COMMITTEE ON DRUGS

STILBESTROL AND ADENOCARCINOMA OF THE VAGINA

One of the most important concepts in pediatric pharmacology is that exposure to drugs or chemicals may have latent, unforeseen effects on the child later in life. Some of the most dramatic occurrences, other than teratogenesis, are those in which hormonal exposure during the fetal or newborn period alters adult sexual development. However, none of these episodes is more impressive and ominous than that reported by Herbst et al. \(^1\) Herbst, an obstetrician at the Massachusetts General Hospital, was intrigued by the presentation of seven patients with adenocarcinoma of the vagina, an extremely rare tumor not previously seen at the hospital. The patients ranged in age from 14 to 22 years and sought medical advice because of vaginal bleeding. Several had benign adenosis, suggesting that the malignant change seen in all was based on a fundamental alteration in the biology of the vaginal epithelium. Six of the patients were treated with radical surgery, and one was treated with wide, local excision. One of the patients died after surgery.

In what could serve as a model of a scientifically conducted, epidemiologic study, each of the seven patients, plus an additional patient from another hospital, was matched with four controls born in the same hospital within four days. Thus, the "control" group was chosen in a manner to eliminate many biases of artificially contrived control populations. A wide variety of possible influences in both mothers and offspring were considered, e.g., maternal age, smoking habits, exposure to X-rays, breast-feeding, birth weight, age at menarche, medications during pregnancy, and so forth. Three common factors were found: (1) a higher incidence of maternal bleeding during pregnancy, (2) a history of past miscarriage, and, most startling, (3) mothers of seven of the eight patients had received stilbestrol (diethylstilbestrol) during pregnancy as compared to none in the control group. In all of these mothers, administration had begun during the first trimester and continued throughout pregnancy.

Soon after Herbst's report, Greenwald and co-workers \(^2\) reported on a review of the New York State Cancer Registry from 1950 to 1970. Adenocarcinoma of the vagina in five women less than 30 years of age was found; all were diagnosed between 1958 and 1971, when the patients were 15 to 19 years of age. Mothers of all five patients had received estrogen during pregnancy; four received stilbestrol and one dienestrol. Herbst et al. \(^3\) also reported receipt of information on some 20 additional instances of adenocarcinoma in adolescents, most of whose mothers had received stilbestrol while pregnant.

Several unresolved questions limit interpretation of these cases as having proved a causal relationship between malignancy and prenatal exposure to stilbestrol. This type of adenocarcinoma, although rare, was known to occur before synthetic estrogens were commercially available. One of the mothers in the initial report did not receive stilbestrol. Moreover, in four of the eight families, five female siblings, aged 18 to 22 years who were also exposed in utero to stilbestrol, did not develop carcinoma or adenosis. During the same period the mothers of the patients were pregnant, 675 patients were recorded as having been treated with stilbestrol at the Boston Lying-In Hospital; yet, there were no known cases of adenocarcinoma in this group. This appar-

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The statements presented herein do not preclude alternatives which may be more appropriate, taking into account local situations and all other relevant facts.

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ent discrepancy may be a dose effect because the mothers of many of the patients had received large doses of stilbestrol (as high as 135 mg/day); the normal replacement dose of stilbestrol is 0.1 mg/day.

An additional unresolved problem is why the cancer, believed to be of Müllerian origin, appears only in females. The answer may relate to the embryology of sexual development. The human fetus at eight weeks is undifferentiated; it has both Wolffian and Müllerian ducts. During the third month, the Müllerian duct in the female differentiates into the uterus and Fallopian tubes, and the Wolffian duct disappears except for vestigial structures such as the epoopheron, paroopheron, and Gartner's duct. In the male, under the influence of organizing substance, the Müllerian duct becomes vestigial and is represented by the appendix of the testis and the utriculus masculinis. This difference in development may explain the absence of this tumor in males whose mothers received stilbestrol during pregnancy.

Information in the literature supports the alleged relationship between estrogens and cancer. Stilbestrol is known to produce carcinoma of the endometrium in rabbits and is a carcinogen in a variety of species. Although its use in the treatment of bleeding during pregnancy is no longer common, it should be pointed out that a large proportion of the cattle and poultry now raised in the United States have been treated with stilbestrol. Apparently in response to the report of Herbst et al., the Food and Drug Administration requirements have been changed. At first they said that the last injection must be at least seven days prior to slaughter rather than 48 hours; later an absolute ban was placed on the use of stilbestrol.

These reports should make the pediatricians aware that no drug or chemical—whether prescription, over-the-counter, or food additive—can be regarded as having been proved to be entirely free of potential harm to the fetus.

The appropriate follow-up for a child exposed in utero to stilbestrol is not established, although guidelines are being developed by the American College of Obstetricians and Gynecologists. On the basis of the data presently available, examination of girls exposed to stilbestrol in utero is not necessary, particularly if they are premenarchial. Unfortunately, the easily performed Papanicolaou smear is of no value. Inspection of the vagina and biopsy are the only appropriate diagnostic maneuvers.

Pediatricians must be conscious of this newly recognized hazard and promptly investigate unusual signs or symptoms in adolescent girls (such as intermenstrual spotting and irregular or excessive flow) by pelvic examination, including visualization of the vagina, and/or by referral to a gynecologist.

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REFERENCES
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ANTIHISTAMINES IN TOPICAL PREPARATIONS

Antihistamines were introduced in France by Halpern in 1942 and in the United States at the end of World War II; they had been investigated extensively during the war for therapy of motion sickness. By the late 1940s, a mass of information on the structure activity relationship had accumulated and most major drug manufacturers had introduced antihistamines into the market for oral, parenteral, and topical administration. Topical use was efficacious in acute dermatitis because the local anesthetic activity of the drugs diminished pruritus.

The first reports of sensitization to the topical antihistamines, which began to appear in 1947, incriminated tripelennamine (Pyribenazine), diphenhydramine (Benadryl), antazoline (Antistine), and pheniramne (Trimeton). In the ensuing 25 years, though thousands of instances of antihistamine contact dermatitis have occurred, many topical antihistamines remain on the market. The Committee is concerned about the use of topical antihistamines which are sold over the counter for use in such conditions as chickenpox and poison ivy. Table I lists most of the preparations currently available for topical use.

CLASSES OF ANTIHISTAMINES

The antihistamines are classified according to their chemical structure into five primary groups as shown in Table II. Each drug carries its own index of sensitization and other adverse effects when employed topically. The ethylenediamine derivatives include the following: antazoline phosphate (Antistine), promethazine hydrochloride (Phenergan*), and tripelennamine (Pyribenazine). They are particularly active in inducing contact dermatitis and were responsible for the cases first reported. Ethylenediamine, because of its dibasic structure, is widely used in various organic syntheses for the preparation of dyes, inhibitors, rubber accelerators, fungicides, synthetic waxes, resins, insecticides, and asphalt-wetting agents. It is valuable for neutralizing the acidity of oils or controlling alkalinity. As ethylenediaminetetraacetic acid (EDTA), it is a ubiquitously used preservative in topical and systemic medications of all types. The induction of contact sensitivity to drugs of this class will result in a dermatitis on topical or oral readministration of agents of this class of antihistamines. The sensitized patient may also react to the oral or parenteral administration of aminophylline, which contains theophylline conjugated with ethylenediamine, as well as to contact with any of the many substances containing ethylenediamines.

The phenothiazines include drugs employed either as antihistamines or as psychotrophic agents. Representative members of this group of compounds are given in Table II. Promethazine hydrochloride (Phenergan) is available as a topical prep-

* Phenergan is both an ethylenediamine and a phenothiazine derivative.
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