there is little protection for readers of "clinical experience" articles. Compare, for example, the requirement for "substantial evidence," "full disclosure," and "fair balance" in the labeling and advertising of drug manufacturers with the free rein that exists for presenting unilateral observations in a "scientific" meeting. The advocacy of DES in pregnancy, blood changes due to use of methotrexate in psoriasis, and visual damage from chloroquin in arthritis suggest the increasing need for a specialist to read beyond his specialty and to keep up with the best informed clinical pharmacology before prescribing any drug. This becomes especially important when the drug is offered for an unaccepted, although not unacceptable, use or in a decidedly unusual dosage or duration of administration.

Perhaps we need a mechanism to pool data concerning medical experience with unusual doses and utilization of existing drugs.

Selected Item from the FDA Drug Bulletin — November 1971

Diethylstilbestrol Contraindicated in Pregnancy: Drug's Use Linked to Adenocarcinoma in the Offspring

WE WISH TO BRING to the attention of all physicians, hospitals, and medical personnel an important possible toxic effect of diethylstilbestrol (DES) reported for the first time in April 1971 by Herbst et al.[1] From their studies the authors concluded that maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed. The authors studied eight cases of adenocarcinoma of the vagina in patients born between 1946 and 1951. The malignancies were identified and treated between 1966 and 1969. In seven of the eight cases, there was a history of maternal use of diethylstilbestrol. Because this type of malignancy in young girls had rarely been reported previously, the authors conducted a retrospective investigation in an attempt to find factors that may be associated with such malignancy in this age group. Four matched controls were established for each patient and the data obtained were subjected to statistical analysis. A statistically significant relationship was observed for three variables: diethylstilbestrol given during pregnancy ($p = .00001$), bleeding in that pregnancy ($p =$ less than .05) and prior pregnancy loss ($p =$ less than .01). It is obvious that the most significant of the variables is the administration of diethylstilbestrol during pregnancy.

Since publication of this study, five additional cases of this malignancy associated with the maternal use of diethylstilbestrol have been reported by Greenwald et al.[2] Dr. Herbst, in a recent communication to FDA, has reported an additional 15 cases associated with use of this drug, bringing the total number of known cases to 27. It must be emphasized that this type of epidemiologic study defines only an association and not necessarily a cause-and-effect relationship. Further studies are underway to clarify the significance of these findings.

In the meantime, the FDA is initiating the following precautionary actions:

1. All manufacturers of DES or closely related congeners (dienestrol, hexestrol, benzestrol, promethestrol) are being notified that appropriate changes will be required in the labeling for such drugs. This change will consist in the listing of pregnancy as a contraindication to the use of diethylstilbestrol and the other above-mentioned compounds.
2. All other estrogens will be required to have the following WARNING in their labeling: "A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy."
3. Epidemiological studies are being initiated to determine the true incidence of this disease in young women, the number at risk, the characteristics of patient populations with this malignancy, and the probability of a cause-and-effect relationship.

Both FDA and the medical profession face a responsibility to help determine whether this reported association constitutes a cause-and-effect relationship. We ask that all physicians consider appropriate steps to assist FDA case-finding and to protect any patients who might be at risk.

It may be possible to trace the offspring of those mothers who received DES during pregnancy. All physicians should be especially alert for young women whose mothers may have received hormonal therapy during pregnancy, particularly those young women who may be experiencing irregular vaginal bleeding. The association should be a routine consideration for physicians whose practice includes young women.

This is a previously unsuspected health problem. Further information is essential to the FDA and to the medical profession. We ask your help in reporting any cases you encounter for entry in a case registry.

FDA will take every possible step to insure that you are kept abreast of new information as soon as it can be gathered and analyzed.

For your convenience, an adverse reaction reporting form is printed below. FDA will forward a supply of forms to each practicing physician as soon as they are printed. Facsimile forms are acceptable.

REFERENCES

1. Herbst AL, Ulfelder H, Poskanzer DC: Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. New Engl J Med 284:878-881, Apr 22, 1971

2. Greenwald P, Barlow JJ, Nasca PC, et al: Vaginal cancer after maternal treatment with synthetic estrogens. New Engl J Med 285: 390-392, Aug 12, 1971

DRUG EXPERIENCE REPORT *(IN CONFIDENCE)*			Form Approved OMB No. xxxxxx
PATIENT INITIALS *(Optional)*			DATE OF REACTION ONSET
SUSPECTED REACTION(S)			
SUSPECTED DRUG(S); TRADE/GENERIC NAME *(Manufacturer's name, if possible)*			
DISORDER OR REASON FOR USE OF DRUG(S) *(Optional)*	ROUTE	TOTAL DAILY DOSE	DATES OF ADMINISTRATION
OTHER DRUGS TAKEN CONCOMITANTLY			
COMMENTS *(Optional)*			
PHYSICIAN'S NAME, ADDRESS, AND ZIP CODE			

FD PROPOSED FORM