INTRODUCTION

The Case for Expanded Phytoestrogen Research (43824B)

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Phytoestrogens are estrogenic chemicals produced by plants. The estrogenic activity of clover was first described almost 50 years ago following the observation that sheep feeding on pastures that contained clover demonstrated hyperestrogenization and infertility (1). Progress in understanding the significance of plant estrogens has been slow, in part due to the scientific isolation of what was thought to be a somewhat idiosyncratic animal husbandry problem. Studies identifying the estrogenically active chemicals and the discoveries of additional plant sources for other estrogens were roughly contemporaneous with our developing understanding of the mechanism of action of animal estrogens. Phytoestrogens are now known to be diverse in their chemical structures as well as in their origins (2). The two major chemical classes, the coumestans and isoflavonoids, each have a number of representatives with different estrogenic potencies; they may have different patterns of biological activities as well (3, 4). Thus, while general statements regarding phytoestrogen effects can be made, additional properties may be associated with specific phytoestrogens.

It was predictable, therefore, that purified phytoestrogens would be examined in the experimental systems being used to elucidate the mechanism of action of estrogens. Observations that phytoestrogens competed with radiolabeled estradiol for binding to the estrogen receptor (ER) and elicited estrogenic responses in estrogen-responsive tissues and cells were crucial in demonstrating that phytoestrogens and traditional estrogens shared a common mechanism of action (2, 5). Even at this juncture, the major research emphasis was on estrogens with a high affinity for the ER, since these are generally the most biologically potent estrogens. In the pharmaceutical industry, this emphasis drove the discovery of estrogenic chemicals with high affinity and biological potency. These studies resulted in major advances in both human health and population control, exemplified by the synthetic estrogen ethynylestradiol. However, the induction of benign abnormalities and malignancies in the reproductive tracts of the offspring of diethylstilbestrol (DES)-treated pregnant women (6) showed that estrogens can also adversely affect humans.

In the meantime, phytoestrogens continued to be of only marginal interest, in large part because they generally showed a low affinity for the ER and a low estrogenic potency in bioassays. However, as the number of plant species demonstrated to contain phytoestrogens expanded, interest increased in the potential for these chemicals to be effective estrogens in human and wildlife populations, and to be used for medicinal purposes. Specifically, the anticarcinogenic activity of some phytoestrogens suggested an antiestrogenic action (7). This hypothesis is consistent with the finding that Asian populations, which consume large amounts of phytoestrogens derived from a soy-based diet, have a lower incidence of breast and prostate malignancies than western populations, which consume a much lower quantity of phytoestrogens in their diet (7, 8). A sequence of findings in experimental animals demonstrated that phytoestrogens possess the same wide range of biological activities previously found with traditional estrogens. Nonetheless, the entire literature on phytoestrogens includes only some 900 references published since the mid 1940s (see preceding Announcement). Most of these studies are concentrated in four areas: effects on livestock; isolation and identification; metabolism; and estrogenic potency. While the literature is sufficiently large to demonstrate the importance of phytoestrogens, there are huge gaps in our knowledge.

At the Second International Phytoestrogen Con-

ference, formal presentations and individual and group discussions helped identify a number of significant deficiencies in our techniques and knowledge. These include the need to develop analytical methods for simple, rapid, accurate, and reliable identification of phytoestrogens. Currently, analytical methods are quite expensive and require substantial effort. Without improved techniques, important problems in various species of interest (such as the identification of sites of metabolism and metabolic products, pharmacokinetic studies, and the determination of phytoestrogen concentration in target tissues and human foods) cannot be pursued in the detail necessary.

Given the interest in the antiestrogenic activity of phytoestrogens, particularly with respect to prevention of breast cancer, there is a clear need to carry out detailed pharmacological studies to define relative agonist and antagonist activities in different tissues and species. The pharmaceutical industry has produced a variety of antiestrogens with a wide range of agonist/antagonist activities. Some of these antiestrogens, such as the mixed agonist/antagonist tamoxifen versus the pure antiestrogens ICI 164,384 and 182,780 (9, 10), appear to act via different mechanisms. These findings suggest that the antiestrogenic actions of different phytoestrogens also could be mechanistically distinct. In addition to anticarcinogenesis, could such chemicals alter regulation of endocrine activity in both males and females? Are there new endocrine drugs awaiting discovery among the phytoestrogens? Only careful, detailed examinations can provide an answer to such questions. Another important issue is distinguishing between phytoestrogen agonist/antagonist effects elicited via the estrogen receptor- versus nonreceptor-mediated, chemical structure-specific outcomes (11). Given the large number of structurally different phytoestrogens, it would be naïve to expect that all their effects are estrogen receptor-mediated.

As with any biologically active chemical, it is crucial to define adverse versus beneficial effects of the phytoestrogens. Some possible benefits have already been discussed. The major adverse activities of estrogens involve reproductive, carcinogenic, and developmental outcomes. Estrogen regulation of fertility is exemplified by oral contraceptives. Phytoestrogens are known to induce infertility in livestock (2) and probably in quail populations (12). It is clearly important to determine if there are additional effects on fertility in human, wildlife, and livestock populations. Estrogens are also involved in induction of malignancies in estrogen target tissues. In humans, chronic unopposed estrogen exposure is a major risk factor for the induction of endometrial adenocarcinomas (13), and tamoxifen also increases the risk for this outcome (14). Are some phytoestrogens also risk factors for malignancies? Finally, despite the compelling example of DES developmental toxicity in humans, there are only a couple of dozen studies on the developmental effects of phytoestrogens in reproductive tract and brain of experimental animals. Even though they are few in number, these studies make it clear that phytoestrogens have some of the same capabilities to induce developmental toxicity as do other estrogens (3, 15–17). However, there are hints that they may differ from other estrogens in certain specific outcomes (3). Given the DES tragedy, it would be foolish to ignore the possibility that some phytoestrogens constitute a developmental hazard.

Even in the few areas highlighted in the foregoing discussion, it is apparent that an extensive biomedical research agenda is necessary. But where are the resources to come from to drive this emerging area? The National Institutes of Health (NIH) could accept a major responsibility for funding appropriate research projects on phytoestrogens. Absent such an initiative from the NIH, progress will be delayed. The food industry could devote more attention to the potential beneficial and adverse effects of phytoestrogens found in human foods such as soy-based products. The interests of the pharmaceutical industry would be well served by supporting basic research as well as drug discovery and development involving phytoestrogens. Regulatory agencies such as the Environmental Protection Agency, responsible for assuring a safe environment, and the FDA, which regulates the safety of drugs and foods, are aware of the regulatory issues involving phytoestrogens. The FDA is actively engaged in phytoestrogen research. Since phytoestrogen research has such clear relevance to so many private and public organizations, communication and coordination of resource allocation among them will be important in increasing our understanding of the impact of phytoestrogens on wildlife, livestock, and humans.

This volume constitutes the first published compendium focussed on phytoestrogen research and is intended to highlight the varied approaches and findings of current investigations. We are hopeful that in the fall of 1995 another phytoestrogen conference can be held that will not only attract even wider attendance but will demonstrate significant progress in our understanding of phytoestrogens.

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