

of data, statistical analysis, etc. However, we now consider that biological factors, of which we are unaware and for which we have not controlled, have the potential to exert developmental effects on testis weight which are at least as great as the maximum effects that can be induced by the addition of a potent estrogen (DES) to the mother's drinking water during pregnancy and lactation. This conclusion, and our other experiences outlined above, have obvious relevance to the ongoing debate regarding the design and application of *in vivo* tests for the detection of adverse effects of hormone disruptors. We consider it our scientific responsibility to bring these matters to the attention of all those involved in this area.

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Authors' note: We are saddened and dismayed to report that the contents of this letter have been communicated without our authority to various sections of the media (Endocrine/Estrogen Newsletter) or in reports being circulated within industry (e.g., by the Chlorine Chemistry Council). These breaches occurred prior even to acceptance of our letter for publication. To add insult to breach of authority, these reports misrepresent our letter as a retraction of our original findings. This is not the case, as anyone who reads the letter above can confirm.

The First Synthetic Estrogen

In the course of a literature review, I encountered a report published in 1933, which described the first synthetic estrogen (1). At that time, an incorrect version of the chemical structure of estrone was in use, but the first synthetic estrogen was derived from it, namely, 1-keto-1,2,3,4-tetrahydrophenanthrene. Estrogenicity was demonstrated by changes in vaginal cytology in ovariectomized rats. Two parts of the discussion section of the paper are beautiful to read, as follows:

This result is of importance, for 1-keto-1,2,3,4-tetrahydrophenanthrene is the first compound of known chemical constitution found to have definite oestrus-exciting activity. There is thus provided the first step in the task of defining the molecular conditions necessary for this type of physiological activity, and there are grounds for hoping that substances of a much higher order of activity will be found before very long. . . .

The observation that oestrogenic properties of a low order are possessed by suitable extracts of such a variety of materials as peat, brown coal, lignite, coal tar and petroleum is of interest, but in view of the fact that many such materials are known to contain carcinogenic constituents, the clinical use of such extracts without very stringent refinement is scarcely to be entertained.

This seminal paper therefore mentions synthetic estrogens, a test for estrogens, hopes for structure-activity relationships among estrogens, naturally occurring estrogens, the anticipated clinical application of estrogens, and a relative risk estimate, with carcinogenicity being weighed against estrogenicity. Within 3 years, the same group had defined bisphenol A as an experimental estrogen (2). Sixty years later, the United States Congress mandated an ordered study of synthetic environmental estrogens (3).

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