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One conclusion may hide another

The American poet Kenneth Koch is perhaps most famous for his poem "One Train May Hide Another."[1] Noticing, as he crossed a railway track, the warning sign that became the title of the poem, he reflected on similar circumstances. For example, "In a poem one line may hide another line … And so when you read, wait until you have read the next line — Then it is safe to go on reading." The same may be true of research.

Koch died at age 77 in the same week that the Women's Health Initiative study of hormone replacement therapy was stopped because of excessive risks of invasive breast cancer.[2] Within the first year of the trial, which involved 16 608 postmenopausal women up to age 79 years, participants who had been randomly assigned to receive a combination of conjugated equine estrogen and medroxyprogesterone acetate (Prempro, Wyeth Ayerst) experienced higher rates of coronary artery disease and pulmonary embolism than participants receiving a placebo (see pages 377 and 387). Later the women receiving the active drug experienced higher rates of stroke and breast cancer. Hip fracture and colorectal cancer rates were lower than in the placebo group. The trial was stopped when the increases in the risk for breast cancer and in all risks combined exceeded predetermined boundaries.

Hormone replacement therapy became popular in 1968 with the publication of a best-selling book by Robert Wilson, *Feminine Forever*,[3] and its subsequent promotion by the author and his wife. Wilson believed that "the menopause is both unnecessary and harmful" and in "the incontrovertible fact that the deficiency disease created by ovarian decline with its painful, disabling and even fatal consequences, *is responsive to therapy* [author's italics]."[4] As reported by Kolata and Peterson,[5] Wilson's book and lecture tours were paid for by Wyeth Ayerst.

On the basis of observational (nonrandomized) studies, estrogen was believed to reduce the risk of heart disease and osteoporotic fractures in postmenopausal women. The science seemed so convincing that an advisory committee of the US Food and Drug Administration (FDA) recommended that randomized controlled trials were not necessary and that estrogen could be marketed as being protective against heart disease. The FDA, under pressure from the National Women's Health Network, overruled its advisors and insisted that hormone replacement therapy be subjected to a randomized trial. Perhaps, as Koch put it, the FDA suspected that "[I]n the laboratory, one invention may hide another invention."[1]

The Women's Health Initiative study serves to remind us that we should wait for the first train to pass. In this issue, David Sackett, long a student and passionate advocate of randomized trials, Anna Day, a leader in the reform of the women's health and research agenda, and Salim Yusuf and Sonia Anand comment on the study (see pages 357, 361 and 363); Yusuf is a member of the data and safety monitoring board for the study. As Sackett points out, it is of no value to simply blame the drug manufacturers for unscrupulous behaviour. By trying to increase market share and profits for their shareholders, they are behaving as a model industry. Perhaps we, the physicians who prescribed the drugs (and maybe even the patients who requested them) are at fault: Why did we accept evidence from nonrandomized studies so readily?

References

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3. Wilson RA. *Feminine forever*. New York: M. Evans and Company, Inc.; 1968.
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