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Endocrine disruptors — putting the mechanistic cart before the phenomenological horse

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Abstract

Despite incontrovertible evidence of the harmful effects of endocrine disruptors, a sound public health policy is still absent. Meanwhile, the press has revealed the hindering role of industry lobbyists and conflicts of interest among members of the regulatory bodies. Here, we identify another hindrance; one that stems from current experimental research practices.

Identifying the ‘elephant in the room’ regarding current practices should help scientists decide what type of evidence they need to gather in order to recommend a change in public health policy. We can uncover the root of the problem by addressing the issues hindering the study of complex biological phenomena, such as the effects of developmental exposure to endocrine disrupting chemicals (EDCs). In this article, we address the different time frame constraints that apply to basic science and compare them to those of applied science used in medicine and public health. We then juxtapose all of the information and discuss it in the context of EDC research.

Basic science

Since the scientific revolution (which began in the mid-16th century), a prerequisite for the practice of successful experimental science has been the formulation of a theory that defines the proper observables, constructs objectivity and provides the framework for the design and interpretation of experiments. Physics is the paragon of such scientific practice. In biology, the practical benefits of applying a good theory are exemplified by the success of Darwin’s theory of evolution, which addresses the long time-frame of phylogenesis. Evidence for the success of this approach is the theory’s persistence while being updated periodically. Biology still lacks a successful theory of organisms that addresses the entire life cycle. Instead of a full-fledged theory of organisms, the 20th century brought about naive beliefs such as physicalist reductionism inspired by 19th century mechanics, which attributes a privileged causal role to molecules. Later on, inspired by the mathematical theories of information, biologists introduced the notions of information and programme as metaphors, and the causal role of genes¹.

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Competing interests

The authors declare no competing interests.

Despite the current limited progress in understanding complex phenomena and diseases, the scientific mainstream continues to operate under the assumption that explanatory molecular mechanisms will be found for all biological phenomena. Hence, the mainstream responds to this lack of progress by doing more of the same, but now on a larger scale, such as with the 'big data' approach. Meanwhile, a minority of biologists using an alternative organicist perspective strive to provide adequate theoretical frames for the study of biological organization^{1,2}. When this controversy ends, biology will find an appropriate theoretical frame and will emerge reinvigorated from this crisis.

Experimentalists have to cope with uncertainty. Both the observer and the object being observed are inside the world; hence, the researcher's access to objects is indirect through the theoretical construction of objectivity. Experimental research thus becomes a process. Therefore, there will always be a new experiment to be done, a 't' to be crossed, an 'i' to be dotted and, from time to time, a theory to be rejected. As exemplified by physics, 150 years elapsed between Copernicus' proposal of the heliocentric planetary system and its acceptance by the scientific community at large, after the theoretical achievements of Galileo and Newton. Time did not matter in that case because this research did not intend to act upon the planetary system but to understand it. But, when individual and public health is at stake, can society afford to wait?

Science and medical practice

Contrary to what counts in the basic sciences, in medical practice time is of the essence. Physicians aim to reach conclusions and act immediately to prevent, cure or save a life based on what they now know. Physicians use science, but there is little time to ponder before acting. In medical practice, one lives with the burden of applying guidelines that later on might be found to have had unintended detrimental consequences.

Science and medical epidemiology

When testing the effectiveness of a pharmacological agent, the objective is to obtain an effective therapy and to avert adverse effects. Therefore, the null hypothesis (no effect expected) is chosen as a default, because it is better to err on the side of a false negative than on the side of a false positive.

Science and public health epidemiology

When studying exposures to potentially harmful agents, choosing the alternative hypothesis (a deleterious effect expected) as a default is a sound practice; here, it is better to err on the side of a false positive than of a false negative.

Endocrine disruptor research

Given the deleterious consequences of exposure to EDCs, 'time is of the essence' in order to preserve health and protect the public. However, scientists working on EDCs are aware that what is 'known' today could be proved to be in error in the future, and thus are reticent about advocating regulatory action. Still, the built-in uncertainty of basic science is an

insufficient reason for postponing action indefinitely in the public health arena. A deleterious effect caused by an EDC would still be detrimental even if its mode of action has yet to be uncovered. For example, using the Precautionary Principle, provisional regulatory action could be implemented while waiting for conclusive evidence, which in turn, could lead to upholding or overturning previous rulings. This plausible compromise of applying what is now known while research continues is not the current *modus operandi* among regulators. Instead, agencies that define EDCs rely on input by researchers who put emphasis on identifying the mechanism or mechanisms underlying harm. Nevertheless, because the molecular mechanisms responsible for complex phenomena seldom appear as a neat linear chain, a shortened but equally ambiguous version of mechanism, called mode of action, has been adopted by regulators³.

Postponing action stems from the idea that molecular mechanisms reliably represent the privileged and definitive level of explanation. Everything else is pejoratively called ‘phenomenological’. For instance, if exposure to an EDC candidate results in transgenerational transmission of decreased fecundity, this evidence will not count for regulation until a mode of action is found. Within this context, under pressure from industry and regulators, experimentalists return to the bench to refine the search for those elusive molecular mechanisms. Simultaneously, they often opt for collecting the type of ‘evidence’ needed to publish their work in high-impact journals, which are likely to be equally invested in the above-referred molecular reductionism. Molecular mechanisms, however, are not the obligatory type of satisfactory explanation for biological phenomena — the ideology of molecular causation will probably lead to an endless research programme. In fact, some philosophers of science and biologists posit that the problems encountered while addressing complex biological phenomena, including irreproducibility, have their roots in what the philosopher Dan Dennett calls ‘greedy reductionism’, as well as in ambiguous and misguided theoretical frameworks⁴.

In summary, the slow transmission of knowledge on endocrine disruption from the bench to medical practice and public health policy is due to the misperceptions that we have pointed out above. Researchers should be able to correct the ideological (reductionism versus organicism) and theoretical ones (lack of a solid theoretical framework to guide organismal biology research). Additionally, being aware of the differences between basic science and applied science approaches will help researchers to decide when ‘enough is enough’ as far as the quantity and quality of evidence necessary to introduce meaningful changes into regulation and clinical practice. Accordingly, researchers should ponder whether it is time to reverse the status quo by placing the phenomenological horse before the mechanistic cart. Finally, as stated by Bradford Hill long before the molecular mechanism mystique became dominant, “All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time” (REF.⁵).

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