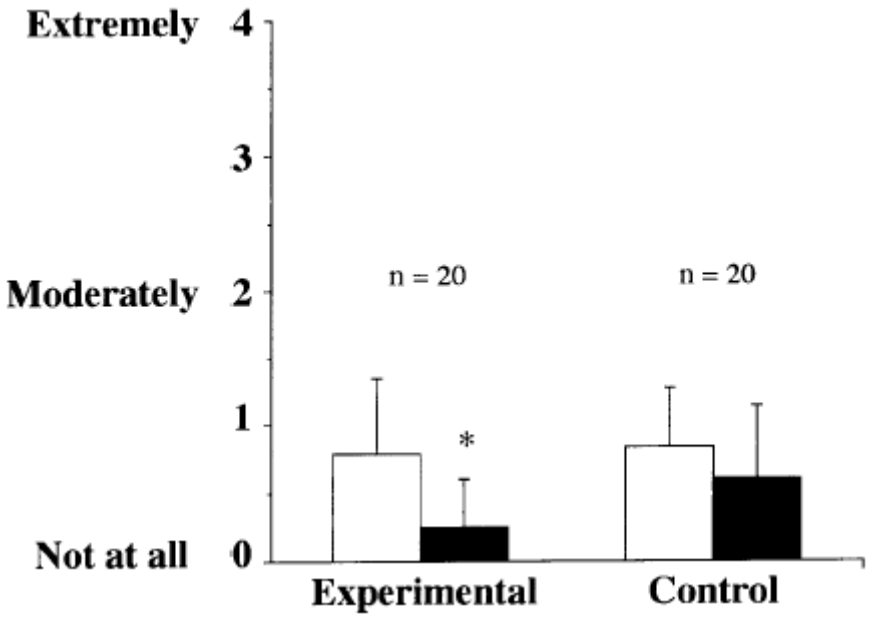

Figure 16: Reduction in negative affect measured with the Derogatis psychometric test before and after exposure to the pheromone androstadienone. White bars – Before exposure, Black bars – After exposure. Source: (Monti-Bloch, et. al., 1998)

In an earlier article, the same group found that changes induced by certain pheromones are highly sexually dimorphic (Monti-Bloch, et. al., 1994). These changes included differences in vomerograms, alpha-cortical activity, electrodermal activity (measured as a difference in skin resistance), and change in skin temperature (Figure 17). In each case, the amount of pheromone was 250 femtomoles (250×10^{-15} mole), an

extremely small quantity of chemical. The chemical names of the pheromones are coded because patents are pending on these compounds by the Pherin Corporation, which presumably plans to market these drugs for pharmaceutical purposes (Monti-Bloch, et. al., 1994; Pherin Corp, 2004).

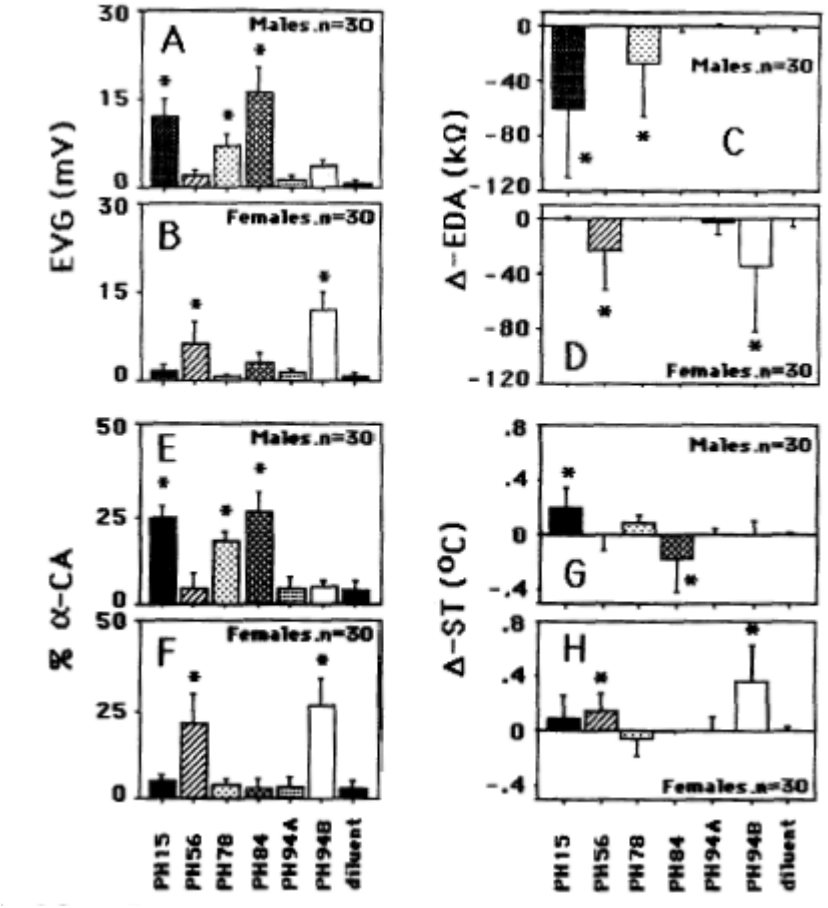

Figure 17: Response of males and females to various pheromones. EVG-Electrovomerogram, α-CA – alpha cortical activity, Δ-EDA – change in skin resistance, Δ-ST – change in skin temperature. (* p < 0.01) Source: Monti-Bloch, et. al., 1994.

While these data show important effects on psychological affect that undoubtedly play a role in social and sexual behavior, of much greater importance regarding transsexualism is the finding that exposure to some pheromones can directly reduce the production of luteinizing hormone (LH) and subsequently, testosterone (T), in males exposed the chemical pregnadienedione (PDD) (Monti-Bloch, et. al., 1998) (Figure 18). Because this result demonstrates a direct effect on LH production, it is possible that exposure to pheromones during development could potentially cause a commensurate change in the programming of the HPG axis during development, thus permanently altering the neuroendocrine response both statically and dynamically. This difference could potentially explain the difference in the size of the BTSc region of the hypothalamus observed by Zhou, et. al. (1995). Because these are neuroendocrine reflex changes that occur at extremely low concentrations of pheromones, they are typically below the threshold of consciousness - an indication that they are beyond the influences of socialization (Kohl, et. al., 2001).

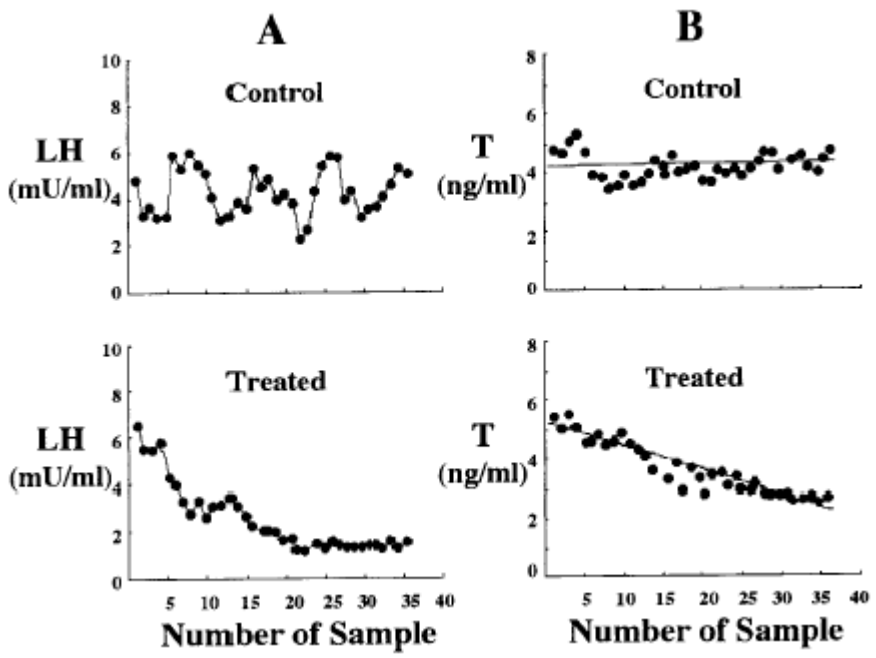

Figure 18: Neuroendocrine reflex changes in males from exposure to the pheromone pregnadienedione (PDD). (n=10) Source: Monti-Bloch, et. al., 1998.

However, the fact that the VNO exists and there are measurable changes in response to pheromones still does not define a mechanism. In order to explain a proposed mechanism, there is need to touch on a philosophical matter which has been raised by Theodore Roszak in The Voice of the Earth: An Exploration of Ecopsychology. Roszak notes that Western society has a historical and conceptual split between "in here" and "out there," as if there were an impermeable barrier between the internal and external environment. Many people believe and act as if they were individual and apart from nature. But as Roszak notes, there is no such clear-cut distinction, and a new type of ecological perspective is developing, especially among ecopsychologists, that recognizes the connections between what is inside our bodies and what is outside (Roszak,1993).

Along these lines, one possibility is that the process of gender identification is merely a comparison of an individual's pheromonal profile compared to that of other males and females. For example, during the course of normal social interactions growing up, a child can compare themselves with others to find out if they "smell" like one sex or the other; if they are similar to males, for instance, they "identify" with male, and "dis-identify" with female. Conversely, if they smell similar to females, they will identify as female and "dis-identify" with male. Again, because pheromone levels are typically below the level of conscious awareness, this all happens at an unconscious level.

This identification is gender identity, to be contrasted with gendered behavior, which is driven by conscious awareness, and which incorporates behavioral patterns and mores of the culture in which a person was socialized. The identification process is shown schematically below; when pheromones are detected by the VNO, this signals commensurate changes in the hypothalamus and downstream glands, which then causes a change in the profile of secreted pheromones (Figure 19). Since both the pheromones produced by the self and others can be compared directly at the level of the VNO, this provides a mechanism for comparison of gender identity that is completely independent of cultural messages and mores. While this system is hypothetical, it fits observational data and suggests a number of experiments involving the VNO that could offer alternative techniques for diagnosis, if differences between transsexuals and non-transsexuals could be identified.

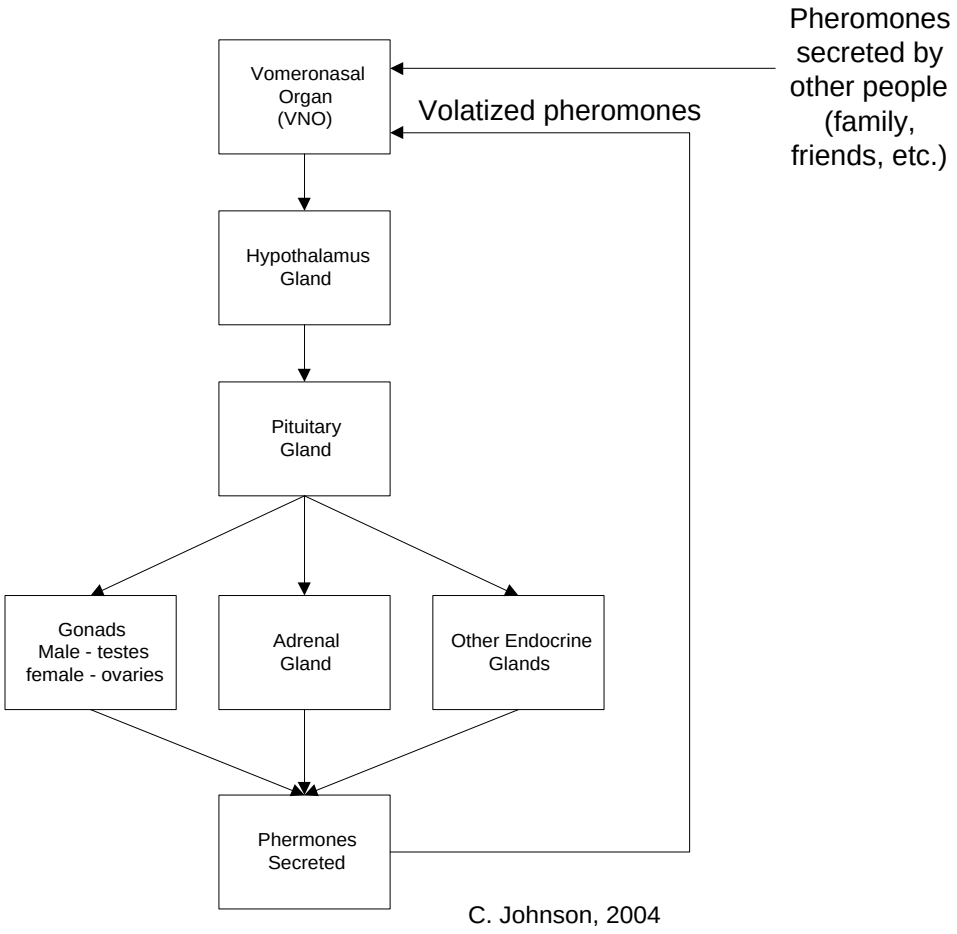

Figure 19: Simplified system diagram showing major components involved in the circuitry of gender identity development. Pheromones produced by self are compared to those of others as part of the correlative process of gender identification.

Importantly, identification requires detection of a pattern, and detection of a pattern requires multiple comparisons, so gender identity must become manifest over the course of time; if there is a consistent pattern, (every test has the same result) the learning is very fast and the matter is habituated and never re-examined. However, if there are inconsistent patterns, ambiguity and uncertainty will be introduced. In Western society, the gender of the child is projected onto to them by doctors and parents, typically based upon the form of the genitals at birth. This situation creates the conditions for a double

bind – a paradox due to contradictory messages at different logical levels (Bateson, pp. 271-278, 1972). As Bateson (p. 278, 1972) notes, "severe pain and maladjustment can be induced by putting a mammal in the wrong regarding its rules for making sense of an important relationship with another mammal." When chemical messages conveyed by pheromones are in contradiction with messages from family and other contacts among society, this can create the prerequisite conditions for a double bind and its associated pain. Interestingly, Zucker, et. al. (2003) have found that many parents of transsexuals also suffer from psychological problems, perhaps an indication that it is not only the child who is put in a double bind. Because the parents are also experiencing mixed messages vis-à-vis the child, presumably they are also at risk for pathology due to the double bind. And like the child, they are experiencing repeated cultural messages that sex and gender are the same thing, and that they are defined by the genitals and phenotype.

It should be made explicit here that the double bind is created by the social expectation, based upon a long history without synthetic chemical production, that the form of the genitals matches the gender identity; hence, to the extent that these social conceptions are now at variance with reality, the person in the double bind described above has five choices: 1) deny the existence of messages from the body that are in contradiction to social expectations, 2) do nothing and live with the pain of the double bind if it is comparatively minor, 3) live a double life, where the tensions created by the pain are resolved by temporary expression of the repressed characteristics, 4) replace one set of epistemological assumptions with a different but still socially acceptable set, or 5) reconcile the conflict by experiencing what has been termed a transcontextual experience

by Bateson in his essay *The Logical Categories of Learning and Communication* (pp. 279-308, 1972).

These options are manifested outwardly as, respectively: 1) the person who appears to be a normal male or female, but who is unwilling to accept the consequences of being transsexual due to the social costs or other reasons and splits-off that part of their self to avoid psychic trauma, 2) the person who, because of commitments to existing relationships or other reasons, decides to forego expression of the unexpressed character, 3) the male transvestite, who dresses in female clothes transiently to experience temporarily relief from the double bind (genetic females do not appear to experience this, perhaps because they have fought to dress and behave as genetic males without consequence), 4) the transsexual who replaces a rigid form of masculinity with a rigid form of femininity, in essence exchanging one set of epistemological premises for another, and 5) the transsexual who experiences a transcontextual experience, akin to the Zen Buddhist who experiences enlightenment by strenuous contemplation of a koan, or an unsolvable problem. None of these options is necessarily right or wrong, they are merely different methods people may use at any given point in time to deal with a conflict created by contradictory messages on different logical levels, depending upon the energy and resources available to them. Probably other options are available, the above list is meant to indicate that there are a variety of options, but the choice will depend in part on the severity of the double bind.

Because a working premise of the proposed ontogeny of transsexualism is that exposure to EDCs changes the hormonal milieu – and consequently the pheromonal milieu, the next section will examine a wide range of evidence from mechanisms to

animal and humans findings, demonstrating that EDCs can alter many aspects of hormonal action and sexual development directly and indirectly. Since pheromones and hormones have significance for sexual development, then it would seem reasonable to assume that pheromones and hormones are closely related, and that a change in one will likely cause a change in the other.

To make these assumptions explicit, I am assuming that pheromones are to communication between people as hormones are to communication between cell groups; thus I am assuming a more or less direct relationship between these two types of molecules because they are carrying the same (or similar) signals of relevance to the various dimensions of sexuality. The main difference is that they carry the signals in different domains: hormones in the bloodstream and pheromones in the air, therefore they cannot be independent. At least one direct relationship was demonstrated empirically by Monti-Bloch and his colleagues, showing that males exposed to the pheromone pregnadienedione (PDD) experienced substantial decreases in luteinizing hormone and testosterone (Figure 18). The field of pheromones is largely unexplored in humans, but early evidence suggests that many chemicals could potentially behave like "pheromone disruptors," analogous to endocrine disruptors in terms of molecules that are capable of inducing a particular response by binding with a receptor, in the case of pheromones by binding with receptors in the VNO.

Endocrine Mechanisms

There are a number of different mechanisms where the normal actions of hormones can be altered either directly or indirectly by an exogenous chemical. In order to identify the pertinent properties of these chemicals, Kavlock et. al. (1996) defined an endocrine disruptor as "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes." The multiplicity of ways in which the endocrine system can be modulated is further increased because each pathway consists of a sequence of biochemical reactions that provide multiple points for interference to occur, and certain hormones are capable of being produced in more than one gland, increasing the difficulty of studying the operation of this highly complex interrelated system (White and Speiser, 2000; Labrie, et. al., 2000; McLachlan, 2001; vom Saal, 1992; Welshons, 2003).

As shown below, all steroid hormones derive from cholesterol, and each step in hormone production requires a specific enzyme, shown in boxes, to catalyze the reaction indicated by the arrows (White and Speiser, 2000) (Figure 20). If one or more enzymes are absent or reduced in concentration due to a genetic difference or exposure to a chemical that inhibits the enzyme, this can lead to an increase in the concentration of precursor hormones and prehormones, and decrease the concentration of end-products, with associated effects (Dörner, et. al., 2001; Collet-Solberg, 2001a; Collet-Solberg, 2001b). Because enzymes are critical catalysts that dramatically increase the rate of chemical reactions, small decreases in enzyme concentrations can have significant effects

on the overall amount of a particular hormone produced, warranting investigation of any chemical that is shown to inhibit enzymes.

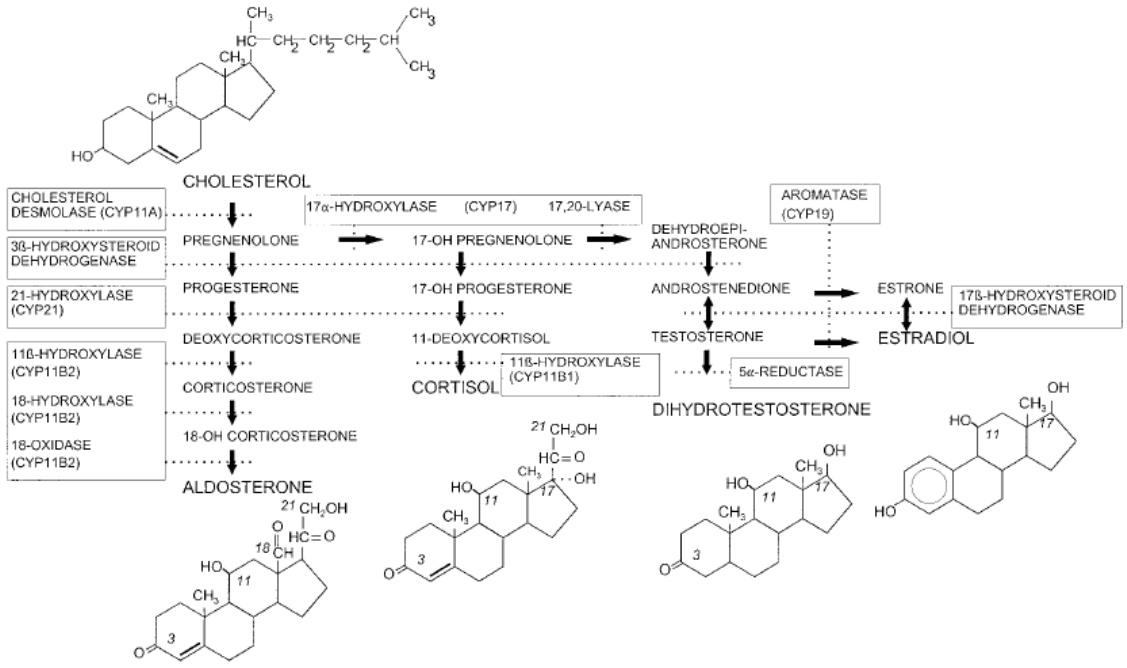

Figure 20: Hormone biochemical synthesis pathways showing intermediate products and required enzymes. Planar structure of selected hormones are also shown. Source: White and Speiser (2000).

The regulating action of a generic homeostatic system is shown diagrammatically below; operation is functionally analogous to a thermostat or a cruise-control on a car (Figure 21). Regulation is accomplished by negative feedback (inhibition) of cell type A, which reduces the level of hormone A generated by cell type A. This reduction in hormone A results in a reduction in hormone B, which then reduces the inhibition, raising the production of hormone A levels. Regulation by higher centers sets the bias point, or operating point of the loop, similar to the temperature setting of a thermostat or the speed setting of a car cruise-control. This "see-saw" behavior is a common feature of

homeostatic systems in general. The time from the initial control signal until the return of the feedback signal represents the time lag of the loop, and is an important parameter that controls loop stability.

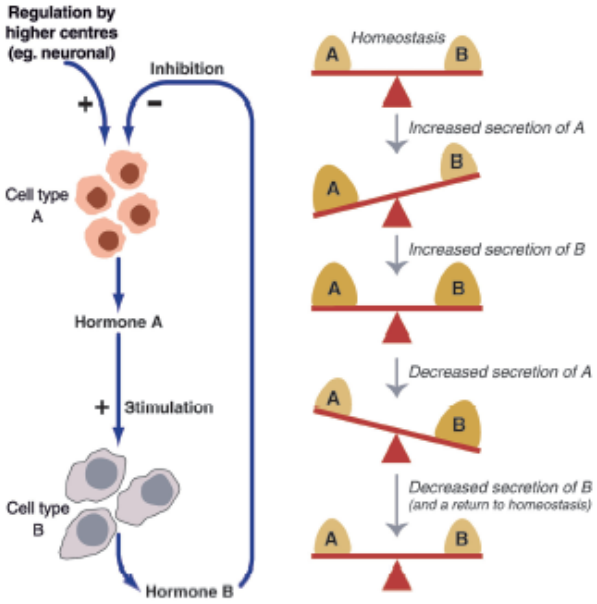

Figure 21: Diagram illustrating the regulating behavior of homeostatic systems. Source: World Health Organization, p. 12, 2002.

At the most basic level, normal endocrine function is mediated through hormones and their receptors. A specific hormone binds with high affinity to its receptor ligand – a protein that resides either on the surface of the cell, enzyme, mitochondria, or cellular nucleus. After the hormone binds with its receptor, it then stimulates mRNA translation to produce specific proteins or hormones (McLachlan, 2001). This concept is shown below; the top left figure represents a hormone mimic that can bind with the ligand, inducing the production of a hormone. The top right figure represents an anti-hormone, which occupies the receptor so that the endogenous hormone is unable to initiate an

effect. Recently it has been learned that co-factors can enhance (coactivators) or repress (corepressors) the expression of genes that play a role in receptor-ligand mediated signaling, indicating that there may be multiple pathways for signaling (Robyr, et. al., 2000, McLachlan, 2001) (Figure 22).

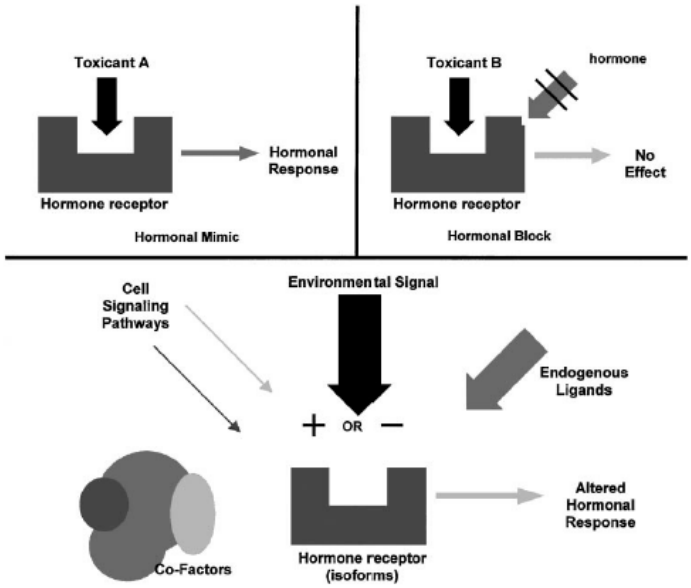

Figure 22: Some Receptor-Mediated Mechanisms of Endocrine Disruption. Top left – Toxicant binds with receptor initiating hormone production. Top Right – Toxicant occupies receptor, blocking normal hormone action. Bottom – Co-factors enhance or repress multiple pathways of signaling, resulting in a combined response, each susceptible to interference. Source: McLachlan, 2001.

Normal operation of the signaling mechanism works as follows: as the hormone (EA) is produced in the gonadal cells, it passes into general circulation where it may bind with sex hormone binding globulins (SHBG), or enter a cell. Once inside the cell, the hormone is free to bind with available receptors (R), which then activates the production of mRNA. This mRNA is then translated to produce a protein chain, which can include

hormones, enzymes, receptors, or growth factors (World Health Organization, p. 23, 2002) (Figure 23).

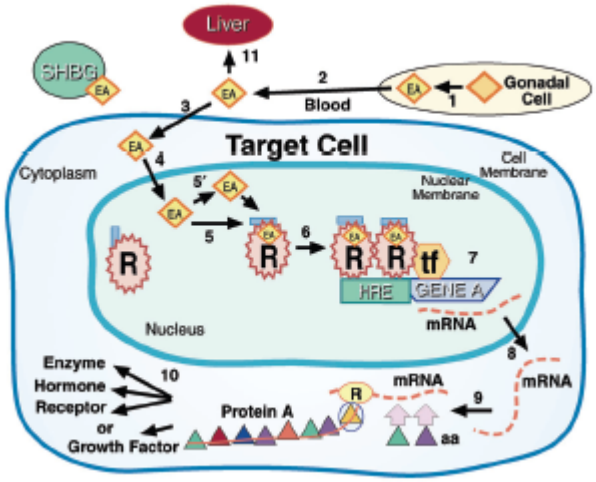

Figure 23: Sites of hormone disruption. See text for discussion. Source: World Health Organization, 2002.

Abnormal signaling may occur at many points in this process, some of which are shown above (Some numbered steps are omitted because they describe normal steps) (Figure 24). (1) Interference with the production of hormones in the gonads, can be achieved with some pesticides, drugs, and inhibitors of CYP450 enzymes, which are required in the hormone synthesis biochemical pathway (World Health Organization, p. 23, 2002). 2) Concentrations of SHBG can be altered by toxicants, and the binding affinity for exogenous hormones may be lower than for endogenous hormones, altering the fraction of free hormone in the blood. 5) Many toxicants are known to bind with the estrogen receptor (ER) and the androgen receptor (AR), resulting in interference with

hormone synthesis by competitively occupying the receptor. 6) After the hormone binds with the receptor, the complex undergoes a conformal change in shape, exposing binding sites of key proteins. 7) Transcriptional factors (tf) attach to the complex, forming a transcriptional unit that then attaches to specific DNA binding sites called hormone response elements (HRE). This complex initiates mRNA production, but certain anti-hormones can interfere with the binding to DNA. 9) Amino acids (aa) attach to tRNA during the synthesis of a protein chain that can result in the production of an enzyme, hormone, receptor, or growth factor (World Health Organization, p. 23, 2002).

Receptor Mechanics

Receptor mechanics are an important part of endocrine system function, defining the response of the cell for a given level of receptor occupancy. Shown below is a hypothetical dose-response curve relating the concentration of estrogen, either endogenous or exogenous, to the response of the cell (Welshons, et. al., 2003) (Figure 24). The vertical dashed line represents the operating point, or bias of the cell under normal conditions; if exogenous estrogen is introduced, the response of the cell will increase, following the green line. Note that the actual threshold is lower than the assumed threshold, and because estrogens are endogenously produced, any exogenous estrogenic chemical of sufficient dose will change the operating point. Estrogenic compounds will move the operating point upwards, and anti-estrogens will move the operating point downwards. Also shown is the error introduced by assuming that the toxicological effects at high doses can be linearly extrapolated to low doses.

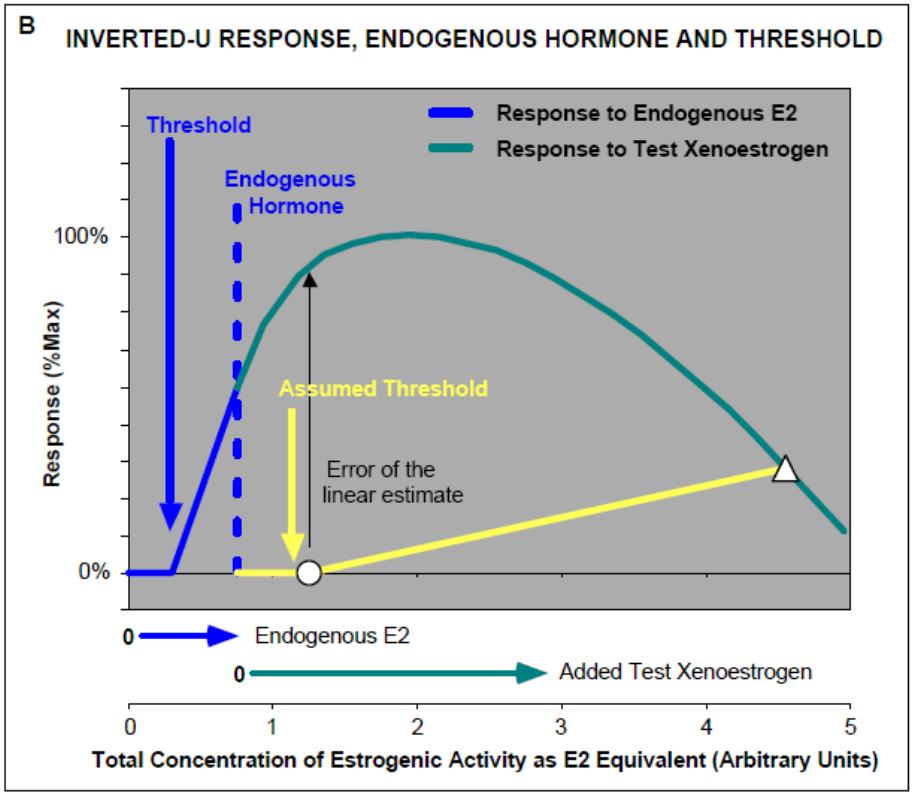

Figure 24: Inverted-U response. Source: Welshons, et. al., 2003.

Nonlinear dose response curves

Cells of the body differ in terms of which receptors are present; areas known to contain estrogen receptors include: the hypothalamus, the pituitary gland, various areas of the cerebral cortex, and gonadal cells. These cells contain a finite number of receptors, and if no receptors are occupied, no response occurs, whereas if 100% of the receptors are occupied, the response will be at a maximum. However, the response in-between these two limits is not a linear function. As shown below, the fraction of receptors occupied increases dramatically at low concentrations, but at high concentrations, a large change in hormone concentration results in only a small change in receptor occupancy (Figure 25). Because receptor occupancy determines the response, the figure shows that

the response of the cell is saturating at relatively low concentrations. This indicates that at low doses, the response is nearly linear, with the occupancy being directly proportional to the estrogen concentration, but as the concentration increases, the effect becomes smaller and smaller, so that at high estrogen concentrations, a large increase in dose has very little effect on the response.

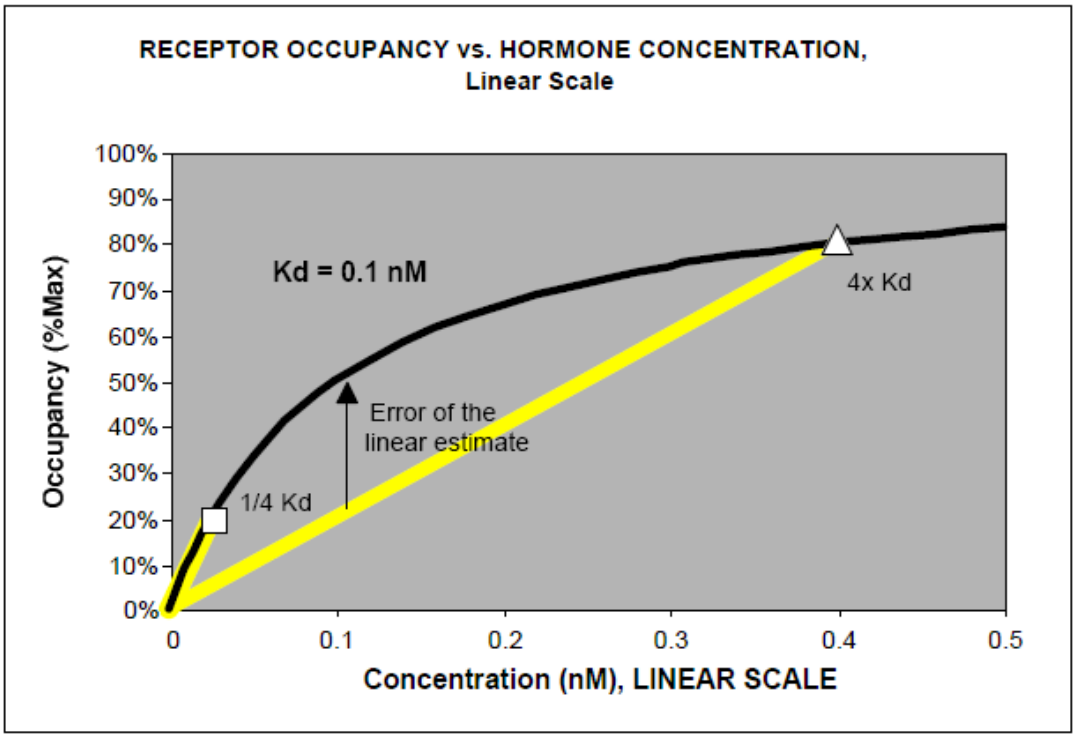

Figure 25: Occupancy of receptors as a function a hormone concentration. Source: Welshons, et. al., 2003.

Welshons, et. al. (2003) conclude from these facets of receptor mechanics that the normal operating region is therefore substantially lower than the dissociation constant Kd. (The dissociation constant is the concentration at which half the receptors are occupied.) They argue that the operating point is probably below 10% receptor occupancy under normal circumstances, because at higher concentrations, the sensitivity

of the response is significantly attenuated (Welshons, et. al., 2003). This has been confirmed in experiments showing that small changes in estrogen concentration yield measurable changes in animal behavior, supporting this hypothesis (vom Saal, p. 17, 1992). These findings suggest that predictions based upon toxicological assumptions may not be valid, a matter that will be revisited later.

3) Empirical Evidence of Endocrine Disruption

Mice and rats are the two most common species for laboratory experiments involving endocrine disruptors. There are several different types of experiments that have been performed: evaluation of differences in sexual behavior of mice who have different adjacent littermates, studies examining anatomical changes with exposure to EDCs *in utero* and in adulthood, and studies examining the behavioral effects of adults exposed *in utero* or neonatally. Several studies have also examined and related both anatomical changes with behavioral changes, providing a basis for predicting similar effects in humans.

Experiments with Mice

Littermate studies in mice have provided excellent evidence of the incredible sensitivity of the developing endocrine system to modulation from exogenous hormones. Frederick vom Saal has shown convincingly what is called the "intrauterine effect"; females who have only adjacent female littermates are the most attractive to males, those with one adjacent male littermate are slightly less attractive, and those with two adjacent male littermates are the least attractive to males and the most masculinized (vom Saal & Bronson, 1980). It is believed that these chemical differences during development change the odors produced by the mice, thus altering the way that males relate to them (Colborn, et. al., p. 34-5, 1996).

These experiments have provided compelling evidence suggesting that the nominal endogenous hormone levels are so small that the influence of hormones from adjacent littermates has a significant effect on adult sexual behavior. While many carcinogens induce cancer at parts per million or parts per billion, the intrauterine effect

is seen in the range of parts per trillion(Colborn, et. al., p 40, 1996); One part per trillion is 1 part per 1,000,000,000,000 (10^{12}).

Studies in mice examining hormonal and anatomical changes induced by EDCs indicate that both natural and synthetic compounds may have estrogenic or androgenic characteristics. Cheng, et. al. (2002) showed that offspring of mice treated with Chromium (III) Chloride, a preconceptual carcinogen, induces a highly significant increase in the concentration of serum corticosterone as well as glucose in both male and female mice, indicating that chromium (III) has endocrine disrupting properties in addition to carcinogenic properties at higher concentrations. Cavieres, et. al. (2002) showed that exposure to a commercial herbicide mixture including 2,4-D, mecoprop, dicamba, and inactive ingredients was able to reduce litter size, but effects were most significant at low and very low doses, suggesting that the dose-response curve has the shape of an inverted U, although the exact shape of the dose-response curve was not determined.

Several studies have examined developmental effects induced in mice by exposure to diethylstilbestrol (DES). Fielden, et. al. (2002) found that exposure to DES during gestation and lactation caused a decrease in the number of Sertoli cells – cells responsible for the production of sperm, a decrease in the sperm count, and a reduction in the ability of sperm to fertilize the egg, *in vitro* (outside of the body). McLachlan (1975) found that prenatal exposure of mice to DES caused lesions in the reproductive tract, including undescended testes, fibrotic testes, or both, in addition to nodular masses in the testes, epididymis, and accessory sex glands. Block et. al. (2000), demonstrated that *in utero* exposure of mice to DES causes alterations in the expression of the Hox gene,

which is responsible for reproductive tract development, suggesting that altered Hox gene expression may be a biomarker for early exposure to DES. Hess et. al. (1997) found that alterations in the anatomical development of the epididymis by DES causes dilution of sperm in ejaculate, reducing the probability of egg fertilization.

Studies have also examined behavioral changes associated with EDC exposure in mice. Kawai, et. al. (2003) exposed male mice to Bisphenol A (BPA), a monomer used in plastics, dental sealants, and as lining in metal food cans, at environmentally relevant concentrations, finding an increase in the serum testosterone as well as an increase in aggressive behavior in adulthood. The increase in aggressiveness was not found to be statistically significant with respect to the elevated testosterone concentration, causing the authors to suggest that another mechanism is at work. Although the testosterone concentration was increased, the testicular weight was reduced, and the amount of the reduction was greater in the case of the lower exposure, again suggesting a non-monotonic dose-response curve. Palanza, et. al. (2002) found that low dose exposure of female mice to BPA in either prenatal life or in adulthood reduced the time spent nursing their pups and increased the time out of the nest compared to controls. Interestingly, when exposed to BPA both during prenatal life as well as during the last third of pregnancy, no differences in behavior from controls were observed. The authors suggest that this indicates that the prenatal exposure permanently altered the expression of genes relevant to the neuroendocrine substrates that regulate maternal behavior, so that when exposed to BPA during pregnancy, homeostatic circuits were responding differently than would be the case without fetal exposure; this is an indication that behavior is tied to the chemical environment, and if the environment changes, so does behavior. Exposure of

neonatal mice to another class of EDCs, brominated flame retardants, also known as polybrominated diphenyl ethers (PBDEs), caused changes in memory and learning functions, and caused permanent changes in spontaneous behavior such as locomotion and ability to swim through a maze (Eriksson, et. al., 2001).

Another type of study relates changes in endogenous hormone levels with both morphological and behavioral changes. These studies are important because they yield clues indicating what types of changes could be expected in humans, given the similarity between mice and humans in terms of the endocrine system. For instance, Grober et. al. (1998) performed an experiment on mice similar to those performed in humans by researchers at the Netherlands Institute of Brain Research (Zhou, et. al. 1995, Kruijver, et. al., 2000, Chung, et. al., 2002). They exposed male and female mice to exogenous estradiol prenatally, and determined that the size of a pre-optic region of the hypothalamus responsible for sexual behavior was increased in males, but not females, compared to controls.

As shown below in figure 26, the number of cells in this region of the hypothalamus are unaffected by estradiol exposure in females, but in males, a significant increase ($p = 0.03$) was found. This appears to be a paradoxical result, since estradiol is traditionally considered the primary female hormone. However, it is believed that the intracellular conversion of testosterone to estradiol through the enzyme aromatase is partly responsible for masculinizing the male brain (Gorski, 1998, Hayes, et. al., 2000). Since exposure to estradiol reduces the concentration of testosterone in the bloodstream, an increase in the size of this region may occur in order to compensate for the reduction in intracellular estrogen aromatized from testosterone. Hayes, et. al. (2001) provides data

supporting multiple forms of feedback in the HPG axis in human males: one form of feedback is a reduction in the GnRH pulse frequency that occurs in the hypothalamus, and another form occurs in the pituitary to reduce the responsiveness of the pituitary to GnRH; multiple forms and locations of feedback complicate the interpretation of experimental data because the endocrine system is compensatory by design, and effects can be obscured by the adaptive nature of the system. The GnRH pulse frequency may be affected by pheromonal cues, but that facet was not studied in this study. Nonetheless, it is clear that changes are occurring to systems important for sexuality in adulthood.

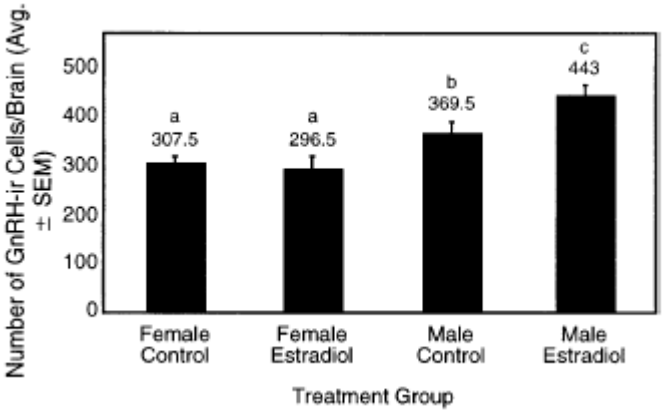

Figure 26: Changes in brain morphology due to prenatal exposure to exogenous estradiol in male and female mice. Source: Grober et. al. (1998)

Experiments with Rats

Studies in rats are almost identical to those in mice. Sharpe, et. al. (1995) showed that male rats exposed to 4-octylphenol (OP), a detergent by-product, butyl benzyl phthalate (BBP), a plasticizer, or the pharmaceutical DES during gestation or early prenatal life resulted in a reduction in the size of the testes as well as a reduction in sperm count in adulthood. Sokol, et. al. (2002) showed that long term exposure to the heavy metal lead in adult male rats increased the amount of GnRH mRNA produced in the

hypothalamus, indicating that lead interfered with signaling between the hypothalamus and the pituitary gland. Effects were seen at lead levels as low as 10ug/dL, which is approximately ten times higher than the blood lead concentration of the average person in the United States, and only double the lead level of those with the highest blood lead levels reported in a recent national study (Centers for Disease Control and Prevention, 2003). Five percent of the population has lead levels higher than the highest level reported by the Centers for Disease Control and Prevention (CDC), indicating that when individual differences in sensitivity to lead are taken into account, the safety margin may be inadequate. The authors indicate that the levels of BBP in the study are also only slightly higher than in measured in the average person.

Hays, et. al. (2002) examined the effects of the dioxin TCDD on rat neurons that have GABA receptors, finding that exposure caused region-specific differences in several areas of the hypothalamus, and that further, the effects on males and females were different. This research suggests that multiple pathways may be operating simultaneously, involving complex genetic and epigenetic effects. Moore, et. al. (2001) demonstrated that *in utero* and lactational exposure of rats to di(2-ethylhexyl) phthalate (DEHP) induced changes in male reproductive system development and sexual behavior in adulthood. Changes included undescended testes, nipple retention, and a reduction in the anogenital distance, which is used as a marker of the degree of feminization in rats. Other findings include a reduction in the weight of: testes, epididymis, glans penis, several regions of the prostate, and seminal vesicles. The data suggests that DEHP acts as an anti-androgen, causing demasculinization. Many phthalates are present in humans in

high quantities and metabolites of DEHP have been found in practically the entire U.S. population (Centers for Disease Control and Prevention, 2003).

Mably et. al. (1992) report that the dioxin TCDD is capable of reducing anogenital distance, delaying testicular descent, and reducing the weights of accessory organs of the male rat reproductive tract both *in utero* and neonatally. Also, sperm production is decreased, sexual behavior is simultaneously demasculinized and feminized, and the regulation of luteinizing hormone (LH) follows a female pattern (cyclic) rather than a male pattern of operation (tonic). The authors suggest that this demasculinization and feminization of the male brain is due to the inhibition of testosterone during a critical period around the time of birth, permanently altering central nervous system development. As adults, these male mice displayed female-typical behaviors such as lordosis, or presentation of the rump to a male for copulation, and displayed female-type endocrine control of LH, which was cyclical in nature rather than regulated to a relatively constant level (tonic).

Bisphenol A in rats appears to cause similar results as in mice. Rubin, et. al. (2001) showed that low doses of BPA cause a permanent increase in body weight, and high doses resulted in abnormal estrus cycles. The authors suggest that the sexual development of the brain is disrupted by BPA, perhaps because protective blood proteins do not bind with BPA as they do to endogenous estrogens, and thus escape the body's defense mechanisms. The pesticide DDT, on the other hand, was shown to induce persistent estrus of female rats after several normal cycles, advanced the onset of puberty, caused follicular cysts to develop in the ovaries, and disturbed female mating behavior (Heinrichs, et. al., 1971).

Findings in Fish

In the last decade, studies have increasingly identified sex-reversal of many fish species living in waters found to be contaminated with various estrogenic EDCs (Jobling, et. al., 1998). The finding that 5% of roach fish (*Rutilus rutilus*, a common cyprinid) living downstream from a U.K. sewage treatment plant were hermaphroditic was a surprise to researchers, who noted that only two hermaphroditic roach fish had ever been reported in the literature, one in 1965 and one in 1979 (Sumpter & Jobling, 1995). Because it is known that the synthesis of vitellogenin, a liver protein used for creating egg yolks in female fish, is mainly under the control of the sex hormone 17β-estradiol, researchers suspected the presence of an estrogen of some sort in the effluent of the sewage treatment facility (Purdom, et. al., 1994). In order to test this hypothesis, they placed fish in cages directly in the effluent of 28 sewage treatment plants around the country to determine if similar results were obtained; five other groups were placed in cages and raised in trout farms, where the water is believed to be unpolluted. For treatment sites, at 13 of the sites all the fish died due to poor effluent quality, but at the other 15 sites, in all cases there was a substantial increase in vitellogenin synthesis in both males and females (Sumpter & Jobling, 1995). Because the fish vitellogenin increased dramatically, from 500 to 50,000 fold, they concluded that something in the effluent was acting as an estrogen, and thus altering development. Since female roach usually exhibit around a 1 million-fold increase in vitellogenin synthesis during the reproductive cycle, this is the basis for suggesting that fish are sensitive indicators of

endocrine disrupting chemicals, and that sexual changes are evidence of exposure to EDCs (Sumpter & Jobling, 1995).

As a result of these early findings, a significant amount of further study in the U.K. has been performed, indicating that wastewater effluent from sewage treatment plants is commonly estrogenic. Purdom, et. al. (1994) initially suggested that the likely sources were birth control pills (ethynylestradiol) or alkylphenol ethoxylates, deriving from surfactants and detergents that partially break-down during the sewage treatment process. A number of studies coupled observations of increased vitellogenin synthesis with laboratory studies aimed at identifying the source of the estrogen. For example, Routledge, et. al. (1998) found that trout (*Oncorhynchus mykiss*) and roach fish exposed *in vivo* to 17β-estradiol or the alkylphenol ethoxylate 4-tert-octylphenol, at environmentally relevant concentrations similar to those measured in U.K. streams, were able to induce similar increases in vitellogenin synthesis, evidence that these chemicals are contributing factors to the widespread sexual disruption seen in these fishes (Jobling, et. al., 1998). More recent studies have confirmed these findings, providing conclusive evidence of widespread sexual disruption of fishes in the U.K. (Lye, et. al., 1999, Harris, et. al., 2001, Williams, et. al., 2003).

Few studies have examined U.S. fish for evidence of endocrine disruption; one study that did examine the question found that 84% of genetically male chinook salmon (*Oncorhynchus tshawytcha*) were sex-reversed in the Hanford Reach area of the Columbia river in Washington State (Nagler, et. al., 2001). The authors suggested that exposure to endocrine disrupting compounds may be responsible, since the United States Geological Survey (USGS) has identified a number of pollutants in the water from this

region (USGS, 2002). Additionally, because the Priest Rapids hatchery supplements this particular run by introducing hatchery raised fish, it is not possible to conclude that the remaining 16% of genetically male fish were not sex-reversed, because only 3% of hatchery fish are tagged by having their adipose fin clipped (Nagler, et. al., 2001). That is, the remaining 16% of males that were phenotypically normal may be hatchery produced fish.

In 2002, the USGS published results from its first national reconnaissance of pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, finding that a wide range of chemicals are present in most streams, and that substantial levels of hormones, detergent metabolites (APEOs), plasticizers such as phthalates, and nonprescription drugs are common (Kolpin, et. al., 2002). The sources of these chemicals are varied, but a large contribution is made by discharge of wastewater effluent from sewage treatment facilities, particularly for chemicals such as pharmaceuticals intended for humans (Daughton & Ternes, 1999).

Another source of endocrine disruptors to aquatic environments includes the runoff from the solid precipitate of sewage treatment, originally called sewage sludge, now euphemistically known as biosolids. A number of studies have shown that biosolids contain substantial concentrations of heavy metals, phthalates, various natural and synthetic hormones, and alkylphenol ethoxylates; when applied to agricultural fields or in forests, runoff removes a fraction of the adsorbed contaminants, thus providing a mechanism for transport to waterways (United States. Environmental Protection Agency, 1990, Hale, et. al., 2001, Baronti, et. al., 2000, Johnson & Sumpter, 2001, Hesselsöe, et. al., 2001, La Guardia, et. al., 2001, de Jonge, et. al., 2002, Layton, et. al., 2000).

Disposing of biosolids is a recent problem, created by the Ocean Dumping Ban act of 1988 that forbid dumping municipal waste in the ocean, and thus forcing waste managers to find alternative places for disposal (United States. Environmental Protection Agency, 1990). Studies indicate, however, that agricultural crops can readily uptake metals and other chemicals, thus posing an unknown risk to public health (Washington State Department of Agriculture, 2001).

Once these chemicals are utilized for their intended purpose, their fate is far from clear, however, as they cycle through all compartments of the environment (Figure 27). There is evidence that many of these chemicals do not break-down into harmless compounds; evidence exists showing that: methylation of inorganic mercury is performed by microorganisms (Drexel, et. al., 2002, King, et. al., 2001), bacteria convert non-hormonally active compounds into hormonally active substances (Panter, et. al., 1999, McLachlan, 2001), estrogens from septic fields and high-estrogen groundwater sources migrate to marine environments (Atkinson, et. al., 2003) and that breakdown is rapid under aerobic (oxygen-rich) conditions, but that under anoxic (oxygen-poor) conditions, breakdown is significantly slower (Ying & Kookana, 2003). All these factors indicate that prediction of chemical products and their subsequent effects will be difficult when there are so many complicating influences.

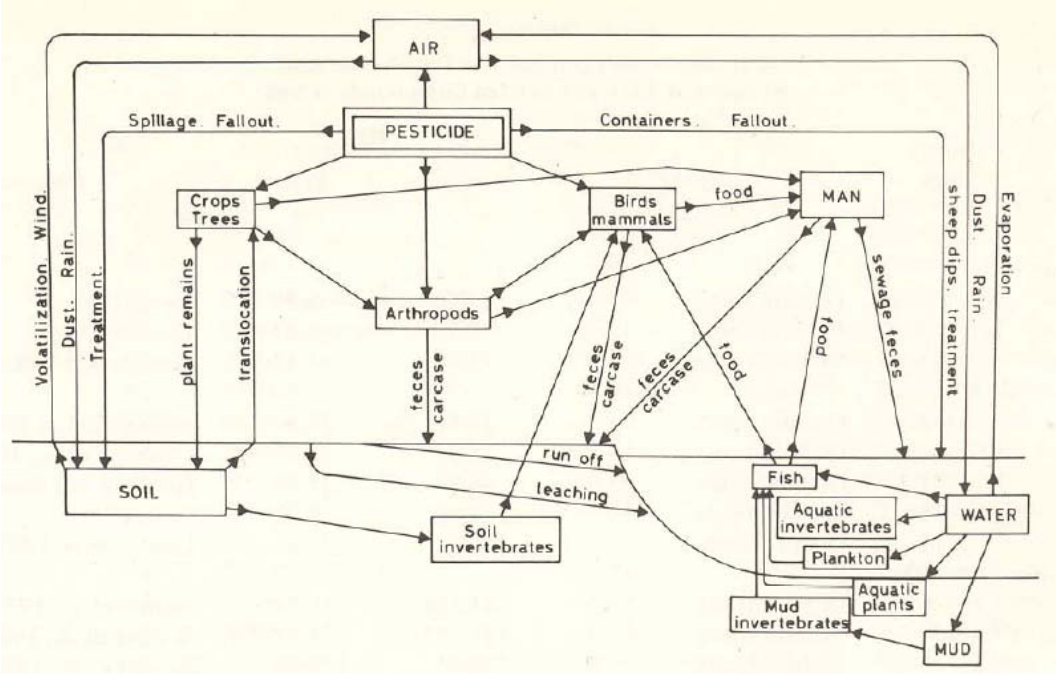

Figure 27: Transport of pesticides through the food chain and different environmental compartments. Source: Edwards, p. 7, 1973.

A variety of fish species have also been studied under laboratory conditions, and findings are in many cases more profound than in mice and rats, as complete sex reversal is a commonly reported phenomenon. As in mammals, fish also have a hypothalamic-pituitary-gonadal axis (Melo and Ramsdell, 2001). In fish, vitellogenin is a protein, produced in the liver and used by the ovaries to produce eggs, that increases in response to exposure to endogenous estrogens. This fact has permitted a simple method of determining if males are being exposed to an exogenous source of estrogen, since the endogenous concentration of estrogens is normally very low in males (Sumpter & Jobling, 1995).

Melo and Ramsdell, (2001) showed that male Japanese Medaka, a fish species, exposed to estradiol developed a female phenotype, and the degree of reversal was

independent of estradiol concentration, but dependent upon length of exposure; these differences were related to sexual differences between male and female distributions of aromatase in the brain. Papoulias et. al. (2003) showed that Medaka exposed to o,p'-DDE, a metabolite of DDT, had altered sexual differentiation; male testes were significantly reduced in size compared to controls and females had abnormal ovaries. Nonylphenol, another by-product of detergents, was shown to increase the production of vitellogenin in female rainbow trout. Also, follicular stimulating hormone (FSH) was decreased as was leutinizing hormone (LH) (Harris, et. al., 2001).

But of all the fish species studied, perhaps none has been examined more than salmon. This is partly due to the fact that the salmon population, particularly in the Pacific Northwest of the United States, is in many cases endangered, threatened, and in some cases, extinct from streams where they were once abundant (Huntington et. al., 1996). As several authors have noted, because salmon stocks are declining, fish managers are especially interested in methods to increase the number of egg-producing females because only a few males are needed to fertilize eggs (Hunter, et. al., 1986, Goetz, et. al. 1979). That is, for fisheries managers, it has been proposed that chemical sex-reversal using estrogens is a viable method of generating a surplus of females.

Goetz et. al. (1979), in an article detailing intentional sex reversal, exposed coho salmon (*Oncorhynchus kisutch*) to estradiol and testosterone to determine the effects on sexual differentiation, finding that 7 of 10 groups exposed to estradiol were completely phenotypically female at four months post-hatch. Coho salmon exposed to testosterone were found to have gonads resembling neither normal females nor normal males; their gonads were composed primarily of connective tissue and occasionally a germ cell.

Donaldson and Hunter (1982) describe a variety of methods whereby normal sexual differentiation of male salmon may be altered to result in a female phenotype that is also able to produce eggs. Hunter, et. al. (1986) showed a large fraction of coho and chinook salmon could be sex reversed using estradiol, ranging from 66% to 96% female. Donaldson and Piferrer (1991) showed that a single 2 hour immersion of newly hatched chinook salmon (*Oncorhynchus tshawytscha*) in ethynylestradiol, (EE2) the synthetic estrogen commonly used in birth control pills, resulted in 100% female salmon. The authors suggest the method could be useful for direct feminization of salmon on a large scale.

However, in a large experiment conducted in the Experimental Lakes Area (ELA) located in Manitoba, Canada, researchers seeded an entire lake with EE2 concentrations similar to those in Canadian and international receiving waters, in order to evaluate changes in sexual development of wild fathead minnows (*Pimephales promelas*) (Palace, et. al., 2002).They found that when exposed to EE2 concentrations ranging between 4.0 and 8.1 nanograms/L (parts per trillion, or ppt), vitellogenin concentrations increased 9000-fold in males and from 8 to 80-fold in females. Histological analysis showed that a number of malformations were present, including widespread fibrosis and reduced testicular development. These findings have rather significant implications, since EE2 is the most commonly prescribed form of birth control in the United States, and monitoring of EE2 in freshwater is generally not performed.

Along similar lines, Orlando, et. al. (2002) found that female Eastern Mosquitofish (*Gambusia holbrooki*) living downstream of a pulp and paper mill were masculinized, although the mechanism is not known. The authors concluded that

masculinized females were due to the presence of androgenic chemicals in the river, rather than a reduction in the aromatase activity as initially speculated, since they had seen differences in aromatase activity in other related experiments.

Endocrine Disruption in Other Species

A number of other species have been studied under laboratory conditions to determine the effects of exposure to different EDCs. Jessen-Eller, et. al. (2002) showed that in the invertebrate surf clam (*Spisula solidissima*), exposure to PCBs interferes with critical regulators of cell cycle production that instruct the cell to die (apoptosis) if too much of this regulatory protein is produced. While not related to sexual development, it is an indication that effects in one species may be completely different from effects in other species, and what is shown to be harmless for one species may not be safe for another, since different species vary in the function assigned to a given information molecule, in their sensitivity to different compounds, and in mechanisms for detoxification of xenobiotic compounds, particularly for invertebrates (Daughton & Ternes, 1999).

Avian Species

One of the earliest papers dealing with sex changes due to EDCs was published in 1950 by two researchers at Syracuse University. Burlington and Lindeman (1950) injected white leghorn cockerels with DDT from 8 days after hatching, continuing daily for at least 60 days. The dose was increased from 15 mg/kg/day for young birds to 300mg/kg/day by the time the birds were sacrificed between 60 and 89 days. They found that the secondary sexual characteristics of the male cockerels, such as large wattles and combs were significantly reduced in size, and approximated those of a hen. Treated animals had testes that were one-fifth the size of controls, and the authors speculated at

the time that DDT may have been acting as an estrogen by inhibiting the pituitary production of LH. Interestingly, they note the close structural similarity between DES and DDT, showing the structural diagram of both molecules in their paper. The results of this paper went largely unnoticed, and in the next decade DDT use would increase substantially despite its estrogenic and anti-androgenic properties. Measurement of DDT and its metabolites in the body fat of non-occupationally exposed people in the United States in 1963 found that the average concentration was 10.71 +/- 1.51 parts per million, or 10.71 mg/kg, approximating the early doses used in this experiment (Dale and Quinby, 1963). It is possible these measurements are overestimates, however, since methods to distinguish DDT from PCBs were not developed until the early 1970s, so both may be represented in the measurement.

Another avian species studied includes the Japanese Quail; Panzica et. al. (2002) performed a study very similar to Zhou (1995), but for their experiment they injected eggs with either estradiol or an aromatase inhibitor so they could determine the sexually dimorphic changes in the quail hypothalamus and associated behavioral changes. Males treated with estrogen exhibited female hypothalamic structures, and lost the ability to engage in copulatory behavior, whereas females treated with an aromatase inhibitor had male-like hypothalamic structures and male copulatory behavior. The authors use the term "behavioral phenotype" to indicate that the behavioral biases have been altered contrary to the quail's genetic sex. They also make a similar claim as Diamond (1965), in saying that the irreversible changes observed are organizational in nature, because hormonal status in adulthood does not alter the hypothalamic structures.

Reptiles

Reptiles have also been studied with respect to changes in sexual development as a result of exposure to EDCs. Willingham et. al. (1999) applied three EDCs: Aroclor, chlordane, and trans-Nonachlor to the eggs of Red-Eared Slider turtles (*Trachemys scripta elegans*). Males treated with Araclor and chlordane had significantly lower levels of testosterone at 6 weeks of age compared to controls. Treated females had significantly lower testosterone, progesterone, and 5α-dihydrotestosterone levels relative to controls.

Several studies have been performed on alligators, due to the fact that Lake Apopka in Florida was polluted with a massive spill of DDT and dicofol (Gunderson, et. al., 2001), resulting in reproductive problems in American Alligators (*Alligator mississippiensis*). Milnes, et. al. (2002) studied the effect of estradiol in this species, whose sexual development is controlled by both the hormonal environment as well as temperature. Eggs incubated at temperatures that typically produce males were exposed to estradiol *in ovo* (applied to the egg), resulting in sex-reversed females with masculinized brain activity but intermediate gonadal function. Crain, et. al. (1997) examined, among other things, the effects of exposure to estradiol and tamoxifen, finding that both induced male to female sex-reversal.

Amphibians

In the early 1990's, conservation biologists noticed that many amphibian populations were in decline, and several plausible factors have been implicated, including ultraviolet radiation, acid precipitation, pathogens, and long-range transport of chemicals (Meffe, et. al., p. 135-7, 1997). Although today most scientists agree that declines are due to a range of factors, the contribution of EDCs to the decline is not yet well characterized. Bevan, et. al. (2003) found that *Xenopus laevis* exposed to octylphenol and methoxychlor

exhibited an increase in mortality, increased apoptosis, and a number of morphological defects. Mayer, et. al. (2003) examined sexual differentiation in the bullfrog (*Rana catesbeiana*), finding that exposure of tadpoles around the time of sexual differentiation to 4-tert-Octylphenol, an alkylphenol ethoxylate used in detergents, caused early gonadal differentiation, as well as altering SF-1 expression, a gene known to be sexually dimorphic in this species. Importantly, the dose applied was in an environmentally relevant range, (~0.2 ppb) and exposure time was short, at one day. Longer exposure times have resulted in a skewed sex ratio towards females in other similar species (Kloas et. al., 1999).

Hayes et. al. (2003) performed a two-part study that compared the effects of laboratory exposure to effects seen in the wild for the leopard frog (*Rana pipiens*). Demonstrating an inverted U type dose-response relationship, they found that 36% males exposed to atrazine at 0.1 ppb had underdeveloped testes, called gonadal dysgenesis, whereas 12% of males exposed to 25 ppb had the same condition. At the 0.1 ppb level, 29% of males were sex-reversed to various degrees, as were 8% of those treated at the 25 ppb level. The sex-reversed males were producing oocytes (eggs) in their testes. Females were apparently unaffected by the exposure to atrazine. Next, Hayes, et. al. (2003) collected *Rana pipiens* in the wild, sampling eight sites arranged in a more or less straight line from Utah to Illinois. Sampling sites were chosen for known atrazine application exceeding 9.3 kg/km^2, and controls were selected from sites with atrazine use below 0.4 kg/km^2 (Figure 28).

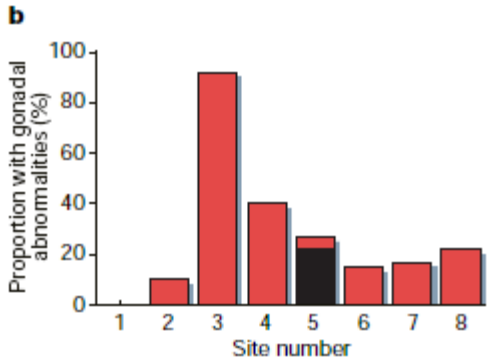

Figure 28: Fraction of wild Leopard frogs (*Rana Pipiens*) with gonadal abnormalities for each sampled site. Black bar – Gonadal dysgenesis; Red bars – Testicular dysgenesis. Source: Hayes, et. al., 2002.

The combination of animal data from the wild and corroborating laboratory evidence is important because it indicates that alterations in the development of sexual characteristics in many species can be attributed to anthropogenic sources of endocrine disrupting chemicals; because of the highly conserved nature of sex-hormones and their receptors in the animal kingdom, these results have direct applicability for predicting sexual changes in humans. The next chapter will examine evidence of human exposures to these chemicals, focusing on their effects on sexual development and behavior.

Human Studies

Udry (2003) has noted that social scientists widely believe that behavior is determined solely by social conditioning. Because many explanations of transsexual behavior, demographics, and prevalence are based on social factors or psychopathology with unknown causal mechanisms, this chapter will examine contrary evidence demonstrating widespread exposure to endocrine disrupting chemicals during development and in adulthood, some of the effects observed to date, and re-evaluate some of the literature asserting social factors as causal. The question is: can these

chemicals and their known and suspected effects can safely be ignored in evaluating the etiology of transsexualism?

From the early 1990s, the endocrine disruptor hypothesis has spurred investigations into several areas of human health, from chemical exposure studies to associated effects on physiology and behavior. A number of exposure studies have been performed, and in recent years, the Centers for Disease Control and Prevention (CDC) has collected normative data for exposures to a wide range of chemicals in the U.S. population (Centers for Disease Control and Prevention, 2001; Centers for Disease Control and Prevention, 2003).

Several studies have identified PCBs in umbilical cord blood and plasma (Sandau, et. al., 2002; Dallaire, et. al., 2003), blood plasma (World Health Organization, p. 120, 2002), and breast milk (World Health Organization, p. 119, 2002). One of the problems with evaluating these studies is that many variants of PCBs exist, known as congeners, and different studies have used different metrics to characterize the total exposure, complicating comparisons among studies. Longnecker, et. al. (2003) attempted to apply a uniform technique for interpreting results from various studies, but because PCBs can theoretically occur in 209 different congeners, this increases the difficulty of associating a specific effect in humans to exposure (Maervoet, et. al., 2004; Schantz, et. al., 2003). Nonetheless, PCBs have been found to alter thyroid hormone levels, decrease binding of sex-hormones to sex-hormone binding globulins (SHBGs), and induce changes in the size of the corpus callosum, a critical brain structure partly responsible for response inhibition, or the restraint of unproductive behavior (Persky, et. al., 2001; Stewart, et. al., 2003).

One recent study of men with testicular cancer found that the concentrations of PCBs in the blood of the mother were significantly correlated to the likelihood of testicular cancer of men in adulthood (Hardell, et. al., 2003), supporting the hypothesis originally suggested by Sharpe and Skakkebæk (1993) that certain types of testicular cancer develop during fetal life due to exposure to estrogenic substances. A particularly relevant study performed in the Netherlands found that higher prenatal PCB levels were associated with less masculine play behavior among boys and more masculine play among girls, whereas high dioxin exposure resulted in more feminized play among both boys and girls, suggesting developmental outcomes that differ between the sexes and that are dependent on the chemical (Vreugdenhil, et. al., 2002). And recently, Weiss (2002) has suggested that non-reproductive behavioral differences between males and females may be useful as an indicator of developmental endocrine disruption, noting that although many attribute cultural factors as causal, evidence supporting the primacy of biological substrates for sexually dimorphic behavior is compelling. Weiss references Zhou, et. al. (1995), noting that hypothalamic nuclei in rats are sexually dimorphic, but curiously, he does not extend the implications to humans, even though the Zhou study was performed on humans. Nevertheless, this paper is important because Weiss is one of the few authors to relate prenatal EDC exposure to sexually dimorphic behavioral differences.

One of the main impediments to reducing human exposure to EDCs is that to a large degree, these chemicals have been integrated into many consumer products, most of which do not disclose their constituents on labels and are widely assumed by the public to be properly tested and regulated (Berkson, 2000; Schettler, 2000). For example, Bisphenol A (BPA) is a monomer that is commonly present in many plastic products that

has been found to be approximately ten thousand to one million times less potent than 17β-estradiol. However, the large number of consumer uses of BPA, including plastic water bottles, plastic food wrappings, as a lining material for canned foods and beverages, baby bottles, and for use in dental sealants and fillings, makes it ubiquitous in human environments, as BPA has been found to leach from all these sources (Matsumoto, et. al., 2003; Schönfelder, et. al., 2002).

Although the current lowest observed adverse effect level (LOAEL) for Bisphenol A in humans is 50mg/kg/day, and the acceptable daily intake is set at 50mg/kg/day, experiments in mice at the low dose of 10mg/kg/day find that daughters have significantly altered maternal behavior in adulthood, spending less time nursing and with their pups than controls (Palanza, et. al., 2002). This result suggests that the LOAEL should be reduced, but does not indicate any level at which effects are not observed, complicating regulatory changes. A study in humans found that BPA crosses the placenta and accumulates in the fetus, that the concentration in the fetus is higher for males than females, and that the levels measured are similar to those used in animal tests that demonstrate low-level effects on reproductive organs (Schönfelder, et. al., 2002). The types of behavioral changes in mice induced by BPA would normally be attributed to factors such as socialization in humans; this raises questions about the importance of socialization to later behavior in humans.

Heavy metals are frequently detected in humans; recent CDC data indicates that virtually all U.S. citizens are carrying measurable amounts of lead, cadmium, mercury, cobalt, antimony, barium, cesium, molybdenum, thallium, and tungsten (Centers for Disease Control and Prevention, 2003). Half the population has measurable urinary

uranium, a heavy metal that may also be radioactive, and in its depleted state is used for ammunition and has been associated with Gulf War Syndrome (Tashiro, 2001). Because of the large number of fish advisories due to mercury contamination, studies have examined the relationship between fish consumption and exposure to mercury, finding that the organic form, methylmercury, is correlated to fish consumption, and can be measured in the placenta (Ask, et. al. 2002; Björnberg, 2003). Evidence from a number of cases of methylmercury poisoning indicates that there may be a latency period of months to years before effects of poisoning are observed, suggesting that the damage only becomes obvious after the systems of the body are unable to compensate for the biochemical changes induced by the exposure (Weiss, et. al. 2002).

Mercury in vapor form (Hg^0) has been found to pass through the placenta and accumulate in the fetus (Ask, et. al., 2002). Eggleston & Nylander (1987) found that mercury in brain tissue was correlated to the number of dental surfaces composed of mercury amalgam, a commonly used form of dental filling typically composed of 50% mercury. Similar results have been observed in sheep and monkeys; several studies, using radioactive isotopes of mercury and whole-body scans, showed that compared to other brain regions, mercury preferentially accumulates in the pituitary gland, with unknown consequences (Hahn, et. al., 1989; Hahn, et. al. 1990; Vimy et. al., 1990) . Although much is unknown about the biological effects of mercury, studies have found that critical processes of neuron formation are significantly inhibited by mercury, implying neurological consequences (Palkiewicz, 1994). Sibulrud (1989) examined the relationship between the number of dental amalgam surfaces and mental health, finding that subjects with amalgams reported more symptoms reflective of poor mental health, suggesting

chronic, subtle effects from low-dose exposure to mercury. Given the proximity of teeth to the vomeronasal organ and that mercury dental fillings have been shown to continuously release mercury vapor, it is possible that mercury has direct effects on the HPG axis via the VNO.

Lead has long been a problem in children, and data from a recent national study indicates that higher lead levels in girls results in delayed menarche (first menstruation) and delayed growth of pubic hair (Wu, et. al., 2003). Although regulatory limits have successively dropped as more is learned about the deleterious health effects of lead, the current limits still may not be sufficiently protective, as changes in hormone levels are found at current lead levels. Another study examining semen quality found that lead and cadmium can impair sperm motility and morphology without resulting in easily observable hormonal impairments, and also finding that there was no dose that could be assumed to be without effect (Telisman, et. al., 2000). Although lead levels have dropped significantly due to its removal from gasoline in the 1970s, lead is still ubiquitous in the environment, particularly in urban environments (Farfel, et. al., 2003). Studies have also shown that cadmium, another ubiquitous heavy metal, activates the alpha estrogen receptor, one of the three forms of estrogen receptor, and interferes with binding of androgens to the androgen receptor (Stoica, et. al., 2000; Martin, et. al., 2002).

The heavy metals are an interesting case, because they provide an explanation for the existence of sexual variation such as transsexuality throughout history, as the heavy metals have been here long before humans. Perhaps not coincidentally, ancient Rome utilized heavy metals extensively, from plumbing to drinking vessels. At the same time, Rome and Byzantine empires were well known for having a sizable population of

eunuchs, suggesting a relationship between heavy metal exposure and alterations in sexual development (James and Thorpe, p. 173, 1994).

Phthalates are another class of chemicals ubiquitous in many modern consumer products, including cosmetics, moisturizers, various toiletries, nail polishes, fragrances, and as a plastic additive for improving flexibility (Koo, et. al., 2002; Adibi, et. al., 2003; Houlihan & Wiles, 2000). Phthalates have been found in human urine with high frequency and in significant quantities (Silva, et. al., 2004, Kato, et. al., 2004; Centers for Disease Control and Prevention, 2003). Latini, et. al. (2003), found that the duration of pregnancy was reduced due to phthalate exposure, and Adibi, et. al. (2003), found that women in New York City and Krakow, Poland inhale significant amounts of phthalates, concluding that phthalate inhalation is an important source of exposure that is poorly characterized in the general public. Another study tested sperm damage due to environmentally relevant phthalate levels measured in healthy volunteers, finding that higher phthalate levels were associated with degraded DNA integrity in sperm. Researchers examining premature breast development among young Puerto Rican women found that significantly high levels of numerous phthalates were found in 68% of the cases, suggesting an association between phthalate exposure and premature breast development (Colón, et. al., 2000).

Studies since the early 1990's finding a decline in sperm counts have suggested that exposure to endocrine disrupting chemicals may play a causal role, since there is a commensurate temporal increase in rates of hypospadias, undescended testes, and testicular cancer in men (Sharpe & Skakkebæk, 1993; Giwercman, et. al., 1993; Carlsen, et. al., 1995; Swan, et. al., 1997; Baskin, et. al., 2001). In normal male development, the

urethra extends to the tip of the penis, whereas in cases of hypospadia, the urethra exits somewhere along the underside of the penis. Although reproductive system problems are believed to be increasing, systems for surveillance of male health have not been adequate to ensure that accurate reporting occurs, resulting in under-estimates of prevalence of male reproductive problems, at least in Europe (Dolk, et. al., 2004). In one study that examined sons of women exposed to DES *in utero*, known as a third-generation study, researchers found a 20-fold increase in the prevalence of hypospadias compared to controls, strongly suggesting that DES plays a significant role in male reproductive problems (Klip, et. al., 2002).

As mentioned earlier, pesticides have been a part of the U.S. culture for over a century, although after World War II, public health insect eradication programs and increased indoor spraying for pests was a fundamental change in the chemical environment in which humans develop. The basic pattern of pesticides use has been to introduce the pesticide to the market, and after many years later it is found to be harmful, taken off the market, and then replaced with another pesticide for which very little data has been collected, and whose safety is unclear.

Insecticide and herbicide exposure is frequent in the United States, through a variety of sources. Agricultural workers are commonly exposed to high doses of pesticides, infrequently wear proper protective gear, and have been found to bring pesticides back into the home, in many cases due to failure to remove work clothes and shoes when returning home (McCauley, et. al., 2001; Curl, et. al., 2002). People living near agricultural fields have been found to have higher concentrations of pesticides, even

if no parent worked in the fields, suggesting airborne drift is a significant exposure route (Koch, et. al., 2002).

A number of studies have examined pesticide breakdown products (metabolites) that are excreted in urine in order to estimate population exposure distributions. Heudorf, et. al. (2001) found that three metabolites of pyrethroid pesticides are found in 60%, 30%, and 16-19% of people unexposed to indoor exposure of pyrethroids in Frankfurt, Germany, suggesting exposure is primarily due to food. A study examining pesticide exposure in Minnesota found that 93% of children have measurable concentrations of metabolites of: atrazine, carbamates and other related chemicals, malathion, chlorpyrifos and similar compounds (Adgate, et. al., 2001). A similar study on organophosphate (OP) metabolites found them in over half the samples, and children aged 6-11 were exposed to significantly higher concentrations than adults or adolescents (Barr, et. al., 2004). Another study on OP pesticides found that 99% of children sampled in Seattle, Washington had at least one OP metabolite in urine, and 70-75% had at least two; higher levels of OP metabolites were associated with garden use of OP pesticides by parents (Lu, et. al., 2001).

Pesticides are also detected in fetal meconium, which contains the intestinal contents of the fetus and is composed of a variety of excretory products that are believed to be promising for estimating cumulative fetal exposure to pesticides from the second trimester until birth. Whyatt, et. al. (2001) found two common OP metabolites, diethylphosphate (DEP) and diethylthiophosphate (DETP), in 59% and 100% of cases, respectively, in New York city; both metabolites are breakdown products of the OP pesticides diazinon and chlorpyrifos, which are common in residential pesticides as well

as several agricultural OPs. In another study, researchers examined concentrations of the DDT metabolites p,p'-DDE, PCBs, and hexachlorocyclohexane (HCH) in amniotic fluid sampled at approximately 18 weeks post-conception. PCBs and p,p'-DDE were detected in 30% of cases, and HCH was detected in 15%. The concentration of p,p'-DDE was significantly higher than levels of 17β-estradiol or testosterone in the fetus, and because this metabolite of DDT is known to have anti-androgenic activity, the authors remark that although they did not test for adverse health effects, the levels are cause for concern (Foster, et. al., 2000).

Interestingly, the study included two sets of twins; in one case, p,p'-DDE and HCH concentrations were similar in both twins, whereas in the other case, widely divergent concentrations of p,p'-DDE were found (0.12 vs. 0.38 ng/ml) but similar levels of HCH, evidence that twins can have unique exposure histories. The authors note that adverse effects on normal development of the reproductive tract and neurobehavior have been associated with *in utero* exposure to EDCs, but that data on any of these exposures during the second trimester were not available prior to their study (Foster, et. al., 2000). A more recent study examining pesticides in amniotic fluid found detection rates as high as 70% for 1- and 2-napthol, and 55% for 2,3-dichlorophenol, showing high rates of fetal exposure to pesticides and confirming the validity of using amniotic fluid as a method of detecting EDCs *in utero* (Bradman, et. al., 2003).

Although it is widely believed by the general public that the food supply is "safe," pesticides are commonly detected on foods and in children that eat conventional diets. In a recent study, researchers found that Seattle children on a conventional diet were above EPA guidelines for OP pesticide metabolites in their urine, whereas children consuming

an organic diet were below the EPA limit, indicating that a substantial fraction of OP pesticide exposure in children is due to food residues (Curl, et. al., 2003). Curiously, instead of questioning the logic of a food safety system that routinely permits pesticide levels that violate EPA standards without monitoring the effects from these exposures, the authors instead suggest that parents should be encouraged to purchase organic food to reduce their children's exposure. This is an ethically tenuous position, as social class and income play a large role in food choices, forcing parents to choose between feeding their children, or knowingly exposing them to pesticides; it also seems to give license to the United States Department of Agriculture (USDA) to continue current pesticide-use policies that may not be sufficiently protective of children's health. Regardless of the ethical problems, this is not a viable solution for all children since organic food comprises less than 0.1% of total U.S. food production and could not possibly accommodate the entire population without a widespread shift in U.S. agricultural policies (Hettenbach, et. al., 1998). Interestingly, in 1997 the USDA proposed standards for organic farms that would permit the use of biosolids on organic crops, which, due to their high content of heavy metals, phthalates, and other endocrine disrupting chemicals, would seem to negate any health advantages of organic food.

Another cultural practice common in the U.S. is indoor use of pesticides in residential settings. One study examined pesticide residues on indoor floor surfaces and children's toys using wipe tests, finding that homes that are judged difficult to clean have higher pesticide residues, and that residues are frequently found on children's toys and hands. Because the sample locations were adjacent to agricultural fields, agricultural pesticide residues were found in half the households, but more importantly, at least one

residential pesticide was detected on the floor in 95% of the homes, were found on toys in 58%, and on children's hands in 46%, indicating widespread exposure of children to residential pesticides (Quandt, et. al. 2004). Other studies have found that 97% of homes sampled in Minnesota have one or more pesticides, and that 88% had used pesticides in the last year; a similar study in New York city found that 85% of pregnant minority women were exposed to pesticides during pregnancy due to pest control in residential settings (Berkowitz, et. al., 2003). Because studies examining residues and exposures in indoor residential settings have only recently been performed, this raises questions about possible effects of past exposures to DDT from 1945 to 1972, since DDT was widely used for residential and public health purposes, in some cases with direct exposure to sprays from trucks.

Studies examining health effects from pesticide exposure have tended to concentrate on pesticide applicators, whose exposures are known to be high. Some health effects found among pesticide workers include: leukemia, increased self-reported chronic illness and asthma, and lower neuropsychological functioning scores (Beard, et. al., 2003). In children, pesticide exposures have resulted in: delayed sexual maturity and reduced testosterone in genetic males (Saiyed, et. al., 2003), deficits in short-term attention and memory, and behavioral and motor skill problems in children (Ruckart, et. al., 2004), reduction in head circumference (Berkowitz, et. al., 2004), and extended time to pregnancy in daughters (Cohn, et. al., 2003). Garry et. al. (2002) found that pesticides applicators in Northern Minnesota have an increased risk for altered offspring sex ratios and for having children with birth defects. They found that male offspring of applicators exposed to pesticides are more likely to have birth defects than females (1.75 to 1),

whereas for workers exposed primarily to fungicides, the sex ratio was 1.25 normal girls to 1 normal boy, and the proportion of males with birth defects was significantly reduced (0.57:1) Because insecticides, herbicides, and fungicides may differ in their mode of action, this finding indicates that effects in males and females differ depending upon the class of disruptor. This finding may have relevance to the ratio of MTF to FTM transsexuals, since MTFs typically exceed FTMs by a ratio of 3:1, and the majority of chemicals commonly found in the environment are estrogenic and anti-androgenic (McLachlan, 2001), suggesting that males would be more likely to demonstrate effects.

Along these lines, a recent *in vitro* study using Chinese hamster ovary cells measured the estrogenic and androgenic activity of 200 pesticides, permitting comparisons between the effects of endocrine disrupting chemicals to the effects of the putative sex hormone alone (Kojima, et. al., 2004). It also permits estimates of the prevalence of the different functional classes of chemicals expected to be present in the environment. They found that 80 of the pesticides mimicked estrogen, 3 inhibited the estrogenic effect for cell surface receptors (estrogen receptor α), 2 inhibited the estrogenic effect for the nuclear estrogen receptor (estrogen receptor β), 66 showed anti-androgenic activity to the androgen receptor, and none showed androgenic effects. Additionally, 34 pesticides had both estrogenic and anti-androgenic effects, which would be expected to cause both demasculinization and feminization of males, but would not be expected to affect females in the same manner. This is due to the fact that at the same level of exposure to an estrogenic chemical, because females have much higher circulating levels of estrogen, a small addition from an EDC will have far less impact than in the case of males, where the circulating estrogen concentrations are normally very

low (refer to Figure 4). Also, anti-androgens would be expected to directly interfere with masculinization by interfering with androgen receptor mediated responses; this impacts male sexual development directly, whereas because genetic females produce much smaller amounts of androgens, any anti-androgenic effect would be small. Thus the difference in sex ratio between MTFs and FTMs may be due to the high prevalence of estrogenic and anti-androgenic chemicals compared to those that are androgenic and capable of direct masculinization of females. Because of the large amounts of DDT used historically, it is worth noting that DDT and all its metabolites were shown to act both as an estrogen and an anti-androgen (Kojima, et. al., 2004), again suggesting that males would be expected to be affected more frequently than females when exposed to this chemical. This is an area that needs more work in order to compare more chemicals using the same metric, but based on existing data, effects would be expected more frequently in genetic males than in genetic females.

Other chemicals have been shown to alter hormone production and have other reproductive effects. In one of the first studies of its kind, fuels and solvents have been found to reduce luteinizing hormone levels in females during the preovulatory stage, suggesting that another area of exposure, inhalation, must be measured in order to determine actual exposures (Reutman, et. al., 2002); the responses of the VNO also should be examined in this context, rather than assuming the all effects are due to exposure through the blood.

In sum, what these and other human studies demonstrate is that there is a substantial amount of evidence suggesting that prenatal exposures to EDCs cannot be disregarded, and therefore they cannot be considered to be without effect since for many

chemicals no threshold effects level can be identified. The evidence of widespread exposure to a variety of chemicals known or believed to be endocrine disruptors and the large production volumes involved are inconsistent with the assumption that human behavior and development is unaffected by chemicals that have physiological significance, that are found in the body, and that result in changes to sexual development, function, and behavior. Because experimental demonstration of the primacy of socialization on gender identity would first require demonstrating that prenatal chemical exposure occurs but does not result in transsexualism, without this empirical data to substantiate the claim of the primacy of socialization, the psychosexually-neutral-at-birth theory is simply an unsupported assumption.

On the other hand, analysis of the endocrine disruptor literature indicates that there are important sex differences that may explain the MTF:FTM ratio, which has heretofore been explained as a purely social artifact. The observations showing sex-dependent effects include: chemicals that have different effects on males and females with respect to frequency of birth defects and the sex ratio (Garry et. al., 2002), PCBs feminize male play but do not masculinize female play, and dioxins feminize both males and females (Vreugdenhil, et. al., 2002), and that for twins, different exposures may occur *in utero* due to differential placental transport of endocrine disruptors (Foster, et. al., 2000). At the environmental level, the number and volume of chemicals that are estrogens or anti-androgens far outweigh in number and in production volume those of anti-estrogens and androgens (Kojima, et. al., 2004; McLachlan, 2001). All these factors indicate that males and females do not respond similarly to the same chemical exposures,

and that an unequal sex ratio would be expected based upon the working premises of the endocrine disruption hypothesis.

4) Hormones, Sexual Development, and Transsexualism

From the time of the first experiments with hormones, scientists immediately recognized the importance of the relationship between sexual changes and hormones (Dodds, et. al., 1938; Dutton, p. 32, 1988). Many animal experiments have since been performed, establishing the importance of hormones in creating sex differences in physiology, morphology, and behavior (Scott, 1962; Young et. al., 1964; Weiss, 1998; McEwen, 1999; McEwen & Alves, 1999; Weiss, 2002; Hayes, et. al., 2003). In March 1981, a series of articles appeared in the journal Science, discussing the role of hormones in sexual development. Although the articles discuss at length the animal data, available human data, and similarities between human and animal endocrine systems, several articles stress the importance of the sex of rearing as a determinant of gender identity, following the psychosexually-neutral-at-birth proponents (Ehrhardt & Meyer-Bahlburg, 1981; Rubin, et. al., 1981; Naftolin, 1981).

One of the articles directly addresses the question of prenatal hormone influences on gender identity; the authors state unequivocally that: "The development of gender identity depends largely on a process of learning (12) (Ehrhardt & Meyer-Bahlburg, 1981)," citing Money & Ehrhardt's 1972 book Man and Woman, Boy and Girl: The Differentiation and Dimorphism of Gender Identity from Conception to Maturity. The psychosexually-neutral-at-birth theory, while first disputed by Diamond (1965), was several years later seemingly supported by a single case that Money reported of an accidental penile ablation (removal) during circumcision, in which the male child was subsequently raised as a female. Curiously, this case was lost to long-term follow-up until 1997, when Diamond and Sigmundson reported that the individual had requested

reassignment back to male gender. The story was later told by Colapinto (2001) in a popular book that was also the topic of a Nova special on the Public Broadcasting System (PBS, 2001). Writing on the case, Diamond and Sigmundson note that in 1973, Time magazine reported: "'This dramatic case … provides strong support … that conventional patterns of masculine and feminine behavior can be altered. It also casts doubt on the theory that major sex differences, psychological as well as anatomical, are immutably set by the genes at conception.'" Thus, the importance of the single case produced by Money was that it led to the widespread belief that gender identity is primarily dependent upon socialization, yet the basis for this conclusion rested upon a single case that was later found to refute the very theory it claimed to support (Diamond and Sigmundson, 1997). On May 4, 2004, the subject of this case, David Reimer, committed suicide, so it is safe to say that the intervention pursued by Money was not without consequences (The Canadian Press, 2004). Surprisingly, in another article discussing David's suicide, Money declined commenting on the case, with his assistant stating that "There's no comment to make (Burkeman and Younge, 2004)."

This finding that gender identity cannot be easily altered through socialization is supported by more recent findings. A group of 16 genetic male patients with a rare condition known as cloacal exstrophy, a major defect involving the lack of a penis but normal testes, were studied with respect to gender identity (Reiner et. al., 2004). Fourteen of the sixteen cases were reassigned surgically, socially, and legally shortly after birth as female due to the simplicity of the vaginal construction surgery compared to the reconstruction of a penis. By the time of the report, eight of the fourteen female-assigned cases were living as male and three had unclear gender identity, although two of the three

declared they were male identified. Five patients were still living as female. Additionally, the two patients whose parents refused reassignment also declared they were male identified. Given that the majority of the reassigned cases have already declared they are male even though they were reared as female should raise serious doubts about the claim that socialization plays a primary role in the formation of gender identity. Indeed, Reiner notes that surgical reassignment at birth when there are genital abnormalities present is problematic for the very reason that doctors do not currently possess a diagnostic tool that can accurately predict gender identity in adulthood, and mistakes in reassignment have become more commonplace as the psychosexually-neutral-at-birth theory provided the justification to perform a large number of reassignment surgeries (Reiner, 1997; Reiner, 2004).

One of the most important difficulties in gender identity research identified by Reiner is that the topic can be uncomfortable to discuss for many people, and past history has shown that a special degree of sensitivity and understanding is necessary to establish trust between the interviewer and the patient with this condition (Reiner, 1997). He notes that existing surveys of adult sexuality, such as the Sexual Behavior Assessment Schedule for Adults (Meyer-Bahlburg & Ehrhardt, 1983) have not elicited spontaneous answers from patients with cloacal exstrophy, and this observation raises questions about the validity of existing methods of assessment for studying questions of gender identity development in general. This problem is particularly relevant for offspring of mothers prescribed DES during their pregnancy, since no studies have been performed that specifically asked about changes in gender identity due to these known prenatal exposures to an estrogenic substance.

In recent years, an attempt has been made to integrate some biological sex differences into sociological theories of behavior. For instance, Udry (1994) developed a biosocial model for female gendered behavior based upon measurements of several sex hormones and sex hormone binding globulins (SHBGs), both in adulthood and during the second trimester of their fetal development, finding that gendered behavior is significantly related to: adult androstenedione, adult SHBG, second trimester prenatal testosterone, second trimester prenatal SHBG, and the product of prenatal testosterone and adult androstenedione. This theory has been amplified more recently, providing evidence that the degree of feminine attitudes and activities expressed in adulthood are correlated to the prenatal hormonal milieu during the second trimester, with increased prenatal androgen exposure leading to lower adulthood femininity scores (Udry, 2000). That is, changes in the hormonal milieu during early development alters sexually dimorphic behavior in adulthood.

Along these lines, there are two epidemiological studies that have examined the relationship between prenatal exposure to endocrine disruptors and subsequent changes in gendered behavior and sexuality. Both studies have serious methodological problems, however, and they expose some major weaknesses in current epidemiological methods.

The first study was a cohort study of men and women exposed *in utero* to DES; the study collected demographic data including: age, education, and ethnicity, and psychosexual characteristics including: handedness, sex partner choice, marital status, age at first intercourse, and number of partners (Titus-Ernstoff, et. al., 2003).

Interestingly, one finding that reached statistical significance was that DES sons had a higher frequency of left-handedness, which the authors associated with

complications during pregnancy; other authors have found that transsexuals also have a higher frequency of left-handedness (Green & Young, 2001), suggesting that questions explicitly asking about gender identity status would be appropriate to add to all future studies examining these relations.

However, there are several problems with the study. The format of the study was a survey questionnaire mailed to exposed and unexposed groups, but ultimately, 49% of men and 50% of women from the cohort could not be located, were dead, or chose not to participate in the survey. Consequently, sampling may be biased to an unknown degree because there is no method of determining if those responding are representative of the whole group. Other problems are that all children exposed to DES *in utero* are assumed to be similarly affected, but because the endocrine disruption thesis suggests that dose and timing is important with regard to outcomes, it is necessary to distinguish when and in what amounts the DES was present in the fetus during critical stages of sexual development. Because the study lacks empirical data regarding prenatal DES exposure, this dramatically weakens the ability of the study to detect differences. Because sexual development proceeds in a number of stages, the timing of the dose is critically important to detecting differences statistically. By considering all those exposed to DES as a homogenous group, effects deriving from exposures during critical periods are obscured, because those exposed outside of these critical windows do not show effects, and therefore they dilute the statistical power of the study. This could be repaired by stratifying the groups by 'period of exposure'.

Another serious problem with the study is that there is no person in the United States that can be considered a control. As mentioned in the history section, DES was

widely used for cattle, thus to a greater or lesser degree, everyone in the U.S. was exposed. Additionally, many other endocrine disrupting chemicals exist, limiting the utility of using a single marker of exposure as an independent variable for changes in sexuality. When these factors are taken into account: high non-response rate, treating all DES exposed persons as a group, and the lack of a proper control, the lack of significance should not be taken as evidence of the lack of an effect.

In a recent teleconference addressing issues of concern to DES sons, Dr. Titus-Ernstoff was asked if there were any plans to study gender identity outcomes associated with DES exposure; she replied saying that their study did not have sufficient statistical power to study "rare" outcomes such as transsexuality (Centers for Disease Control and Prevention, 2003b). However, the DES Sons' International Network, an internet based research, education, and advocacy group, has found that transsexualism is a common outcome of fetal exposure to DES among sons, indicating that studies on DES exposed persons should be examining endpoints related to altered sexual development. Of their total membership of 600 genetic males, among those who could verify their DES exposure, 52 (8.7%) consider themselves to be transsexual, 26 (4.3%) are transgendered, 9 (1.5%) are gender dysphoric, and 3 (0.5%) are intersex (Kerlin, 2004). When all these conditions are considered together, the total rate is 15%, indicating that for DES sons, the frequency of gender identity issues cannot be considered rare. When those who strongly suspect, but who are unable to confirm DES exposure are included, the total number of people who self-identify using one the above categories is 153, or 25% of the network membership.

If the rate of transsexuality in the U.S. is assumed to be 1 in 100,000 (Pauly, 1968), and if the number of DES exposed mothers ranges from 3-5 million, the number of transsexuals expected in the entire DES sons population would be 15-25, assuming that DES did not increase the probability of developing transsexualism compared to the general public (Table 1). Since the DES Sons' International Network already has double that number of transsexuals alone, this is evidence that among DES sons, the condition is not as rare as Titus-Ernstoff claims, and therefore failure to study the problem may have reasons other than a lack of statistical power – i.e. the decision not to examine the issue may be politically motivated.

Table 1: Number of DES sons expected to be transsexual if the rate of transsexualism is actually 1:100,000.

For TS rate = 1:100,000 From Pauly (1968) for the U.S.

	minimum estimate	maximum estimate
# DES exposed mothers	3 million	5 million
# DES sons	1.5 million	2.5 million
rate of MTF TSism (1:100,000)	0.00001	0.00001
expected number of MTFs	15	25

Even if a much higher rate of transsexualism in the U.S. is assumed, the numbers do not change very much. For example, if the prevalence of transsexualism in the U.S. is assumed to be the same as in the Netherlands, there should be between 126 and 210 transsexuals in the U.S. due to DES exposure (Table 2). Because the DES Sons International Network already has 52 transsexuals in their network, this would mean that they have found between 25 and 41% of all transsexuals whose transsexuality can be attributed to DES. Given the membership totals only 600, this seems extremely unlikely, and instead suggests that DES is capable of causing transsexualism, thus explaining the

dramatic increase in the frequency of transsexualism in the DES sons group compared to the general public.

Table 2: Number of DES sons expected to be transsexual if the rate of transsexualism is actually 1:11,900.

*For TS rate = 1:11,900 From Bakker, et. al., 1993 for the Netherlands

	minimum estimate	maximum estimate
# DES exposed mothers	3 million	5 million
# DES sons	1.5 million	2.5 million
rate of MTF TSism (1:11,900)*	8.4E-05	8.4E-05
expected number of MTFs	126	210

The second epidemiological study examined gender differences due to exposure to PCBs and other EDCs in fish among a group known as the New York State Angler Cohort (Sandberg, et. al., 2003). The study found that increased maternal fish exposure during pregnancy increased masculine behavior among boys, and in girls feminine behavior increased with increased breast-feeding duration, whereas more masculine behavior was associated with older age and more previous live-born siblings. Even though the authors found significant changes in gender expression of offspring from increased maternal fish consumption, they explain the differences in children's gender-dimorphic outcomes by suggesting that fish consumption alters maternal behavior, which then induces corresponding changes in gender expression in offspring. This explanation is in contradiction to the Wingspread Consensus Statement, in that the effects in offspring are expected to be organizational in nature and therefore permanent, whereas in adults effects are activational and not permanent (Colborn & Clement, p.1, 1992). There are no reasons provided that would substantiate the claim of more dramatic effects in adults than in developing children, and the authors note that the form of the study did not permit answering that specific question.

However, in support of their interpretation, the authors make a number of statements that are categorically incorrect. They state that: " … studies in animals have demonstrated that environmental toxicants classified as endocrine disruptors act as antiandrogens12." The citation is from the National Research Council's 1999 Hormonally Active Agents in the Environment, but nowhere in this text is it stated that all endocrine disruptors are antiandrogens; the citation spans a wide range: pages 52-76, but nowhere in these pages is the statement made that "environmental toxicants classified as endocrine disruptors act as antiandrogens." To the contrary, most identified EDCs are estrogenic (McLachlan, 2001; National Research Council, p. 38; 1999; Kojima, 2004). While it is true that some PCB congeners are antiandrogenic (National Research Council, p. 44, 1999), this does not justify the statement that EDCs are antiandrogenic. Because exposure is quantified with respect to fish consumption, the form of the study obscures the different mixtures of chemicals fish may contain, and hence potentially important differences in chemical exposures are ignored. Additionally, the predicted effects depend critically upon timing and dose, and these factors are ignored with all exposures treated equally, even though exposure during critical periods is more important than total exposure.

Another argument against chemical effects mentioned by the authors is that a small exposure to an androgenic EDC would be overwhelmed by endogenous testosterone production in males. While the male body can only create a finite amount of testosterone, there is no such limit for exogenous endocrine disruptors. As will be discussed later, no exposure can *a priori* considered to be without effect, because the

endocrine system is already physiologically active, and thus any change in hormone concentrations will have an effect – regardless of the ability to detect the change.

A possible explanation of the masculinization of males and females were the very high concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in Lake Ontario that peaked around 1970, and which returned to levels suitable for lake trout survival in the early to mid-1980s (Cook, et. al., 2003). Because the effects of TCDD are mediated via the arylhydrocarbon receptor, the mechanism of operation is different than those involving estrogen or androgen receptors. One of the actions of TCDD is to activate protein kinases, signaling molecules inside the cell, thus interfering in complex ways with other signaling systems that require these same molecules for signal transduction (Hays, et. al., 2002). Because of the complex interactions that can occur with dioxins compared to EDCs that express activity through the estrogen receptors or the androgen receptor, predictions about possible changes in sexuality are less clear. Ideally, a specific interference mechanism should be identified that results in the observed phenotype, as has been elucidated for congenital adrenal hyperplasia (CAH) (Collet-Solberg, 2001a; Collet-Solberg, 2001b; White and Speiser, 2000).

Another problem with this study is that the "normal" distribution of gender behaviors was based on a 1994 sample from New Jersey that is assumed to be without endocrine disrupting influences on the shape of the distribution (Figure 29). However, because of the proliferation of EDCs since WWII, there are reasons to suspect that these distributions have substantially changed shape in the last 50 years, and therefore, the use of this distribution as a reference may be diluting the actual size of the effects of sport fish consumption on gender identity.

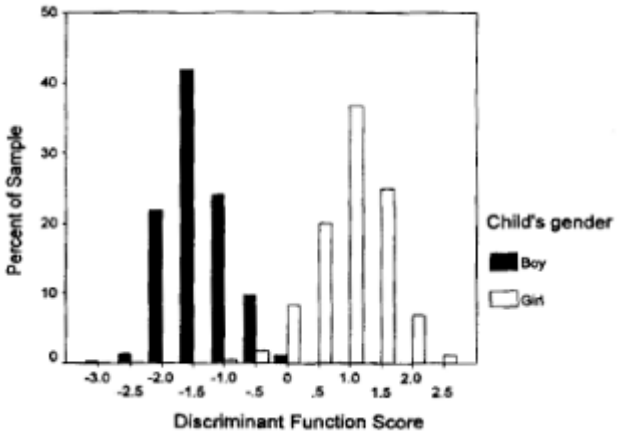

Figure 29: Distribution of gender identity scores for the reference group. Source: Sandberg, et. al., 2003.

Both of these studies demonstrate serious problems inherent in attempting to characterize changes in gender identity and sexuality, in particular, the problems associated with depending upon survey results to determine causal relations and uncertainty related to identifying an acceptable control group. These problems raise the question of what constitutes valid evidence of causation. As noted by Bateson (pp. 27-30, 1979), science is not capable of proving anything. Although the belief that science is capable of proof is widely-held, the foundational premise of science is that empirical results inform us of certain patterns in nature, but it is important to recognize that the identification of a previously existing pattern does not tell us anything about the present or the future, if the conditions under which those patterns were identified change. So, if we change the chemical environment of the planet, should we assume, *a priori*, that the social patterns that developed in the absence of these changes should stay the same? Science cannot answer this question.

Bateson gives an excellent example of this problem. Imagine that we have the following string of numbers:

2, 4, 6, 8, 10, 12

Now, if we use past experience to predict the next number, we would guess that the next number in the sequence is 14. But this is a guess, based upon a previously existing pattern. What if the next number is actually 27. In that case, the pattern is now:

2, 4, 6, 8, 10, 12, 27

Now clearly it is obvious that there was a more complicated pattern that only became manifest after the occurrence of an anomaly in the sequence of observations. The existence of the anomaly is evidence of a more complex pattern.

Epidemiology – the detection of disease patterns, is plagued by this problem; the inability to detect a pattern cannot be taken as evidence that a relationship does not exist, because as this paper has endeavored to show, EDCs are ubiquitous in the environment and in people, and therefore there is a low signal to noise ratio because there are few differences between those with known exposure and those with unknown exposures. A basic epistemological error embedded in the above two studies is that the control group is *a priori* assumed not to be experiencing any effect from endocrine disrupting effects. But given what has been learned in the last two decades regarding the distribution of EDCs throughout the environment, this assumption is clearly invalid. Thus, the power of epidemiology to detect patterns of disease when the changes are comparatively slow (over the span of generations) is virtually zero.

Instead of epidemiology, I would argue that there should be a special focus on transsexual physiological differences, because transsexuals are for the most part

anomalies in the experience of society, and to the extent that this represents a fundamental change in our conceptions of sexuality, it is necessary for us to understand the role that decisions to use chemicals may have beyond what we are told by teachers, government officials, or industry representatives.

Along these lines, a much more important paper with respect to the relationship between environmental chemical exposures and transsexualism specifically examined people born before and after extensive DDT use in East Germany (Dörner, et. al., 2001). The authors found that the prevalence of transsexualism (TS), polycystic ovaries (PCO), and idiopathic oligospermia (low sperm count with no identified cause, IO) increased 3-4 fold following the period of extensive use of DDT. Additionally, the authors found that there was a different enzyme deficiency associated with transsexualism before and after extensive DDT use (Figures 30 and 31).

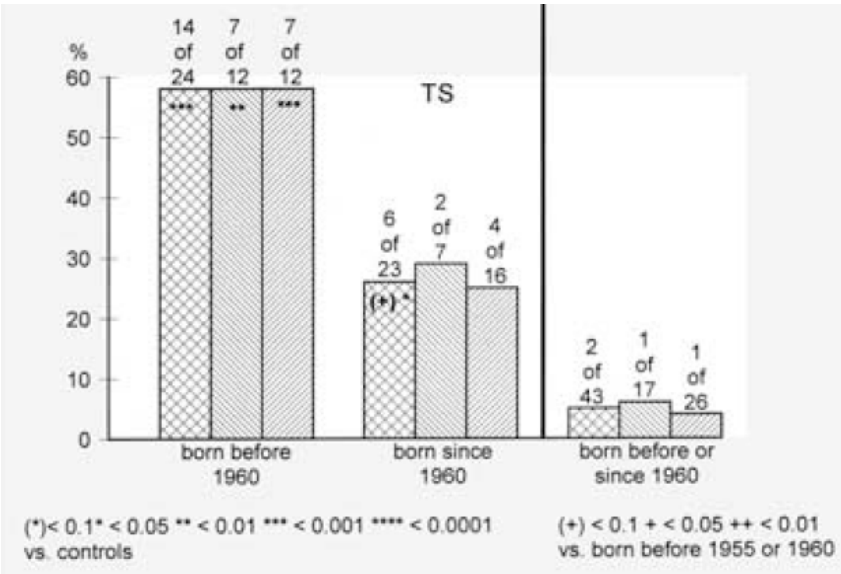

Figure 30: Occurrence of partial 21-hydroxylase deficiencies in transsexual patients (TS), before and after extensive use of DDT in East Germany, compared to controls. Source: Dörner, et. al., 2001.

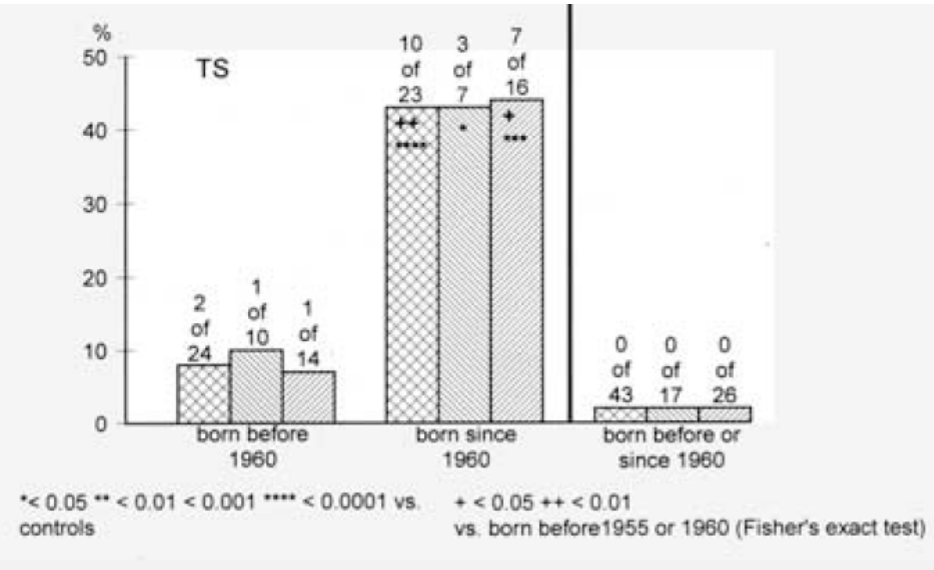

Figure 31: Occurrence of partial 3β-hydroxysteroid dehydrogenase deficiencies in transsexual patients (TS), before and after extensive use of DDT in East Germany, compared to controls. Source: Dörner, et. al., 2001

The authors found that the 21-hydroxylase enzyme was deficient for most people with PCO and transsexualism, and some with IO born before extensive use of DDT (see Figure 19 for location of the enzyme in the hormone biosynthesis pathway). For transsexuals born before 1960, this enzyme deficiency was found to be due to heterozygous mutations of the CYP21B gene, leading to the observed hormonal change (Dörner, et. al., 2001).

Conversely, in the period of extensive DDT use, most patients with PCO or TS and some with IO were found to have elevated levels of dehydroepiandosterone and its sulfate (DHEA, and DHEA-s), suggesting a 3β-hydroxysteroid dehydrogenase deficiency. No genetic mutations were found. Both enzyme deficiencies involve interference with critical pathways for hormone production, resulting in accumulation of

hormone precursors, which may then be converted into other, more potent hormones (Dörner, et. al., 2001). In earlier work, Dörner reported that DDT and its metabolites inhibit the 3β-hydroxysteroid dehydrogenase enzyme, and suggests that endocrine disruption is a form of epigenetic change that is capable of inducing transsexualism.

In the same paper, Dörner and his colleagues come to the conclusion that transsexualism is an unnatural sexual variation, and that either 1) endocrine disrupting chemicals that cause these effects should be prohibited, or 2) patients with TS, PCO, or IO should be treated with glucocorticoids as a form of prophylaxis. These options will be revisited later in this paper.

5) Prevalence of Transsexualism

A number of studies have reported the prevalence of transsexualism but the majority have examined only European countries, and these findings cannot simply be extrapolated to the United States. The only existing paper studying the U.S. is from Pauly (1968), who estimated the prevalence of MTFs at 1:100,000, and FTMs at 1:400,000. A close reading of his paper shows that he simply added four figures: cases reported in the open literature, cases reported by Benjamin in 1966 and 1967, letters received and reported by Hamburger in 1953, and applications received at John's Hopkins University from people requesting sex reassignment surgery, totaling 1,891 surgeries or applications; apparently he then increases this figure by 25%, resulting in the reported prevalence, although he does not explain the justification for this step in his paper. He repeatedly states in the paper that this figure is an underestimate, but there has not been another epidemiological study examining the question since this 1968 paper. It should be noted that this prevalence reported for the U.S. is substantially lower than in every other country studied, indicating that the figure calculated by Pauly (1968) underestimated prevalence. Figures reported from other countries are shown below (Table 3).

Table 3: Prevalence of Transsexualism in various countries

Year	Country	MTF	FTM	sex ratio (M:F)	reference
1967	Sweden	1:37 000	1:103 000	2.8	Wålinder (1968)
1968	United States	1:100 000	1:400 000	4:1	Pauly (1968)
1974	England	1:34 000	1:108 000	3.2	Hoenig & Kenna (1974)
1981	Australia	1:24 000	1:150 000	6.1	Ross, et. al. (1981)
1982	Ireland	1:35 000	1:100 000	3.0	O'Gorman (1982)
1988	Singapore	1:2 900	1:8 300	2.9	Tsoi (1988)
1996	Germany	1:42 000	1:104 000	2.3	Weitze & Osburg (1996)
1980	Netherlands	1:45 000	1:200 000	4.4	Eklund, et. al. (1988)
1986	Netherlands	1:18 000	1:54 000	3	Eklund, et. al. (1988)
1990	Netherlands	1:11 900	1:30 400	2.5	Bakker et. al. (1993)

Interestingly, Singapore has a much high reported prevalence than other countries, which Tsoi (1988) explains by three factors. He claims: 1) Sex reassignment surgery (SRS) in Singapore is well established, thus transsexuals avail themselves of medical care, 2) that the study was more recent than other studies and hence more transsexuals had come forward, and 3) that police do not harass transsexuals, and therefore they have fewer reasons to conceal their identities. Additional factors that improve the accuracy of reporting is that Singapore is an island nation with clearly defined boundaries and a national identity card system that permits cross comparisons between medical and psychological records (Tsoi, 1988). Undoubtedly these factors result in increased reporting, but this does not explain the dramatic prevalence difference between Singapore and other countries such as the Netherlands, where it is claimed that 95% of all transsexuals are included in demographic statistics (van Kesteren, et. al., 1996). To explain the rate difference, he suggests that because homosexuality is illegal in Singapore, this forces homosexuals to become transsexuals. However, one of the diagnostic indicators for transsexualism is a desire to rid oneself of genitals (American

Psychiatric Association, p. 247, 1994), and there is no evidence suggesting that homosexuals who are not cross-gendered would make such a request despite Singapore's legal requirements, nor does the author provide supporting evidence of this claim.

On the other hand, in a recent study, the coastal waters of Singapore were found to have significant amounts of EDCs including estrogenic and androgenic chemicals, which are attributed to the large amount of shipping traffic in the region, as well as industrial and sewage effluent (Gong, et. al., 2003). The authors found that the effects of sex hormones added to the seawater mixture were from 200-900% higher than the putative sex hormone alone, when measured using an *in vitro* bioassay. And because the measurements were based on sediment cores from regions surrounding the island, they represent past contamination, and therefore the much higher rate of transsexualism in Singapore may be related to this past contamination, since the levels are physiologically relevant. The authors note that there is now a monitoring program in place to collect information on endocrine disruptors in coastal waters, but this study casts significant doubt on sociological explanations regarding the high prevalence of transsexualism in Singapore.

A number of studies have examined prevalence rates in the Netherlands; as shown above in table 3, the prevalence has increased over the period from 1980 to 1990, although more recent data indicates that the incidence, or the number of new cases per year per 100,000 people in the population, began decreasing around 1989, although it is too early to be sure this is an actual decrease (Bakker, et. al. 1993) (Figure 32).

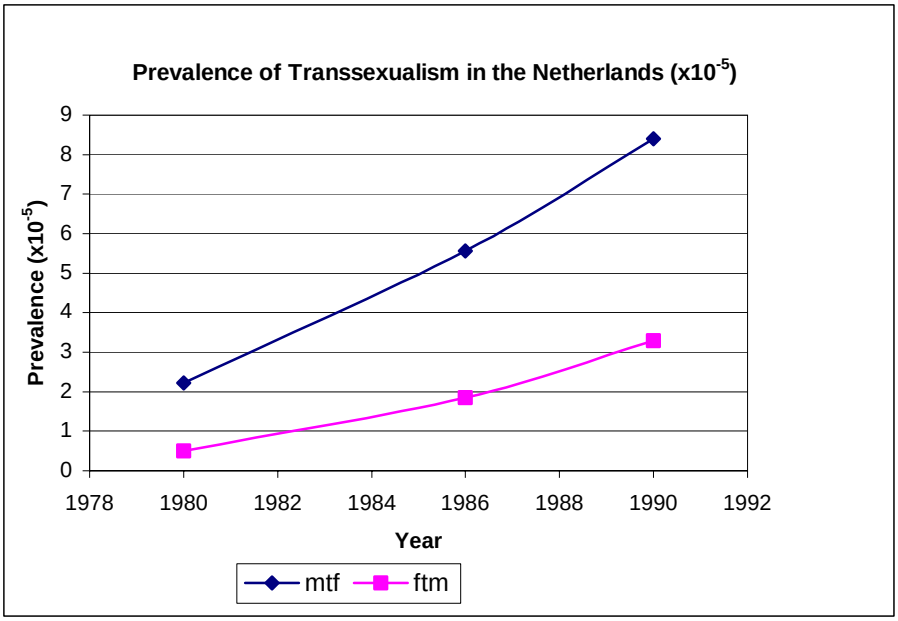

Figure 32: Prevalence of Transsexualism in the Netherlands. Data from Bakker, et. al., 1993.

One serious problem with the prevalence studies in table 3 is that while some provide data on the age distribution of transsexuals at the time of treatment, there is no data on the number of transsexuals by year of birth, which is more relevant for detecting patterns that may have an environmental component. That is, what is reported as the prevalence is the number of people seeking treatment in a given year or time period, but this is not a count of all transsexuals, and hence it is not useful as a measure of the number of transsexuals in a given population, which is what the term implies. Future prevalence studies should instead make an attempt to map the temporal and spatial distribution of transsexuals based upon the time and place of their birth in order to facilitate the identification of any patterns that may exist.

What these data demonstrate is that the reported prevalence of transsexualism is widely variable around the world, and factors such as cultural practices appear unable to explain these differences, for instance, the much higher prevalence in Singapore. Similarly, the difference in the ratio of MTF to FTM transsexuals is not adequately explained by social factors, an indication that more emphasis, and hence more research funding, should be allocated for biological studies, and less emphasis should be placed on social studies.

6) Risk Assessment and Toxicology

Risk assessment is a conceptual framework that attempts to quantify and limit health risks to the public; it generally consists of a procedure that includes the following four stages: 1) identification of a hazard to the public, 2) estimation of the extent and degree of possible harm, 3) evaluation of the risk relative to other hazards, and 4) implementation of policies in order to manage and limit the risk (Shrader-Frechette, p. 5, 1991). Each of these stages relies on value judgments that can result in erroneous risk assessments; under conditions of uncertainty, different norms for rational decision-making can result in widely different evaluations of risk, the third stage in risk assessment (Schrader-Frechette & McCoy, p. 158, 1993).

In an extensive review of the factors that play a role in evaluating risk, Covello made the following observation:

> The overall conclusion of [the risk] literature is that risk is not an objective phenomenon perceived in the same way by all interested parties. Instead, it is a psychological and social construct, its roots deeply embedded in the workings of the human mind and in a specific social context. Each individual and group assigns a different meaning to the risk information. As in the Japanese story Roshomon, there are multiple truths, multiple ways of seeing, perceiving, and interpreting events. Each interested party – including those who generate the risk, those who attempt to manage it, those who experience it – see it in different ways. An appreciation of this diversity of views is critical to the development of effective risk comparisons (Covello, 1987).

In line with these observations of the value-laden nature of risk assessment, the purpose of this section is to examine: some of the theoretical and practical problems with risk assessment aimed at regulating production and use of chemicals, efforts of the chemical manufacturers to undermine these regulations, and the consequences of 'expert' control over the production and interpretation of risk data. Type I and type II errors will

be discussed in the context of formulating an appropriate response to the problem of endocrine disruptors in general, and will also be applied specifically to the problem of transsexualism.

Effects of Endocrine Disruption are difficult to identify

Identification of risk concerns the ability to detect an endpoint that is deemed to be undesirable. Although a variety of endpoints have been used historically, death is the most commonly applied (Schrader-Frechette, p. 58, 1991). Obviously, identification is strongly biased towards those risks for which a causal connection can easily be made between a certain activity and the probability of death. Therefore, activities such as driving an automobile are easily correlated with deaths, and so identification of the risk of fatality is straightforward. For chemicals, cause and effect relationships are much more difficult to determine (Daughton & Ternes, 1999), and this has led to biased representations that emphasize the benefits of chemicals, while at the same time, underestimate the number deaths due to chemicals because the deaths were attributed to other causes.

In addition to the difficulty of relating chemical exposures to deaths are the large number of endpoints other than death, some of them exquisitely subtle (Daughton & Ternes, 1999). Endpoints such as cancer and endocrine disruption, both of which can manifest in a large number of possible outcomes, are processes that appear to derive in many cases from exposure to chemicals during fetal and neonatal development (Colborn & Clement, p. 1, 1992). Long temporal delays between exposure and appearance of the effect dramatically increases the difficulty of relating specific endpoints to chemical exposures.

Harm due to Endocrine Disruption is difficult to estimate

Because the endocrine disrupting thesis is new to science, having been formally articulated in 1991 (Colborn & Clement, 1992), it is currently difficult to estimate the harm caused by such chemicals. Science is only now beginning to carefully examine effects believed to be due to endocrine disruptors. Because cause and effect relationships between a given chemical and its effects are not well understood, it is not yet possible to measure chemicals in the body, for instance, and estimate the probability of endocrine disrupting outcomes. Also, because proposed causal relationships are contested by those who benefit from these chemicals, including producers and users, there are no clearly defined criteria by which harm can be assessed. Tools used for estimating harm such as epidemiological studies, suffer from: 1) a lack of adequate exposure data, 2) difficulty in finding individuals who could serve as controls, since all citizens in the United States have been exposed to a large number of chemicals, and 3) assumes that specific effects can be uniquely associated with a specific chemical (Schettler, 2000). Because there are now over 85,000 chemicals registered with the EPA, and approximately 3000 used in volumes exceeding one million pounds annually, the chances of associating a specific effect with a specific chemical is virtually zero. This difficulty is exacerbated by the fact that the widespread use of these chemicals proceeded understanding of their effects by approximately 50 years, permitting the number and volumes of chemicals in commerce to increase far beyond the ability of epidemiological or other diagnostic methods to assess their effects (Landrigan, et. al., 2003). Further complicating estimation, although some scientists argue that animals are sentinels for effects in humans (Guillette, 1995), others have said that if we want to learn about effects in humans, then we should study humans (Hamilton and Chandler, 1998). (Quote from Stephen Safe) However, since experiments

that would deliberately expose humans to chemicals believed to be endocrine disruptors are widely considered to be unethical, the refusal to rely on animal test data to serve as a guide for effects in humans has been undermined.

Low Dose Effects of Endocrine Disruptors

Chemicals now believed to be endocrine disruptors were once only considered in terms of their toxicity, or ability to cause acute damage or death (Carson, 1962). Toxicity standards were first applied to chemicals in 1927 by the U.S. Department of Agriculture, when Secretary of Agriculture William Jardine set an arsenic tolerance on fruit from arsenical pesticides at 0.025gr./lb. The standard was based upon what the industry thought could be achieved with the current technology for cleaning fruits, not based on health effects (Dunlap, p. 46, 1981). In 1941, after a series of problems concerning residues, a study was performed in Wenachee, Washington, where 20-25% of U.S. apples were grown, to determine acute health effects of arsenical pesticides; the study found that cases of poisoning were rare and not important clinically, supposedly justifying the current limits (Dunlap, p. 53, 1981). Thus, concerns about low-level exposure and the chronic effects of long-term exposure were removed from consideration entirely (Dunlap, p. 53, 1981). This pattern has been repeated for every new chemical that entered production; we now have 85,000+ chemicals in commerce, and approximately 3000 are produced in volumes exceeding 1 million pounds per year, yet fewer than 20% of these high production volume chemicals (HPVs) have been studied with respect to developmental or pediatric toxicity (Landrigan, et. al., 2003). This has resulted in a chemical-by-chemical regulatory approach that makes a number of assumptions about chemical safety that recent evidence indicates are invalid.

Some of the assumptions used in traditional toxicological risk assessments are discussed at length by Welshons, et. al. (2003). They make four important observations about the fundamental mechanisms of endocrine disrupting chemicals that invalidate traditional toxicological assumptions. First, they note that it is possible to predict with accuracy the low-dose hormonal mechanisms of action and physiology of delivery, both of which have been missed by traditional toxicological assessments. Second, because receptor-mediated responses are saturable (no response above 100% receptor occupancy), the assumption that it is valid to extrapolate from high test doses to low doses common in the environment is invalid. Third, the traditional toxicological assumption that "the dose makes the poison" has traditionally been interpreted to mean that effects increase as the dose increases, and further that there is linear relationship between the dose and the effects (Rodricks, p. 56, 1992). Recent findings, however, have shown that responses may first increase and then decrease at higher concentrations, resulting in a dose-response curve that has the shape of an upside-down U, invalidating the assumption of linearity (Figure 33). Fourth, the endocrine system is already physiologically active, and therefore exogenous estrogens will not exhibit threshold effects.

The authors of this study provide an elegant example of the effects of low-dose exposure, showing how a lack of positive controls can lead researchers to falsely conclude that a given chemical is not an endocrine disruptor. Using MCF-7 breast cancer cells that express estrogen receptors, and a line of cells called C4-12-5 derived from the MCF-7 line that do not express estrogen receptors, they have shown that cells with receptors that are exposed to estrogen respond in two regions: initial response to estrogen is increased in the low-dose range and it stays at this level for over 5 orders of magnitude

difference in concentration, until the concentration is high enough to induce toxic effects, and the cell dies. C4-12-5 cells without estrogen receptors do not exhibit effects in the low-dose range, but still exhibit cell death at approximately the same concentration as the MCF-7 cells. Finally, if the estrogen receptor expressing MCF-7 cells are contaminated with 3 parts per trillion (ppt) of DES, a synthetic estrogen, the response in the low-dose range is obscured, but the toxic effects at high concentrations are still observed. From this evidence, they conclude that many experiments that have falsely concluded negative findings with respect to low-dose effects from endocrine disruptors may be due to a lack of positive controls and inadvertent contamination of the sample by an estrogenic substance (Figure 33).

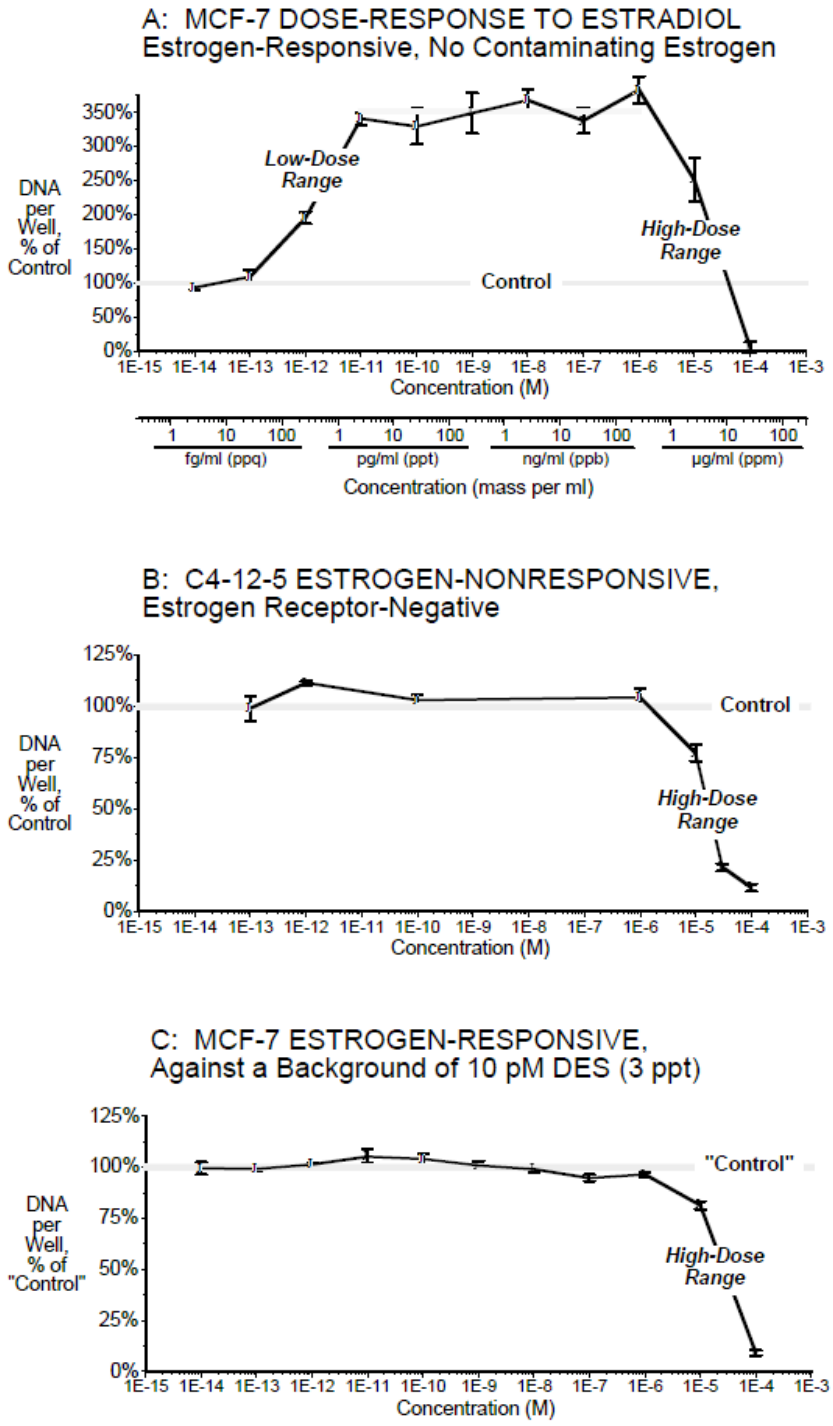

Figure 33: Dose-response curves of MCF-7 and C4-12-5 cells. A) estrogen responsive cells exposed to estradiol, B) estrogen non-responsive cells exposed to estradiol, and C) a positive control showing that 3 ppt of DES is capable of obscuring low-dose effects of estradiol. Source: Welshons, et. al., 2003.

Until very recently, toxicologists have been taught Paracelsus's dictum: "the dose makes the poison." This concept assumes that all chemicals are toxic, but that a threshold must be reached before effects are manifested, and the manifested effect is typically some sort of toxic effect such as cytotoxicity – toxicity that results in cell death or some observable effect. Shown below is the error introduced by assuming that a threshold must be reached before effects are manifested and that linear extrapolation is valid (Figure 34). As Welshons, et. al. (2003) cogently explain, for the endocrine system no such threshold exists because the system is already physiologically active; any change in hormone concentrations will change the operating point, and non-monotonic dose-response curves invalidate the linear extrapolation assumption. These points illustrate that the current toxicological risk assessment paradigm is inadequate for predicting effects due to endocrine disruption.

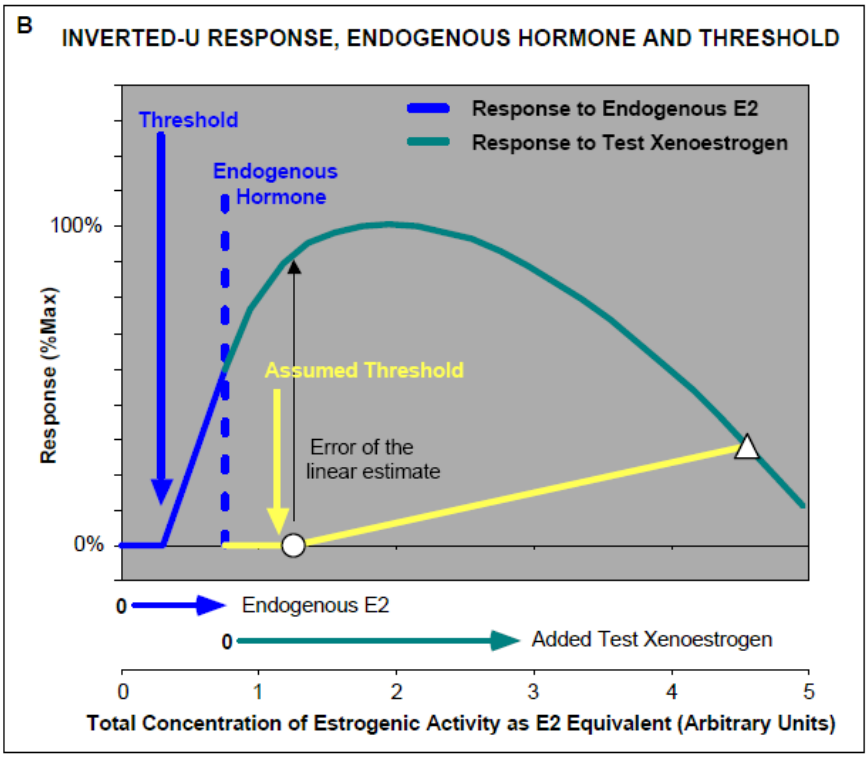

Figure 34: Dose response characteristic for a theoretical homeostatic system and errors introduced by assuming linear estimate and threshold effect assumptions are valid. Source: Welshons, et. al., 2003.

Figure 34 (green curve) shows a hypothetical dose-response curve for a chemical with a non-monotonic response. The triangle represents the dose required to produce toxic effects in a fraction of the cases. The yellow line represents the assumed dose-response curve; also shown is the assumed threshold before effects occur. The figure shows that in cases of non-monotonic dose-response curves, a significant error is introduced because the shape of the dose-response was assumed rather than being based on empirical evidence.

From a practical standpoint, there is a threshold, but rather than an absolute value, it must be determined relative to the concentration of the endogenous hormone, taking

into account the particular chemicals' potency with respect to the endogenous hormone. For example, if the exogenous chemical is estradiol (which is the same as the endogenous hormone), there is no difference in potency, so if the exogenous concentration of estradiol was smaller than 1% of the concentration of the endogenous estradiol, the effect would be a minor perturbation, unlikely to result in harm. The point is that the dose-response curve must be determined empirically in order to determine whether a perturbation is likely to occur; assumption of the shape of the curve is simply invalid, and likely to lead to inappropriate conclusions regarding risk.

One of the major advantages of the approach suggested by Welshons, et. al. (2003) is that the determination of the shape of the dose-response curve can be determined *in vitro* (outside the body using a small number of cells). The cost of this approach is low, and the method enables testing over a wide range of concentration, an impossibility for animal experiments due to the large number of animals required. It is possible to easily and accurately test a large number of compounds, mixtures, and exposure conditions that would be impractical if performed in animals. Finally, it reduces the instrumental use of animals in experimentation, an issue that is of increasing concern both from an ethical and moral standpoint.

Once the dose-response curves of the different cells that comprise a given system are elucidated, the functional behavior of the system under various exposure scenarios can be determined using well-established techniques of system analysis. That is, there is a reductionistic component and an integrative component, both of which - when combined, explain the operation of the system. This approach has been used with great success in

the field of engineering, and appears equally useful for problems of biological systems, which share many system features.

Unknown unknowns

Another factor that plays a role in risk assessment is the fact that of all the chemicals in production and commerce, only a small fraction can be detected in the environment by the methods of analytic chemists (Daughton, 2003). The figure below illustrates that identified chemicals are a small subset of the universe of chemicals in the environment (Figure 35). This subset of chemicals are those that can be extracted, resolved, and identified based upon the best methods and knowledge. The figure graphically illustrates that what can be counted is not all that counts (Daughton, 2003). Those factors not accounted for are typically assumed to contribute zero risk (Shrader-Frechette &McCoy, p. 158, 1993, Daughton, 2003).

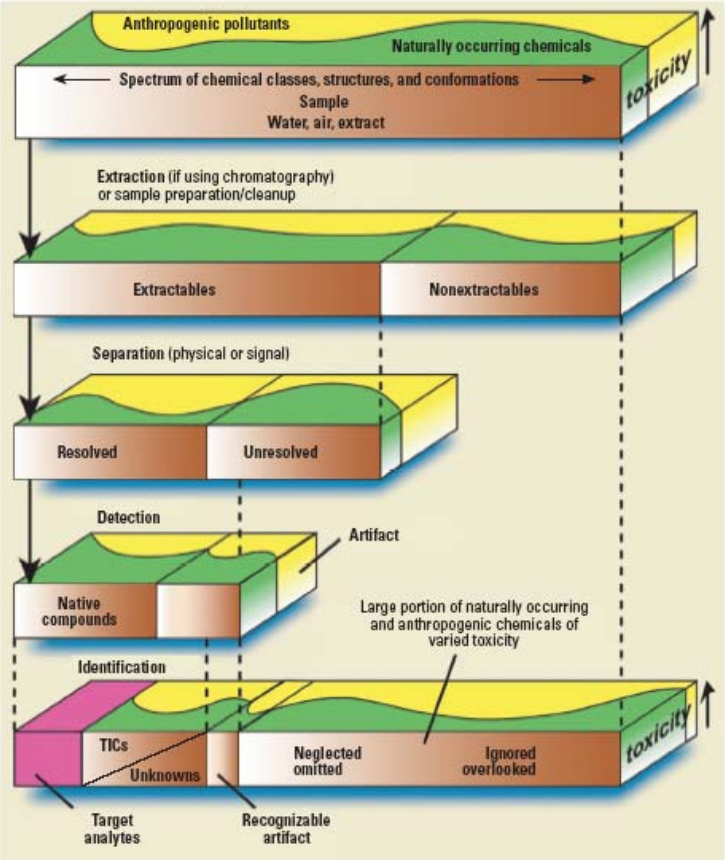

Figure 35: Detection of chemicals in the environment and limitations inherent to monitoring. Source: Daughton (2003)

A person's total exposure is the sum of all the various chemicals that are acquired through all the different pathways of exposure, considering all possible mechanisms of action and endpoints, which may combine additively or synergistically in some cases (Figure 36). Each of these three classes: chemicals, pathways, and endpoints, are all poorly characterized, contain large amounts of uncertainty, and from a practical standpoint, assume that chemicals, pathways, or endpoints that are not known are assumed to be zero (Daughton, 2001). That is, all risk assessments underestimate risk if performed according to this framework because it is impossible to account for a large

number of small and distributed influences which, when taken together, may have an effect (Gleick, p. 8, 1987).

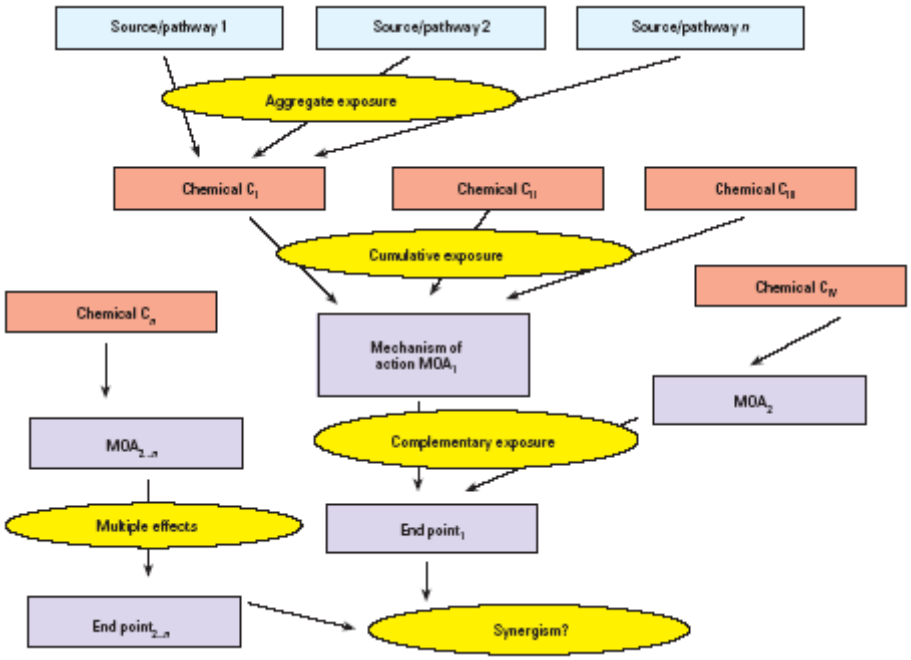

Figure 36: Endpoints (Effects) can be caused by a number of sources, each operating through a number of pathways. Source: Daughton (2003)

For example, in one experiment researchers exposed estrogen-responsive cells to eleven different chemicals, each below their respective no-observed-effects-level (NOEL), finding that the combined action of the mixture induced dramatic estrogenic effects (Rajapakse, et. al., 2002). This experiment indicates that the effects of estrogenic substances can be considered as additive, when their relative potencies are compared to 17β-estradiol. A similar experiment with 8 weakly estrogenic chemicals also yielded a significant response, raising serious questions of regulations that consider chemicals one at a time (Silva, et. al, 2002).

Evaluation of the risk relative to other hazards

Evaluation of risk relative to other hazards is also problematic, due to the aforementioned problems in identification and estimation. It assumes that we can compare risks that are well known, such as deaths due to automobile accidents, with risks that are largely unknown, such as endocrine disruption. That is, the risks are unknown, and it is not known which factors are unknown. Beyond the unknowns are the criteria used for evaluating risks. Several different forms of rationality are applied to problems of risk, and each results in different conclusions regarding policy choices. Two commonly applied schemas are scientific rationality and ethical rationality.

These two approaches reflect different epistemological beliefs regarding harms that are to be avoided in making assessments of risk. For instance, scientific rationality has a strong bias for minimizing type I errors; a type I error is when one concludes that a chemical has a given effect when in reality it does not. Type I errors have consequences for chemical manufacturers because if a chemical is found to have a deleterious effect, it may be taken off the market. Type II errors, or concluding that a chemical does not have an effect, when in reality it does, have implications for public health, as people may be exposed unnecessarily to harmful chemicals (Shrader-Frechette and McCoy, p. 158, 1993). These two approaches are contradictory because scientific rationality errs on the side of protecting manufacturers while potentially harming the public, while ethical rationality errs on the side of protecting the public while harming manufacturers. To the degree that policy-makers rely on scientific rationality for making policy decisions, public health will be harmed because of the bias of scientific rationality towards minimizing type I errors.

Apart from making the wrong decision by using an inappropriate form of rationality, is the problem of environmental surprises, which Holling said occurs when "causes turn out to be sharply different than what was conceived, when behaviors are profoundly unexpected, and when action produces a result opposite to that intended – in short, when perceived reality departs qualitatively from expectation (Holling, p. 294, 1986)" That is, we can be wildly wrong about the cause of a particular effect, because we cannot account for all the factors which may influence a certain outcome. These considerations must be taken into account before a chemical is produced; in the absence of evidence, policy-makers should exercise precaution in order to avoid future surprises. This is the epistemological premise incorporated into the precautionary principle.

Matters of Consent, Who Benefits and Who Pays?

Any discussion of chemical risks would be incomplete without asking the following questions: 1) Does everyone exposed to these chemicals provide informed consent, 2) who benefits and who pays for chemical use and 3) who decides what risks are acceptable, and what is the underpinning rationality used to support their conclusions?

As to informed consent, there is clearly not consent, nor is there an adequate understanding of the full range of effects from chemicals. For my part, I have never been asked to sign a consent form for anyone else to use a chemical. And does the fetus consent to exposure in the womb? Can a fetus give consent? Does the mother consent? Does the mother comprehend the full range of possible outcomes to her fetus if she, for example, uses hair spray, cosmetics, nail polish, or any one of the millions of products known to contain endocrine disrupting chemicals? Have the media or educational

institutions notified the public about newly identified risks from endocrine disrupting effects? Answering all these questions in the negative, I conclude there is not consent, and informed consent implies an understanding we do not possess.

Regarding who benefits and who pays, there is clearly a separation, in that some people clearly benefit from chemical production and use - some much more than others, while others pay. It is the people, animals, and other forms of life who pay the costs by being exposed to chemicals once they have been released into the environment. There is clearly little impetus for people who use chemicals to stop if there are little or no costs associated with their use. Thus, these costs, shifted onto those who receive little or no benefits, are externalized costs. Additionally, there is no easy way to internalize these costs, because it would require estimations of harm, which as been mentioned, are difficult, if not impossible to determine. Certainly, future generations will be paying the long-term costs for the benefits we claim to receive today, so there are also intertemporal market failures, where the cost of the future is discounted. Thus, statements such as "the children are our future," take on a hollow meaninglessness.

The cost of transsexualism is another externalized cost. Electrolysis (removal of the facial hair for male to female transsexuals), hormones, and surgery require significant amounts of money, and so to the extent that chemical manufacturers and users who benefit from chemical use can avoid paying these costs, it increases their return on investment by lowering their costs. In addition to these costs of changing gender, there are social costs borne by transsexuals, including: access to health and social services, access to education, hate violence, fear of asserting ordinary rights to avoid retaliation, chronic unemployment and underemployment, abusive treatment by law enforcement,

public humiliation, marginalization, exclusion, denial of housing and unemployment and access to shops, restaurants, and public transportation (Currah and Minter, 2000).

There are also a wide range of legal issues involved, including legal status as a male or female, marriage, divorce, child custody, wills, trusts, and inheritance, issues with immigration, employment discrimination, and access to private and public health benefits, and a panoply of issues related to the management of legal identity papers (Currah and Minter, 2000). Medical issues are similarly problematic, as it has been noted that there is severe discrimination against transsexuals by the health care community, including denial of medical treatment, ridicule by treatment providers, inability to receive ongoing medical care, inability to pay for hormones or surgery, as in most cases these are specifically excluded from medical insurance policies, including Medicaid, Medicare and private health insurance plans. Feinberg (2001) gives a lucid description of the types of problems routinely faced by transsexuals, describing the experience of being turned away at an emergency room with a 104^{o}F fever, and being told by the doctor that the fever was "because you are a very troubled person."

Finally, regarding who decides what risks are acceptable, as was described in the history section, there is a strong bias towards announcing the benefits of chemicals through education and the media, but there are few places where the risks of chemicals are conveyed to the public. Although groups such as the Washington Toxics Coalition and the National Resources Defense Council are trying to educate people about the risks of chemical use, this is clearly an uphill battle, as chemicals have been integrated into virtually every aspect of modern life and many people are myopically focused solely on immediate benefits.

Government risk assessors who regulate chemicals one at a time ignore effects from multiple chemicals, effects on fetal development, and make a large number of invalid assumptions about the mechanism of operation of these chemicals – an indication that they are describing a world different from the one we live in. People are exposed to a large number of chemicals, not one or two, so any claim that a given chemical is safe when considered in isolation from the other exposures people experience is a simply in error. Nobody can conclude that an individual chemical is safe, because safety is a social construction, and social constructions are collective agreements, not statements of absolute truth. Scientific rationality is not a valid basis for public policy decision-making because it makes a number of errors concerning the nature of what science can and cannot tell us. Public policy regarding chemicals must instead be founded on ethical rationality, where evidence of harm is an automatic trigger for reductions in production and use. The time delay between evidence of harm and steps taken to reduce these harms must be substantially reduced. Scientific controversy is not an adequate justification for delay; this approach is one of the tactics utilized first by the tobacco companies and now increasingly being used by chemical companies as a form of subterfuge to introduce uncertainty and hence delay regulation of their products (Montague, 1995)

7) A New Set of Questions

As this thesis has demonstrated, there is ample evidence that EDCs are playing a role in changing human sexuality, and this evidence raises a number of new questions: 1) Is there a difference between transsexuals and non-transsexuals with regard to the response of the VNO when stimulated with various pheromones? 2) Which set of chemicals are behaving as pheromones that affect sexuality? 3) How many pheromones

are in the environment and in consumer products, and in what amounts? 4) To what degree are these pheromones altering social and sexual behavior? 5) How do various EDCs change the hormonal milieu, and how do these changes affect the production of the pheromones?

The common thread in all these questions is that they focus on problems that have been introduced by the separation between natural science and applied science. The former aims to understand, while the latter aims to produce a desired goal. But because goals are value-laden, embedded in a cultural context and with a unexamined commitment to a given set of epistemological premises (Bowers, 1996), goals must be explicitly examined for their coherency and consistency. As Bateson (pp. 488-489, 1972) has cogently observed,

> "… all *ad hoc* measures leave uncorrected the deeper causes of the trouble, and worse, usually permit these causes to grow stronger and become compounded. In medicine, to relieve the symptoms without curing the disease is wise and sufficient *if and only if* either the disease is surely terminal or will cure itself."

Seen in this wider context, *ad hoc* approaches that aim to resolve transsexualism, or indeed any outcome associated with endocrine disruption, are likely to compound the problem because the source of the problem is never addressed. Through formal education and media, Western culture has inculcated a certain set of epistemological beliefs, but these beliefs are ultimately destructive and antithetical to the continuation of life. For instance, Bowers' book *Let Them Eat Data* examines the myth that access to more information and data via computers is equivalent to a better understanding of the world and of our proper place in it. Drawing from a wide variety of academic disciplines, he shows that all forms of modern technology – including computers – perpetuate the view

that technology is neutral, while in reality these technologies act as filters on our perceptions, further reproducing the myths of the culture.

An important concept that arises in Bowers' work is the idea of the mythopoetic narrative – a sort of story about the world that embodies the beliefs and experiences of the culture and which serves as a base framework for further learning. So what are some of the common mythopoetic narratives in our culture? A few he identifies are that change and experimentation are inherently good and represent "progress," that the individual is autonomous and entirely separate from the environment, that the market system is the best method for assigning values, that our system is demonstrably superior to other "uncivilized" cultures, and that because of its superiority it should be exported to the entire world (Bowers, 1996). One part of his analysis is that traditional cultures have valuable lessons to teach us about living in harmony with the planet, but because they have a different set of guiding root metaphors, the "unscientific" knowledge connected with their understandings is what he calls low-status knowledge. School learning, on the other hand, is a form of high-status knowledge - mainly for the reason that in this culture, people with more formal education are credited with having a better understanding of the world than those with less, and this gives them credibility and authority to act. However, these "learned" people then often apply these epistemologically erroneous beliefs to the natural world in particularly insane ways – pesticides, nuclear weapons, dams, and so forth - all of which clearly epitomize disharmony with respect to the natural world.

The separation between transsexual etiology and treatment may have initially been seen by doctors as necessary, but this perspective may no longer be viable, as there are strong indications that transsexualism may be caused by endocrine disruption rather

than due to social influences or psychopathology; this misattribution is an indication of a basic epistemological error that is now endangering the stability of social structures that developed over a long period of time, that are codified in many religions and law, and which are vehemently defended by those who have a commitment to maintaining their epistemological beliefs. That is, certain options are removed from consideration entirely, because they require re-examining these basic beliefs; since many of these ideas are habituated and therefore not available for direct examination, they are ignored or set aside from the class of viable alternatives.

A clear-cut example of this type of thinking is evidenced in the paper by Dörner, et. al. (2001) where it is suggested that early treatment with glucocorticoids is a valid treatment for transsexuals. The authors note that this is only possible when genetic mutations leading to enzyme deficiencies are identified, but it is clear from the evidence they reported in their paper that many transsexuals do not demonstrate such mutations. Thus, this is not a solution at all, and will lead to a compounding of the problem, as the approach is centered on the individual, and offers no remedy for addressing the larger problem. Their other solution, prohibition of EDCs, however, *does* address the source of the problem, and will not compound the problem. Thus this is the only viable solution. However, this option has been removed from consideration, to a large degree because many people see clear benefits in products that contain or generate EDCs, and until a direct relationship between chemicals and their consequences are made manifest, there will be no change.

Therefore, this thesis concludes that the single most important thing that can be done by advocates is to undermine these unexamined epistemological premises by

educating the public of the evidence demonstrating a relationship between EDCs and transsexualism. When presented with evidence, contradiction in epistemologies can force a new perspective, enabling people to question the logic of what are ultimately self-destructive cultural beliefs. As the title of this thesis alludes, transsexualism is an *unacknowledged* endpoint of endocrine disruption, and all that is required to change this situation is simply acknowledgement. Then this knowledge becomes part of our cultural heritage and better decisions may result from this fuller knowledge of the facts. From this, beliefs can change; different beliefs lead to a different set of actions, and it is in the domain of action where this must ultimately be addressed. But before that can be achieved, habituated beliefs must be made visible.

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