Xenoestrogens and Breast Cancer

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Introduction

Is there reason to believe that estrogen-like substances might be a significant etiological factor in the apparent worldwide rise in the incidence of breast cancer?

What the following does not address is the reality of such a rise. Could it be an artifact brought about by such factors as improving female health allowing them to reach the ages at which breast cancer develops, or improved health statistics, diagnostic techniques and health surveillance?

Other possible etiological factors are not considered although one, the genetic, has a particular importance for me. My mother and my sister both developed breast cancer. What will happen to my two daughters and my granddaughter? I admit bias.

The start for me was an article in the *Scientific American* by Davis and Bradlow.[1] Their summary of the case suggested xenoestrogens as a cause of breast cancer, including a list of some of the known estrogen-like substances, and effects on wildlife. The effect might be due either to the impact of the substances on the estrogen receptors, or upon the immune system, or both.

At the time I was a member (as it turned out to be, the only active member) of the Pesticide Subcommittee of the Environmental Health Committee (EHC) of the British Columbia Medical Association (BCMA). Because of the apparent importance of the issue I suggested to the EHC that I pursue the matter.

Xenoestrogens are defined as substances which can function biologically like estrogens but which are not identical to the physiologically normal hormones, nor interact with the estrogen receptors in a physiological manner. Generally they are of three kinds. There are naturally occurring xenoestrogens, such as the saponins and saponinogens found in differing concentrations in the various yam species, for which there are effective detoxification mechanisms. There are the deliberately manufactured estrogen analogues such as those used for oral contraception and for hormone replacement therapy in peri- and post-menopausal women, and whose deleterious effects, though uncommon, are well known. Then there are substances manufactured for entirely different purposes but whose estrogen-like properties are inadvertent findings, and for which the detoxification mechanisms are either weak, or not present at all. Often, because of the lack of detoxification, they tend to be cumulative in the environment. These last are the subjects of this paper.

Davis, et al[2] listed 78 references suggesting such a linkage. They also hinted at a link with male reproductive disorders such as reduction in sperm count and a rise in the incidence of testicular cancer (see below). In a later paper[3] they provided further backing references. Marshall[4] presented a series of anecdotes raising serious doubts and questions about the current orthodox attempts to prevent breast cancer backed by 21 references.

Much of the case specifically implicating xenoestrogens as a factor in the causation of breast cancer has been published in *Environmental Health Perspectives,* 103, Supplement 7, Oct.1995, as per the following items:

Bradlow, et al,[5] described an assay method for the 16-α/2hydroxyestrone ratio which may prove of value as a measure of breast cancer risk. They also described how the risk ratio alters experimentally on exposure to a wide variety of pesticides. Feldman and Krishnan,[6] suggested that estrogen-like substances are far more common and ubiquitous than hitherto believed,

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also showing that many apparently innocent and common petrochemicals can easily be converted to such substances, all with the potential to confound studies, directed either to show or disprove a relationship with breast cancer. Twenty Seven additional references were provided.

Katzenellenbogen,[7] considered the variety of substances which have demonstrated estrogenic activity, and their pervasiveness, the natural ones occurring in humans, synthetic versions, versions which occur naturally in the environment, food additives, pesticides, and commercial chemicals and impurities. McLachlan and Korach,[8] summarized a symposium on estrogens in the environment, which was held 9-11 January, 1994, in Washington D.C. An initial meeting was held in 1979.

Metzger,[9] summarized research findings which challenge the receptor-mediated mechanism (acting on the expression of genes) as the only means by which estrogens act. The fundamental problem is that very often estrogens act far faster than this mechanism can explain. Some of the faster mechanisms were described.

Wolff and Toniolo,[10] described mainly congeners of PCBs and their relationship to breast cancer with 35 references. This last prompted me to request the help of the World Wildlife Fund Canada (WWF). What I said in my request was "I have never taken the attitude that somehow human beings are immune to what is deleterious to the other species with which we share the Biosphere (Gaia)." If something affects the species with which we share the Earth and with whom we share so many biochemical mechanisms, it would seem rash indeed to presume that we are somehow immune until proven otherwise.

Non-Human Effects

The following is a short account of numerous research studies on the endocrine effects of organochlorine (or other halogenated) pesticides on non-human organisms, from the unicellular to the higher vertebrates. These are the commonest artificial xenoestrogens delivered into the environment.

Atrazine was shown to have endocrine effects in species from molluscs, through rats and alligators, to humans. The effects included clear-cut tumour genesis in a variety of tissues.[11-27]

Dodson and Hanazato[28] looked at the effect of Carbaryl on the behaviour and reproduction of Daphnia species, a key member of aquatic ecosystems. Hill[29] looked at the avian toxicology of anticholinestrases (i.e. herbicides of which Carbaryl is an example). Carbofuran is a pesticide of the DDT-like group. It has major effects on the humoral immune response as well on the endocrine systems of many systems.[30-34]

Cyanazine is a herbicide of particular importance. Munger, et al.[35] related intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. Rologg, et al, showed induced chromosome damage by this agent at concentrations which did not inhibit cell growth.[36]

Dicofol is a DDT analogue to which the ban against the latter does not apply, and is equally persistent in the environment.[37] It has also been shown to have effects on both behaviour and reproductive function in reptiles and birds.[38-41] MacLellan, et al, in a particularly important paper, called into question all studies reporting negative effects of xenobiotics on single generations of experimental animals. This study showed that deleterious effects appeared significantly in the subsequent generations.[42]

Kime[43] studied the effects of pollution, especially by Endosulfan, on reproduction in fish and came to the conclusion that humans may be particularly susceptible to the effects observed in fish because of our position on the food chain. Rastogi, and Kulshrestha,[34] and Vonier.[27] came to similar conclusions.

Lindane is commonly used for the treatment of fomite infestations (fleas and lice) in humans and their pets, as well as being a wood preservative. In rats and mice, however, it has been shown to cause marked estrogenic dysfunction and immunotoxicity.[44-49] But what of humans? Westin and Richter, in the Israeli breast-cancer anomaly,[50] and Gerhard, et al., (1991)[51] found endocrine and immunologic disorders in women.

Malathion was another of the pesticides studied by Kime[43] with the same conclusions as with Endosulfan. This agent was found to be carcinogenic by Reuber.[52] Other studies[53-54] found endocrine reproductive dysfunction in experimental aquatic animals.

In two separate papers, Gray, et al,[55-56] found that Methoxychlor induced estrogen-like alterations of behaviour and the reproductive tract in the female rat and hamster, as well as alterations of reproductive development and function in the rat.

I eliminated ten pesticides from further consideration because of lack of references to relevant effects to this review at this time. It should be noted that none of these references from the WWF deal with the estrogenic effects of other environmental pollutants such as PCBs or Dioxin, for example, and their role as xenoestrogens, and their possible role in the induction of breast cancer, or other endocrinopathies in either humans or other species.

Distribution

How do the pesticides get to us? How are we inadvertently exposed to them?

Baker et al,[57] found significant ambient air concentrations of pesticides in California.[57] Hill, et al., found seasonal variations in herbicide levels detected in shallow Alberta groundwater.[58] Meanwhile, Hill et al, found numerous pesticide residues in urine of adults living in the United States.[59] In Europe, Mogensen and Spliid[60] studied the occurrence and effects of pesticides in Danish watercourses. Pereira, et al., studied the distribution, transport and fate of synthetic agrochemicals in the lower Mississippi River and its major tributaries.[61] A draft report for the state of Illinois found that Environment Protection Agency standards were frequently exceeded by the degree to which contamination of drinking water was polluted by herbicides.[62] A 1991 USA Government survey of the Mississippi found considerable contamination by Atrazine and Alachlor (another alleged xenoestrogenic pesticide).[63] Waite, et al. reported considerable atmospheric deposition of pesticides in a small southern Saskatchewan watershed.[64] *Tapwater Blues, Herbicides in Drinking Water,* a book by Wiles, and his co-authors[65] looked at the degree of contamination of drinking water by five herbicides at various locations throughout the USA.

There are also anecdotal reports of DDT, which is still legal in Southeast Asia, being deposited in various sites in North America. In other words, merely because the use of a pesticide/herbicide is restricted to any one particular place does not mean that it cannot be widely redistributed, even on the other side of the planet.

Contrary Viewpoint

That dissenting opinions might be present is no surprise. An information package from the Canadian Chemical Producers Association was been kindly made available to me from the *BC Medical Association News.*

Ahlborg, et al.,[66] looked at organo-chlorine compounds in relation to breast cancer, endometrial cancer and endometriosis. This review, by a distinguished international team, cites 318 references, perhaps the most massive paper I have ever read. While it casts doubt on the hypothesis that xenoestrogens are a cause of breast cancer (as well as cancer of the endometrium and endometriosis), the authors equally admitted that the evidence available at the time their review was published did not permit

them to reject the hypothesis conclusively. Heinze,[67] on the other hand, actually offered no evidence of either harmlessness or harmfulness of xenoestrogens but is cited by others as showing absence of proof of harmfulness of xenoestrogens. Neither did it show proof of safety of these substances. Safe,[68] a member of the Department of Veterinary Physiology and Pharmacology of the Texas A&M University, looked at both the issue of xenoestrogenic effects on breast cancer and on sperm counts, citing 84 references. However only 14 of the references dealt directly with the issue of the possibility of induction of breast cancer. The author stated in his abstract that the suggestion that industrial estrogenic chemicals contribute to and increased incidence of breast cancer in women is not plausible while acknowledging that further research is required. If it is not plausible, then why is further research required?

In addition I was able to locate the paper by Heindel, et al.,[69] which was an attempt to assess the effects of realistic human concentrations of such mixtures using experimental animals, showing no deleterious effects on any of the parameters studied. However they made no mention of multigenerational effects–see MacLellan above.[42]

Conclusion

I am reminded that the absence of proof is not proof of absence–in either direction. If the citations numbered 1-65 have any credibility, then there is reason for concern. Prudence demands that the industries which provide such alleged toxic substance equally have an onus to prove their safety. Alternatively, do we accept the suffering and demise of many millions of women worldwide as the price of the comfort of the shareholders in these companies?

Orthomolecular physicians well know such arguments, dealing as they do with the harmful effects of the products of the food and tobacco industries.

Additional Comment

Both sides cite evidence of either a rising incidence in the rates of testicular cancer, or lack of such an increase, to back their claims. Fortuitously, new evidence has now become available which may help to change the climate of opinion. Weir, et al.,[70] looked at trends in the incidence of testicular germ cell cancer in Ontario by histologic subgroup, in the years 1964-1996, while Klotz, asked "Why is the rate of testicular cancer increasing?"[71] Both considered pesticide effects as a likely causative factor.

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