By Harry K. Ziel, MD

Skepticism and Research

"Science is self-correcting." If an error is reported as truth, the error will in time be discovered and corrected.
Stephen Jay Gould

We live in a world of fact and fiction: We are constantly discovering that old truths are fiction and that new truth comes from skepticism of the old truth. To skeptics who are really worth their salt, the new truth is not so apparent. Such skeptics are a rare breed; indeed, we recognize their type of intellect with the Nobel Prize. Their names reverberate in the scientific community. We have honored and esteemed these individuals from time immemorial.

More often than not, however, the new truth stares us in the face, and only blind bias keeps us from recognizing it. Such is the case I'd like to illustrate here.

Twenty-three years ago, Jack Gordon (now deceased) (Fig. 1) was our director of clinical pathology at Kaiser Permanente Medical Center in Los Angeles. A huge volume of surgical specimens gave Jack vast experience—and superb skills—in interpreting histology slides. As this story will tell, Dr. Gordon really deserves much of the credit for associating use of estrogen (Premarin®) with endometrial cancer.

Premarin® is actually a mixture of ten different estrogens (primarily sodium estrone sulfate) derived from the urine of pregnant mares. Eructation causes some women taking Premarin® to note a uriniferous odor and thus to think they have a bad case of halitosis!

At our weekly departmental meetings, Jack would project slides of interesting cases from the preceding week. A colleague, Emil G. Holmstrom (now also deceased) (Fig. 2) reviewed the slides and corresponding patient charts before the conference and would present the patients' histories (drug exposure, age, parity, weight, etc). Because he had diligently abstracted information from the charts and correlated drug exposure with disease, Emil, too, deserves much credit for associating estrogen use with endometrial cancer. Emil had been chief of obstetrics and gynecology at the University of Utah Medical Center in Salt Lake City and had examined physicians for board certification after they had completed their residencies and had been in practice for several years. He had been a student of the famous German pathologist, Robert Mayer, and had himself become a thoroughly accomplished gynecologic pathologist.

Fig. 1. Jack Gordon, MD (Reproduced by permission of Richard Snyder, MD, and Marilyn Gordon.)

At our weekly pathology conferences, the obstetric and gynecologic staff heard Premarin® (the principal brand of estrogen used in the 1970s) mentioned so often when a slide of endometrial cancer was projected on the screen that it didn't take a genius to suspect a more-than-casual relation—in other words, a causal relation—between Premarin® use and malignancy. Jack became so convinced of an association between estrogen use and endometrial cancer that when he projected a slide of endometrial cancer, he no longer would say, "Endometrial cancer"; instead, he would say with a straight face, "Premarin effect!"

Fig. 2. Emil G. Holmstrom, MD (Reproduced by permission of the Manuscripts Division, J. Willard Marriott Library, University of Utah, Salt Lake City, Utah.)

I agreed with Dr. Gordon, but how could the association be proved? Our medical director, T. Hart Baker, who formerly headed our department of obstetrics and gynecology, introduced me to an epidemiologist whom he had hired to help him study the quality of care. The epidemiologist was William D. Finkle, PhD, whose father I had known as our radiation safety officer prior to his death. Bill and I just sort of clicked, and Bill knew immediately and decisively how to proceed with the estrogen question.

Moreover, doing a retrospective case-control study was child's play for Bill, a brilliant MIT graduate, who became so excited about our study that he virtually stopped work on the study he had been hired to do.

To speed our findings into print, Bill literally hand-carried a draft of our paper to various *New England Journal of Medicine* reviewers across North America and incorporated their criticisms and comments into the article before we submitted it. The editor, Franz Inglefinger, accepted the paper without change in October and presented our paper just two months later—in the December 4, 1975 issue[1]—along with a similar report by a group from The Mason Clinic in Seattle.[2] We used community controls matched to the study patients; the Seattle researchers selected as controls women who had types of gynecologic cancer other than endometrial cancer. This selection of control patients was less desirable than our selection of community controls. The Seattle researchers reported a 4.5 times increased risk of endometrial cancer after exposure to estrogen, whereas our paper reported a 7.6 times increased risk of endometrial cancer after exposure to Premarin®. Our results meant that if the normal rate of endometrial cancer among women not exposed to estrogen were 1 case per 1000 women per year, the rate of endometrial cancer among women

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exposed to estrogen would be 7 to 8 cases per 1000 women per year. The lower 95% confidence limit—4.7—was far greater than 1.0, thus indicating a strong statistical probability that a causal relation existed. (A risk ratio >4.0 indicates certainly that a causal relation exists; it is nearly impossible for study bias—even deliberate bias—to mimic a true association when the risk ratio is >4.0.) With a risk ratio of 7.6, we knew that we had "hit pay dirt." Kenneth Ryan, chief of obstetrics and gynecology at Harvard Medical School,[3] wrote a very supportive editorial in the same issue of *The New England Journal of Medicine.*

We felt like the statisticians who had come up with a risk ratio of 13—the risk ratio which causally associated tobacco use with lung cancer. Bill had great fun testifying before the United States Senate about our study: Senator Edward (Ted) Kennedy was particularly interested, especially when Bill stated that the entire project was done for only $1800, the cost of the abstractors' salaries! We were invited to present our findings at grand rounds at the University of Southern California. I even had occasion to appear on national television during the evening news hour! I also participated in panel discussions published in magazines such as *Contemporary OB-GYN* and *Controversies in Therapeutics* as well as several lively continuing medical education programs with the big names in our specialty. Some sessions were held as far away as Hilton Head, South Carolina. Much of what was said was less than complimentary.

After publication of the 1975 articles in the *New England Journal of Medicine,* the disbelievers had a heyday trying to discredit our findings. The critics even speculated that our pathologists couldn't diagnose endometrial cancer properly. The manufacturers of Premarin®, Ayerst Pharmaceuticals, arranged with Jack Gordon to have three renowned, highly respected pathologists visit with us for one week to personally review the slides in question. The experts were Arthur T. Hertig from Boston, James W. Reagan from Cleveland, and Donald G. McKay from San Francisco. We were proved right.

I know of no other institution that has voluntarily opened itself to such a review. Nonetheless, although understandably nervous about it, Jack Gordon was equal to the challenge. Dr. Inglefinger was eager to publish the findings of the experts' review, and I wanted Jack to be recognized for his efforts. When we finalized the last draft of the review, I made sure that Jack was credited with senior authorship of the paper.[4] Only one expert (Reagan) allowed us to include his name on the paper. McKay, still disbelieving, required us to remove his name from the coauthorship credits.

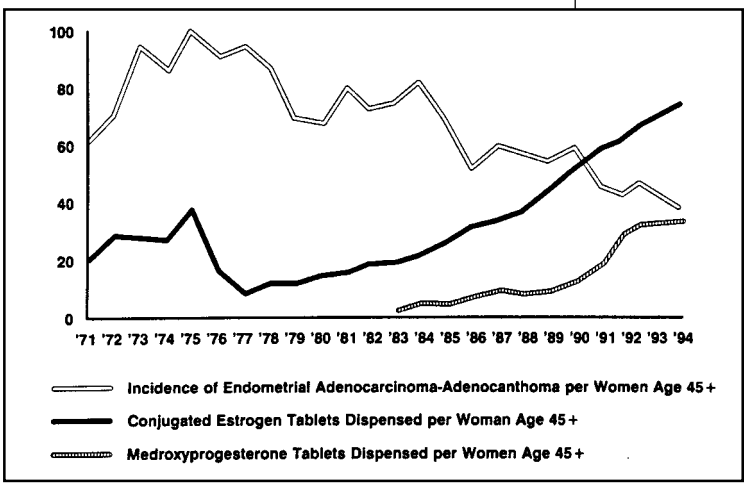

Fig. 3. Incidence of endometrial adenocarcinoma and adenoacanthoma and use of conjugated estrogens and medroxyprogesterone in the Southern California Kaiser Foundation Health Plan among women aged >45 yr. Open line shows incidence of endometrial adenocarcinoma and adenoacanthoma per 100,000 women; solid line shows number of tablets of conjugated estrogens dispensed per woman; crosshatch line shows number of medroxyprogesterone tablets dispensed per woman. (A similar graph depicting milligrams of conjugated estrogens instead of tablets dispensed appears in: Ziel HK, Finkle WD, Greenland S. Decline in incidence of endometrial cancer following increase in prescriptions for opposed conjugated estrogens in a prepaid health plan. Gynecol Oncol 1998;68:253-5[8].)

Ayerst Laboratories virtually forced Arthur Hertig to take his name from authorship.

By now, numerous other centers were using their own data bases to repeat our study. As each of their articles confirmed our findings, the critics were gradually silenced. The world biomedical literature now contains about 50 articles confirming the causal association between estrogen use and endometrial cancer. So ended an era of iatrogenically induced cancer.

The U.S. Food and Drug Administration responded to these findings by saying estrogen given to control menopausal symptoms should be used only for the shortest time, at the lowest dose. Within two years, use of Premarin® dropped to one sixth the number of tablets dispensed in its peak sales year, 1975—the year our articles were published. The most commonly prescribed dose of Premarin® had been 1.25 mg; now, the most common dose represented a dose reduction by half, to 0.625 mg. The only women continuing to receive long-term estrogen therapy were those not at risk for endometrial cancer, ie, women who had already had a hysterectomy. Many mares were probably put out to pasture as a result of our findings.

Gambrell reported in 1980[5] that if a progestin were given in conjunction with estrogen, the progestin would protect the endometrium from neoplastic

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change. We recognize now that progestins reduce the number of estrogen receptors in endometrial tissue so that the tissue is unable to incorporate estrogen into its DNA. At first, too little progestin (only 5 to 8 days per month) was prescribed, and some endometrial cancer still occurred. Ultimately, we learned that taking progestin for at least 10 (better yet, up to 14) days per month was needed to prevent estrogen-induced endometrial cancer. At first, the progestin was added to estrogen on the last days of a treatment cycle. We later learned that this type of sequential hormone therapy given for more than five years was still associated with a 2.7 times increased risk of endometrial cancer.[6] Consequently, most physicians now prescribe estrogen and progestin combined. Combination hormone replacement therapy (HRT) is not associated with endometrial neoplasia (Fig. 3) unless HRT was started after a period of unopposed estrogen use (ie, no progestin added). We have found that the neoplastic effect of unopposed estrogen use will last (ie, has a latency period) as long as four years after estrogen therapy is stopped.[7,8] ❖

" ... the entire project was done for only $1800 ... "

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Sails and Tents

Pattern making for sails and tents speak to us about a specifically western way of knowing, yet their unstated and even repressed intent is one of pleasure: the excitement of sailing ever faster on the high seas, and the pleasure of voluptuous architectural curves in light and shadow. As spectacle, tents embody the dream world of fleeting possibilities.

"Nature's Tailor: The Art and Science of Pattern-making"
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