An Epistemological Inquiry into the Endocrine Disruptor Thesis

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ABSTRACT: For about a decade the term *endocrine disruptor* has become synonymous with a new research initiative that has been investigating the effects of hormonally active xenobiotics on biological systems. The scientific thesis behind the new research initiative is discussed and it is argued that there is a need for more emphasis on theory development and conceptual clarification that will give coherence to a field experiencing a rapid growth of empirical studies. Reflections on scientific methodology in this field will also help clarify whether endocrine disruptors symbolize a new etiology of chemically induced disease or represent variations of traditional chemical toxicology.

KEYWORDS: endocrine distruptors; theory; methodology; epistemology; model; xenobiotics; chemical signaling; scientific theory

INTRODUCTION

For over fifty years scientists have known that DDT can affect the testes and secondary sex characteristics of young roosters.[1] For over twenty-five years scientists have known that occupational exposures to pesticides could "diminish or destroy the fertility of workers."[2] Two decades ago scientists became aware that industrial and agricultural chemicals exhibited estrogen-like properties, and introduced the term *environmental estrogen*.[3] Barely ten years ago the more generalized term *endocrine disruptor* entered the scientific lexicon to describe chemicals that exhibit "hormone-like" effects or that interfere with hormonal signals of an organism.

The concept of endocrine disruptor was loosely connected to one of several generalized propositions that have been referred to as the Environmental Endocrine Hypothesis or the Endocrine Disruptor Hypothesis. While the number of studies discussing endocrine disruptors has risen sharply in the past few years, very few of these reflect on the methodological and philosophical issues that are germane to an emerging research paradigm. After investigating the scientific origins of the so-called Environmental Endocrine Hypothesis, I was struck by the lack of clarity in the scientific literature of the interpretation given to the epistemic entity that has been the centerpiece of research and debate over endocrine disruptors.[4] Various formulations of the endocrine-disruptor thesis include causal explanations, hypotheses, bio-

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chemical mechanisms, and generalized statements about the link between chemicals and neurobehavioral, developmental, and reproductive abnormalities.

Like others, I have been impressed by the mounting evidence (wildlife, epidemiological, laboratory animal, and *in vitro* studies) that has been associated with the thesis that xenobiotics (both synthetic and natural substances) can interfere with the body's complex endocrine-signaling system. However, despite the explosion of published work, there has been very little reflection within the scientific literature (and probably at scientific meetings, as evidenced by proceedings) on developing a theoretical framework that provides coherence to the empirical studies. Until that happens the epistemic nature of the entity of which endocrine disruptor is a seminal concept remains elusive and vague. Do we have a falsifiable theory, a model, a loosely framed generalization, a cluster of several independently testable hypotheses, an explanatory framework that guides hypothesis generation but is not itself testable, or the rudiments of a mechanistic explanation for studying the effects of exogenous chemicals on the signaling pathways of organisms, and eventually on diseases and developmental pathologies?

While the epistemic status of the endocrine disruptor thesis hasn't been adequately discussed and examined in the literature, that hasn't stopped some individuals from claiming it is false, disconfirmed, refuted, tentative, or definitive for wildlife but speculative for humans. But what is the "it" to which they refer? The ambiguity about the philosophical foundations of this relatively new research field and its impact on reaching scientific consensus was raised in a 1999 panel report on endocrine disruptors issued by the National Research Council: "Much of the division among committee members appears to stem from different views of how we come to know what we know. How we understand the natural world is the province of epistemology. Committee members seemed to differ on some basic epistemological issues, which led to different interpretations and conclusions on the issues of HAAs [hormonally active agents] in the environment."[5]

Controversies in science take many forms, ranging from narrowly framed debates over the interpretation of data in an experiment to more global disagreements over the adoption of theoretical principles seminal to a research field. Before we can appreciate the nature of the controversies over endocrine-disrupting chemicals, we have to know what is at stake.

UNRAVELING THE DISCOURSE

Science progresses in different ways, including data-gathering, hypothesis-testing, measurement innovations, new interpretations of existing data, model building, and theory construction. The term theory also has a different significance across the fields of natural science. In physics, empirical research is guided by a set of mathematical equations, some of whose terms correspond to properties of the physical world under investigation. From the set of equations, hypotheses can be inferred that allow the theorist to make a prediction. Both the development and refinement of theory and the generation of new data are critical to the growth of physics. As an example, Bohr's initial model of the atom went through many refinements. To paraphrase the philosopher Immanuel Kant, theories without data are empty and data without theories are blind.

In molecular genetics, the basic components of the theoretical framework consist of a structural analysis of genes; the relationship between genes, amino acids, and proteins; and the mechanism behind gene expression. Some areas remain unexplained, and are the subject of further theory building and hypothesis testing, such as the process of protein-folding and gene–gene interactions.

For the field of study identified by the term endocrine disruptors I shall argue that the generation of data is far outpacing conceptual analysis, which leaves the data without a locus of interpretation and multiple hypotheses ungrounded in generalized principles. As a result, one cannot easily tell whether a study on endocrine disruptors supports, disconfirms, or is neutral to a general theoretical principle.

How can we understand the nature of the scientific activity involved in the study of endocrine-disrupting chemicals? Does the activity represent the emergence of a research framework awaiting a new set of theoretical assumptions? Or is it more like "normal science," as Thomas Kuhn characterized the application of conventional theories and concepts to new empirical questions?[6] In the former case, we might view the term endocrine disruptor as merely a placeholder for traditional studies in reproductive toxicology. What is the significance of the introduction of the neologism "endocrine disruptor" in 1991? To my mind, it represents a new synthesis of disciplinary interests and a more generalized approach to the etiology of chemical toxicity. Endocrine disruptor is a much broader concept than the terms *reproductive toxin*, *carcinogen*, *neurotoxin*, or *teratogen*. Scientists who associate themselves with the study of endocrine disruptors use one or more of the preceding terms to describe the chemicals that define their investigations. At the very least, the term endocrine disruptor has brought attention to a class of postulated mechanisms involving hormonal signal disruption that may help to explain abnormalities in humans and animals that arise at varying stages of development, in diverse physiological systems, for a number of clinical endpoints, and in response to different levels of exposure to hormonally active chemicals. Under this interpretation, the new concept does not imply new theoretical principles or the falsification of traditional principles. Rather, the field of toxicology is considered sufficiently robust to encompass the issues raised by endocrine disruptors.

There is also reason to conclude from the scientific discourse that the recent attention given to endocrine-disrupting chemicals represents a change in the science that is substantive and not nominal. What are some of the factors that contribute to this interpretation? First, the generalizability of the mechanisms of action across species, encompassing many diverse disease outcomes, is more powerful as a potential explanatory thesis than conventional toxicological theories and etiological frameworks. Second, a set of concepts that add nuance and complexity to the study of chemical endocrine disruptors, and in some instances defy traditional thinking, such as "timing of exposure," "organizational versus activational effects of contaminants,"[7,a] "additive and synergistic effects," [8] "natural and synthetic endocrine-modulating substances," and "nonmonotonic dose response curves,"[9] speak to the need for a new synthesis that will integrate these concepts into a coherent explanatory framework. Third, the use of feedback models in toxicological research rather

[a]Very generally, organizational effects occur early in an individual's lifetime (*in utero* and postnatal) and induce permanent changes, while activational effects usually occur during adulthood and produce transitory changes.

than linear models, introduces additional levels of complexity. The field of endocrinology may have been aware of this approach, but for traditional toxicology it raises new challenges for modeling chemical effects. An animal-testing model that shows a safe high dose for a particular chemical does not ensure that a low dose of the same chemical will be safe to the organism.[10] According to Sheehan and vom Saal: "Unique outcomes may occur in response to environmentally relevant doses of endocrine disruptors that may be much lower than doses used in toxicological research."[9]

All of this adds up to the fact that, to date, the study of endocrine disruptors, "a group of exogenous chemicals that exhibit biological hormonal activity,"[11] has forced a rearrangement of disciplinary approaches, perhaps even a superposition of disciplines, to investigate whether human and wildlife effects may result from subtle chemical exposures, which would go unnoticed were it not for a new lens of analysis. The theoretical work that awaits us includes: clarification of concepts; generalized principles of inquiry that define the boundaries of the research program; and the classification of mechanisms that would qualify use of the term "endocrine-disrupting chemical." It remains to be seen whether the conceptual clarification of the subject of study and the new synthesis of empirical research encompassing several disciplines will result in the emergence of a new paradigm of chemical etiology or lead to incremental changes in existing toxicological frameworks.

To its credit, the National Research Council panel on Hormonally Active Agents in the Environment acknowledged, but did not resolve, some of these issues:[5]

> The charge to evaluate the endocrine-disruptor hypothesis begins with ambiguity about what the exact hypothesis—and hence the charge to the committee is. In its simplest form, the hypothesis is that some chemicals in the environment mimic estrogens (and other sex-hormones) and hence interfere with (disrupt) endogenous endocrine systems, with adverse effects. Interpreted narrowly, it would pertain to one or more species in at least one place. Interpreted broadly, it would mean that the impact of HAAs are uniform and global. [p. 16]

What can we learn from the history of science? First, new theoretical frameworks emerge from new ways of looking at familiar data. Second, the stimulus for new theories (or paradigm shifts) are anomalies in the canonical ways of understanding. Third, new theoretical frameworks have gestation periods during which scientific models evolve from simpler to more complex structures. The next section provides a meta-analysis of the process of theory construction, including conceptual clarification, for the thesis of endocrine disruptors.

ELEMENTS OF A THEORY OF ENDOCRINE DISRUPTORS

A theory consists of a lattice of concepts and propositions delineating a region of phenomena that constitute the object of study. The theoretical propositions provide a framework for inferring hypotheses that can be empirically tested. Within the structural lattice of the theory, there are links between the empirical evidence, the hypotheses, and the generalized statements that form the superstructure (see, for example, Ref. 12). Confirmed or falsified hypotheses inferred from the superstructure provide evidence (positive or negative) of the validity of the theory. The theory should contain some generalized causal statements with both explanatory power and

predictive implications. Mechanistic theories have been a cornerstone of modern science, as evidenced by the role of genetics in biology, molecular pathways in chemistry, and atomic structure and elementary particle interactions in physics. The history of science does provide cases of successful theories that are not mechanistic. One such example is Newton's universal law of gravitation, which does not offer an explanation of the mechanism by which the gravitational force operates. The universal law of gravitation, in conjunction with Newton's Second Law of Motion allows one to make predictions about the motion of celestial bodies. Scientists are still developing theories about the mechanism of the gravitational field and its relationship to other fundamental forces in the universe.

A theory of endocrine disruptors might consist of a well-defined nomenclature; a generalized set of propositions that delineates the areas of study; one or more causal relationships between a given class of chemicals and their effects; operational definitions that link concepts to experimental measurements; and mechanistic explanations that describe the events between causes and effects at a more reductionist and less phenomenological level. Without unraveling the mechanism of chemical action, only circumstantial evidence from clinical endpoints could link the chemical to a hormonal pathway of an organism.

The scientific literature reveals a number of nascent theoretical developments. First, there was the discovery (or the reaffirmation of discovery) that foreign substances can behave like endogenous hormones. In 1987 McLachlan and Newbold wrote: "exposure to exogenous estrogens during fetal development will profoundly alter sexual differentiation."[13] The authors were referring to observations made from a few chemicals. They introduced the terms *exogenous estrogens*, *hormonally active xenobiotics*, and *environmental estrogens*. Second, there was the discovery that some of these environmental xenohormones operate by a mechanism that involves the molecular binding affinity of chemicals to hormone receptors.[14]

One of the earliest generalized statements of the endocrine-disruptor thesis (not to be confused with a hypothesis or an embryonic theory) was adopted by 21 scientists who attended the 1991 Wingspread meeting.[15]

> We are certain of the following:
>
> A large number of man-made chemicals that have been released into the environment as well as a few natural ones have the potential to disrupt the endocrine system of animals, including humans. Among these are the persistent bioaccumulative, organohalogen compounds that include some pesticides (fungicides, herbicides, and insecticides) and industrial chemicals, other synthetic products and some metals.

On the surface, this statement is an observation. It is not sufficiently concrete to develop a testable hypothesis. Moreover, the observation that chemicals are interfering with the hormonal systems of animals is not new. By the 1970s, pesticides such as DBCP and kepone were known to cause male sterility among workers who were exposed, and that the latter was known to activate very specific estrogen-associated genes in the oviduct of chickens that natural hormones activate. In *Silent Spring*, Rachel Carson speculated that foreign chemicals could interfere with the body's ability to eliminate estrogens. An overestrogenized body, she believed, would result in cancer.[16]

The Wingspread statement asserted: "A large number of man-made chemicals…." Does this become an important scientific thesis because of its scope of ap-

plication? I believe this is, in part, a reason for its impact. If there is a theory lurking behind the statement, its universe of application is fairly broad. The scope of the claim includes many different species and potentially scores of chemicals. The discovery that some new effects are postulated to occur among many different species is too broad to be labeled a mere hypothesis, which is often relegated to cause–effect relationships of limited scope (e.g., *Heliobacter pylori* is the cause of duodenal ulcers, or PCBs damages the reproduction of salmon.).

Not only did the Wingspread scientists emphasize "a large number of chemicals" but they also cited a large number of species that are covered by their findings:[15]

> The impacts include thyroid dysfunction in birds and fish; decreased fertility in birds, shellfish, and mammals; decreased hatching success in birds, fish, and turtles; gross birth deformities in birds, fish, and turtles; metabolic abnormalities in birds, fish, and mammals; behavioral abnormalities in birds; demasculinzation and feminization of male fish, birds, and mammals; defeminizatioin and masculinization of female fish and birds; and compromised immune system in birds and mammals. [p. 2]

In addition to the diversity of species effects, the range of effects is also quite varied and gets more varied as we introduced new findings over the ten years since the Wingspread meeting. So we have a general statement that a class a chemicals has the potential to disrupt the endocrine system of animals comprising a diverse group of species and resulting in a wide range of effects. The statement, while too broad and unspecific to be a hypothesis, which is usually in the form of a bounded set of testable consequences, is also not in the form of a theory—a set of propositions that are closely integrated, and from which one is able to derive testable hypotheses. Theories ought to be falsifiable—that is, one should be able to imagine negative evidence.

The National Research Council 1999 report titled *Hormonally Active Agents in the Environment* refers to the "endocrine disruptor hypothesis" (see Ref. 5, p. 2). The NRC includes under the hypothesis: (a) chemicals with hormonal and antihormonal activity; (b) effects on adult vertebrates and the developing organism; and (c) endpoints such as reproductive changes, developmental defects, neurobehavioral abnormalities, immunological deficits, carcinogenesis.

If we reconstructed the NRC "hypothesis" based on these criteria and its published statement: "In its simplest form, the hypothesis is that some chemicals in the environment mimic estrogens (and other sex hormones) and hence interfere with (disrupt) endogenous systems, with adverse effects" (see Ref. 5, p. 16), we might have the following formulation:

> Chemical agents $C_I \ldots C_k$, which exhibit hormonal and antihormonal activity, can cause effects $E_j \ldots E_v$ on adults or the developing organisms of vertebrates $V_1 \ldots V_n$.

This is a generalized statement of possible causality, connecting a class of chemicals to a set of effects on a group of vertebrates. If we identify the chemicals purely by the effects at the organismic level, then we have an inductive generalization based on the current availability of data. If we find a few of these chemicals, the hypothesis is confirmed. It certainly doesn't give us a causal law or allow us to make predictions. The generalization will obviously grow as more instances are added to the inventory. It is difficult to derive or infer any hypotheses from this formulation or to establish the basis for a biological generalization.

The statement of the hypothesis is what philosophers call an "existence proposition," namely that there exist some chemicals in the environment that (a) mimic estrogens or other sex hormones; (b) interfere with endogenous hormones within the endocrine system; and (c) result in adverse effects to the organism.

The theory can become predictive if it has four components:

- An independent means of identifying the chemicals with hormonal or antihormonal activity.
- A mechanism(s) of action (signaling disruption through hormonal pathways).
- A relationship between the mechanism, the chemical(s), and the effects.
- A set of contextual conditions that distinguishes the mode of action of "endocrine-disrupting" chemicals from other toxic chemicals.

If there were an independent means of classifying the chemicals by structure or through *in vitro* assays, then we can break the purely descriptive character of the general hypothesis and make it into a predictive statement. The mechanisms of action will help to explain why certain chemicals identified as hormonal or antihormonal do not result in the adverse effects. The relationship between the mechanism and the effects takes us from one level of biological organization (biochemical pathways) to a more complex level of organization (developmental pathology in reproductive organs or behavior).[b] The contextualized conditions help to distinguish the theory of chemical endocrine-disruptors from other theories of chemical toxins (e.g., mutagenesis). Without the distinguishing conditions, the thesis about hormone disruptors might turn out to be a convenient way for researchers to find new funding for their traditional studies, without any consideration of the need to change the theoretical structure on which their work was based. A possible list of contextualized conditions are:

- The chemicals of concern have entirely different effects on the embryos, fetus, or perinatal organism than on adults.[7]
- The effects are most often manifested in offspring, not in the exposed parent.
- The timing of exposure in the developing organism is crucial in determining its character and future potential effects on the mature organism.
- Although critical exposure occurs during embryonic development, manifestations at the organismic level may not occur until maturity.

Clearly, if there were a describable, specifiable, and novel mechanism(s) of action for toxicity, that would satisfy the conditions of a new theoretical framework. Then one form of the theoretical framework could look like the following:

> A certain class of xenobiotic chemicals (X_I) at concentrations c_k that act through mechanism(s) M_i involving hormone pathways when in the presence of the developing fetus of organisms O_j at stage of development S_k (that do not affect the adult) will, with some probability P_r, adversely affect the development of the offspring, manifest through effects e_n. Moreover, mechanism M_i is different than that which describes the acute

[b] "For the endocrine-disruptor hypotheses to be understandable, some effect of some chemical on or through the endocrine system must be documented" (see Ref. 5, p. 17).

toxicological or gross birth effects of these substances, in that M_I operates within a feedback system.

Now we have a generalized thesis that clearly distinguishes itself from more conventional toxicological hypotheses/theories. This new perspective on toxicology is based on the idea of *chemical signaling*. It states that the toxicology of some environmental pollutants may be the result of a "natural" signal being sent by an unnatural signaling molecule. For the past decade scientists have been trying to fill in the gaps. Let us call this formulation of the environmental endocrine hypothesis the Theory of (Xenobiotic) Hormone Disrupting Chemicals (THDC).

The constructed theory about hormone-disrupting chemicals might have the following components:

(a) Some class of chemicals called "endocrine disruptors."
(b) Chemicals in the class interfere with natural signaling mechanisms of an organism.
(c) The effect is most pronounced in the developing fetus (offspring of pregnant animals) below concentrations of the chemical that would be harmful to adult animals.
(d) The effects may not follow a monotonic dose response relationship, for example, higher concentrations may show no effect, while at lower concentrations an effect is observable.

There are already observed cases, which support this thesis. But we cannot make any predictions from the lattice of propositions so long as we do not have an independent means of classifying the chemicals as "hormone disruptors." Since we cannot make any predictions, we cannot make any false predictions. We can still use the framework to establish guesses and then focus our research on determining whether the guesses are plausible and whether they are consistent with the framework.

For example, we know that in certain parts of the country, a sex-ratio skew in the breeding of gulls has been observed. The male population has been reduced relative to females. Also, there have been observations of female–female pairings in the nesting behavior of gulls. We have an effect. Can we show that the effect is consistent with the propositions in the endocrine-disruptor theory? First, we need a chemical agent that could be the cause of some effect. The pesticide methoxychlor has been identified as one possibility. Is there a mechanistic explanation that would tie methoxychlor to one of several outcomes: (a) the larger number of females in the population through some hormone-mediated process (it could be that developing males are more sensitive to the pesticide and that it is not a hormone-mediated process; (b) a behavioral change in some female gulls that take on male roles; (c) behavioral changes in some male gulls who have been developmentally feminized, that is, who exclude themselves from breeding?

We might also find some cases that meet the antecedent conditions (chemicals affecting hormonal pathways) that do not harm the development of the fetus. Does that refute the theory? A single falsifying instance might not be a crucial test, but if enough cases are found that are anomalous to the theory, then either its scope could be severely restricted or it could be discarded. The hormone-disruptor thesis as currently formulated is more than a hypothesis because of its breadth. But it is less than a theory because its propositions are not tightly connected and because we cannot derive testable (and therefore falsifiable) hypotheses from it.

So what is its current status in science? On the one hand, it can be considered a model or framework for the study of the chemical etiology of disease and abnormal development in animals (including humans). A model or framework is not falsifiable in the sense that Aristotle's theory of motion is falsifiable and was refuted by Galileo. On the other hand, if there were an independent means of identifying a hormone disruptor (by structure or short-term assay), the endocrine disruptor thesis could meet the conditions of an empirically testable theory. Let us consider a group of hypotheses inferred from what we have referred to as THDC.

THDC

H_1 = Endocrine-disrupting chemicals are the cause of alligator reproductive abnormalities.

H_2 = Endocrine-disrupting chemicals contribute to the incidence of breast cancer.

H_3 = Endocrine-disrupting chemicals contribute to the decline in sperm count.

H_4 = Endocrine-disrupting chemicals contribute to cognitive and behavioral impairment in children.

H_5 = Endocrine-disrupting chemicals are the cause of hypospadia in infants.

The fecundity of the theory will depend upon how many hypotheses can be confirmed. There is strong evidence that chemicals have been implicated in reproductive abnormalities of Florida alligators. As the mechanism of this process becomes more fully understood, it may point to one of several signaling pathways that are characteristic of hormone-disrupting chemicals, thus reinforcing the theory.

With respect to hypothesis H_2, scientists have been studying the relationship between certain organochlorines, namely PCBs and DDT (or its metabolites), and breast cancer. The hypothesis has to be tested indirectly, since we cannot easily perform experiments on humans. The data are not consistent. One of the most recent and comprehensive studies shows no relationship between serum concentrations of DDT and PCBs and breast cancer.[17] The exposures are measured in adults. However, the postulated theory suggests that the initiating causes of the outcome are critical exposures that occur *in utero*. If that is the case, then the exposures for the breast cancer hypothesis must be measured during gestation. Moreover, the female neonate must be followed until she reaches maturity. The theory suggests that the imprint of breast cancer occurs during pregnancy, perhaps through a certain group of abnormal cells. H_2 could be falsified (or confirmed) for specific chemicals if the longitudinal studies were done. Also, the primary metabolite of DDT (DDE) and the most persistent of the PCB congeners are antiandrogens. Thus, studies designed to explore a hypothesis inferred from the THDC about the causes of breast cancer, might more profitably look at purely estrogenic compounds, perhaps the estrogenic potency of aggregate compounds found in tissue and serum.

As formulated, the THDC is based on fetal exposure. A variant of the theory might involve a different mechanism that operates during adulthood. One such mechanism has been postulated by Devra Davis and Leon Bradlow.[18]

Hypothesis H_3 implies that endocrine-disrupting chemicals lower sperm count. An issue that is contested is whether there is a global decline in sperm count among males in industrial nations. The evidence points to certain regional declines, but there is debate over whether those declines in conjunction with the exceptions constitute a trend. Studies in rodents show that single maternal exposures to dioxin and PCBs reduce semen quality in adult offspring. It will take a very imaginative experiment to test the hypothesis for humans. The fact that there are regions in the world that do not show declines in sperm count does not refute the hypothesis that *in utero* exposure to some chemicals can result in lower semen quality in some adult populations.

Hypotheses H_4 and H_5 imply that *in utero* exposure to endocrine disruptors can result in human cognitive deficiencies, behavioral abnormalities, or pathologies of the reproductive organs. The data are epidemiological. Pregnant women who ate higher amounts of PCB-contaminated salmon had children with lower IQs and more behavioral problems.[19] These results are based on associational studies that do not demonstrate causality. However, if the mechanism by which these chemicals could affect brain development is worked out, they will provide a stronger confirmation of the hypothesis.

The EPA's testing program for endocrine disruptors is based on the premise that short-term *in vitro* assays that measure hormone receptor binding and short-term animal tests that measure any developmental abnormalities (a frog metamorphosis assay or a fish gonadal assay) would be predictive of human effects, if there are any.

NOMENCLATURE

There are reasons why a uniform nomenclature is critical to the progress of science. Without standardized terminology, comparison of data from different experimental regimes would be impossible. Moreover, operational definitions provide the linkage between theory and experimental systems. Theoretical concepts must eventually be connected to a set of operational measurements.[20,c]

The term *endocrine disruptor* has several useful roles in the development of the theory. It helps to sort out the chemicals of interest. "Any definition provides a semantic filter of sorts that limits the number of substances reviewed" (see Ref. 5, p. 21). It places the idea of *abnormal* or *disruptor* at the center of the theoretical framework. This is not a theory about normal processes, but a theory about the abnormal. The success of the theory will be, in large part, its capacity to generate testable hypotheses that causally connect chemicals to pathologies in the organism. The theory fails in so far, as it falls short of this outcome.

[c]"Science aims at knowledge that is objective, in the sense of intersubjectively certifiable, independently of individual opinion or preference, on the basis of data obtainable by suitable experiments or observations. This requires that the terms used in formulating scientific statements have clearly specified meanings and be understood in the same sense by all those who use them."

The NRC chose the nomenclature *hormonally active agent* (HAA) in lieu of endocrine disruptor. There is both a political and an epistemological basis for this choice of definition. Politically, the term implies that a substance so designated is not necessarily dangerous. Disruptor is a pejorative term, whereas "hormonally active agent" appears less so. Phytoestrogens are considered hormonally active but generally safe.[21,d] (For a discussion of the health effects of dietary phytoestrogens, see Ref. 22.)

Epistemologically, the term HAA makes a distinction between the mechanistic role of the chemical in the biological system and the relationship of the chemical to a pathology. The term HAA is about mechanism and not pathology.[21,e] In contrast, "endocrine disruptor" is about pathology. The provisional definition of an HAA is a compound that affects a hormonal pathway of an organism. The hormonal pathway must be defined through a mechanistic analysis. Black box studies provide circumstantial and not definitive evidence that a substance is an HAA.

The NRC panel study recognized that the idea of hormonal pathway offered additional complications. It raised the question whether there are any exogenous chemicals that do not, in some fashion, affect a hormonal pathway. If so, then the theory would have to distinguish between direct and indirect effects of a chemical through hormonal pathways.[21,f] A theory would also require an explication of the concept of "hormonal pathway." There should be sufficient theoretical concordance over the conditions that are satisfied when the term is applied.

LEVELS OF GENERALITY

In the history of science, theories, models, and nomological relationships often evolve from lower to higher orders of generality. This point is illustrated by the path from Galileo to Newton to Einstein on the laws of motion, and from Boyle's Law to Statistical Mechanics. With respect to the nascent THDC, some evolution has already taken place, as evidenced by the generalization of the terminology: environmental estrogens; environmental hormones; endocrine disruptors; hormone modulators; signal disruptors. The term "environmental estrogens" is considered by some to be too narrow to account for the range of disturbances and their effects. Will the term "signal disruptor" suffice, or will it prove to be too broad?

[d]The uncertainty about the effects of natural and synthetic estrogens are reflected in the advice given to physicians. From a popular physician's handbook: "It is recommended that estrogens, both steroidal and non-steroidal, natural and synthetic, not be utilized during pregnancy. There is no proof that they are beneficial, and there is good evidence that the non-steroidal estrogens may produce female genital tract anomalies and disease."

[e]"Thus the use of HAA was meant to describe those agents without regard to the outcome of any critical evaluation of their mode or mechanism of action…Indeed, the problem of defining HAAs is inseparable from the mechanism problem." [p. 21]

[f]Is a compound an HAA if it can affect hormonal pathways, or is it an HAA only if in a particular case it does affect a hormonal pathway? If it is the former, then should all the biologic effects of such a compound be considered in this report, even if they are unrelated to hormonal pathways? Is it even theoretically possible to describe a biologic effect of an HAA, indeed any chemical, as completely unrelated to hormonal pathways?" [p. 22]

What will define the area of research of "chemical signal disturbances"? When a foreign substance enters the body, it may interact with many different signaling pathways. What constitutes a disruption? Which modes of signal disruption will correlate with a pathology at the organismic level? Should the generalized theory be directed at one class of signal disruptors, let us say those that fit the paradigm of "signal transduction"? In this paradigm signals are initiated by the interaction of extracellular molecules (such as hormone adhesion molecules and neurotransmitters) with receptors on the cell surface. The signal transduction framework can be used to explain pathology as well as therapeutic pharmacology, where interference with intercellular proteins is critical for ameliorating a disease process. Moreover, signal transduction is only one of many signaling mechanisms in the body.

How would the theory distinguish between hormonal signal disruptors and other disruptors? Carcinogens, mutagens, and heavy metals are capable of interfering with the body's natural signaling. What about chemicals that affect the "wiring of the central nervous system" or chemicals that disrupt signal transmissions at nerve synapses, all under the rubric of signal disruptors? How would the theory distinguish between natural and synthetic hormones? Are we ready for a theory of xenobiotic signal disruption that encompasses all toxic disturbances that chemicals can have on living organisms?[23,g]

In conclusion, science is still in its very early stages of theory building with respect to endocrine disruptors. As a result, the endocrine-disruptor thesis as currently formulated is less a theory than a heuristic or framework that guides research. It suggests that if there is an abnormality that looks as if it could be developmental and not genetic, that one clue might be the exposure of the developing fetus or the adult organism to endocrine disrupting chemicals. Those who claim that a single disconfirming test (male sperm counts in a region of the world) weakens or falsifies the entire edifice make such claims without a clear understanding of the theoretical edifice in question. The pursuit of theory in studies of endocrine-disrupting chemicals will heighten and sharpen the explanatory power of the science and will provide a compass for future research. I can only surmise the reasons behind the paucity of attention to theoretical foundations: (1) the subject of interest crosses disciplinary boundaries, and therefore requires a reconfiguration of concepts that cross fields such as endocrinology, toxicology, molecular pharmacology, and wildlife biology; (2) a collection of empirical studies brought attention to the issues and the subject remains rooted in empirical research; and (3) public health and environmental threats provide the primary stimuli for research. Theory and generalization play a secondary role to the task of identifying problematic substances. Black box or phenomenological science can justify policy decisions, but does not advance theory building. To move from a stage of inductivist, descriptive, and empiricist science, with a strong emphasis on eliciting the mechanisms of chemical action, to theory-building, scientists will have to show a willingness to take risks by positing bolder and more generalized hypotheses. Those hypotheses that survive the test of time can serve as the building blocks for a new theoretical framework. For those who are uncomfortable with theoretical constructions in biology, I remind them of Charles Dar-

[g]"Estrogens, indeed all hormones, are chemical signals, and as such are important links in the body's internal communication system, helping cells in various organs to sense and respond to changing physiological circumstances." [p. 455]

win's words to Henry Fawcett in 1861: "About thirty years ago there was much talk that geologists ought only to observe and not to theorise and I remember someone saying that at this rate a man might as well go into a gravel pit and count the pebbles and describe the colours. How odd it is that anyone should not see that all observation must be for or against some view if it is to be of any service."[24]

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