Epidemiology, biology, and endocrine disrupters

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Where next?

For much of the 1990s the plausibility of the endocrine disrupter hypothesis (EDH) as a useful model for the aetiology of a number of disorders of hormonally regulated biological systems in nature, and ultimately the relevance of the EDH to human disease, has preoccupied interested biologists, toxicologists, and epidemiologists. There is an ever increasing battery of evidence for environmental and industrial chemicals, which show evidence of hormonal activity in vitro, and there is considerable observational evidence of sexuality modifying effects of these chemicals in wildlife. Secular trend data in disorders of hormonally controlled physiological systems in humans have also been examined to identify likely candidate human outcomes for endocrine disruption. The now well rehearsed list of such disorders includes testicular cancer (for which there is convincing evidence of a rise in prevalence over the past century); decreasing sperm counts (for which there is less convincing evidence); and also the congenital anomalies hypospadias and cryptorchidism (for which there is the least convincing evidence).

Sakkakbaek et al have suggested that these disorders are related and may usefully be considered as part of a syndrome which they have termed “testicular dysgenesis syndrome”. Sharpe and colleagues have recently reported a putative animal model for this syndrome: where offspring rats display all or some of these outcomes (excluding testicular cancer) when the mothers are exposed to putative endocrine disrupting chemicals. Reviews of the endocrine disrupter question have tried to draw the diverse findings together and have pointed out limitations in the generalisability of the in vitro, animal, and wildlife studies to humans. For example, the toxicological studies tend to require high doses (circa 500 mg/kg of putative endocrine disrupting chemical) to produce their effects. These doses are well above levels of human exposure to the same chemicals. Furthermore, discussion of these animal model studies has tended to focus away from the occurrence of non-hormonally related anomalies in offspring which are often reported and would indicate the occurrence of a more general toxicological process than one mediated through endocrine pathways.

There are clearly benefits to adopting the term testicular dysgenesis syndrome if these disorders are indeed the syndromic outcome of the same pathophysiological process, which has a real clinical significance beyond toxicological experimentation on laboratory rats. However, if the mechanisms of the individual pathologies differ, albeit sharing a nominally “hormonal mechanism”, then treating these three disorders as a related syndrome may impede rather than assist our understanding, and hinder the development of relevant regulatory assays for industrial chemicals. The next step for regulators might be to employ the animal models recently described by groups including Foster and colleagues and Sharpe and colleagues to test chemicals for endocrine disrupting activity. However, in the absence of good epidemiological evidence for a role of endocrine disrupting chemicals in human disease, such tests might initially satisfy the impatience of regulators and those advocating the so called “precautionary principle”, while measuring something which may have limited clinical relevance to humans.

“It is perhaps time to pose the endocrine disrupter hypothesis clearly in its public health context”

Since one can never prove the null hypothesis (that is, that chemicals pose no danger), and absence of evidence of risk is not evidence for absence of risk, the endocrine disrupter hypothesis is particularly problematic to untangle. It is perhaps time to pose the endocrine disrupter hypothesis clearly in its public health context. This is a question with a number of parts:

1. Are EDCs clinically significant rather than potential or even statistically significant risk factors for disease?

2. If so, what is their “evidence based” attributable risk? (that is, how much disease can be attributed to them?)

3. Can there ever be satisfactory assays to detect them?

4. To what extent is the risk modifiable and what are the opportunity costs to public health in taking action required to modify that risk?

The report by Vrijheid et al in this issue is one of a few, yet growing number of epidemiological studies to address the first of these questions (that is, evidence of whether endocrine disruption causes human pathology). The others remain to be answered. Vrijheid and colleagues’ choice of hypospadias as the endpoint of interest is notable since hypospadias, like cryptorchidism, offers the opportunity to examine the endocrine hypothesis over a very short period of time since these anomalies are evident at birth. Other proposed outcomes of endocrine disruption such as low sperm count and testicular cancer are far less amenable to epidemiological study because of the prolonged period between exposure and outcome. Thus prospective studies would need to be very large and would require many years before the outcomes could be measured. Retrospective studies would be hindered by the difficulties of recall as well as the likelihood that clinical material from which measurements might be made are likely to have been discarded. The exposure measure, chosen by Vrijheid et al, is crude, as they freely admit. It is severely limited not only because of potential misclassification of occupational exposure but also because the exposure within each occupational group has been estimated on the basis of expert opinion where quantitative information about actual exposure is absent. This issue of limited exposure assessment poses a major obstacle to progressing an epidemiological approach to these questions. However, high quality quantitative biological data from blood and urine, reflecting exposure to putative endocrine disrupters, are being accumulated through the National Health and Nutrition Examination Survey. Its latest findings are due in early 2003 and will provide an estimate of the distribution of population exposure to putative endocrine disrupting chemicals which will permit linking concentrations of chemicals in the environment with levels found in people. This linkage will inform job exposure matrices of the type used in the study Vrijheid et al.

Before further progress can be made in this area some key issues remain:

• Epidemiological studies are difficult because their focus is on rare diseases, most with a long natural history, where there are poor measures of exposure leading to exposure misclassification and where the excess risk is low. More detailed human studies, which focus on exposure to specific chemicals and on the exact timing of that exposure, offer opportunities for the future.

• Also, before meaningful laboratory tests of endocrine disruption are possible, further elucidation and clarification of the existing animal models and in vitro studies is necessary, to identify
relevant biomarkers and to distinguish clinically relevant endocrine disruption, at a relevant dose, from a toxicological poisoning effect of a high dose of an otherwise inactive chemical.

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