

Editorial

MedGenMed's Selection of the Top 10 Medical/Health Stories of 2002

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Science grinds slowly with each new investigation or observation seeking "truth." Only rarely does one such event find scientific "truth." Rather, our best versions of truth come about as a continuum, an eventuality, following reports of many such temporally sequenced composite or disparate events. In any one modern calendar year, much is observed and reported; some likely to be lasting, and some not. It may be difficult to separate out those that are transient from those that might have more permanence. At best, scientific truth is a moving target, a work in progress. Nonetheless, we editors at *MedGenMed* decided to have a go at choosing what we believe to be the most important experimental results, medical observations, public health occurrences, or policy reports that appeared during 2002 to share with our readers, in part to inform, in part to stimulate their thoughts and memories, and perhaps to invite a bit of controversy.

Although we are working in the United States, we attempted to think globally, as Medscape is global, and as, of course, medicine and public health are of necessity global. The authors are themselves, by citizenship, Canadian, Italian, and American, respectively. Here is our shot at the top 10.

1. The demise of postmenopausal hormone replacement therapy

Thirty-five percent of postmenopausal women in the United States take combined estrogen and progestin therapy (eg, drugs such as *Premarin* and *Prempro*), reflecting the medical community's ever-intensifying touting of the benefits of postmenopausal hormone replacement therapy (HRT) over the past decade. Thus, it came as a shock to physicians and millions of patients when, on July 9, 2002, the National Institutes of Health's National Heart, Lung, and Blood Institute announced that it had terminated the study arm of the Women's Health Initiative (WHI) involving HRT for healthy menopausal women. The findings of the WHI were reported the following week in the July 17 issue of *JAMA*,^[1] only 2 weeks after 2 equally concerning studies of HRT from the Heart and Estrogen/progestin Replacement Study Follow-up (HERS II) were published.^[2,3]

The WHI enrolled 161,809 postmenopausal women (50-79 years of age) into a set of 5 clinical trials, 2 of which involved HRT -- 1 with combined estrogen-progestin in women with an intact uterus and 1 with estrogen alone in women who had had a hysterectomy.^[1] The data and safety monitoring board recommended stopping the combined estrogen-progestin trial owing to a 26% (95% CI 0-59%) increased risk of invasive breast cancer and a predefined global outcome measure indicating net harm from the active treatment. Other end points

indicating adverse effects from the treatment included statistically significant increased risks of coronary heart disease, stroke, and pulmonary embolism.

The treatment group did experience benefit in terms of reduced fracture rates (eg, the risk of hip fracture was reduced by 34%; 95% CI 45-0.98%), though the treatment group in HERS II experienced no such benefit.

The Heart and Estrogen/progestin Replacement Study (HERS)^[4] was the first randomized, blinded, and placebo-controlled trial of the impact of HRT with conjugated estrogens and medroxyprogesterone on coronary heart disease (CHD). Among 2763 postmenopausal women with documented CHD, no significant differences between the treatment and placebo groups emerged in terms of the primary or secondary cardiovascular outcomes. Some researchers wondered if longer follow-up would have allowed beneficial impacts of HRT to manifest themselves (the HERS trial had an average follow-up period of 4.1 years), especially as post-hoc analysis revealed that the treatment group experienced more CHD events in the first year, but significantly fewer thereafter. The additional 2.7 years of follow-up provided by HERS II (6.8 total years of observation) did not bear out the anticipated late or net benefit of HRT in reducing cardiovascular events,^[2] or even a benefit in reducing fractures.

These results from WHI and HERS II have effectively ended the period of enthusiasm about the promise of HRT in disease prevention for postmenopausal women. In fact, the totality of existing evidence makes it difficult to justify HRT for any indication other than relief of menopausal symptoms.^[5] Physicians prescribing HRT even for this indication must take into account the documented increases in adverse events (especially thromboembolism,^[2,6] but also cancer and biliary disease^[1,3]).

Clinicians may well wonder how it came about that so many previous studies had so strongly supported the benefits of postmenopausal HRT. Recent reanalysis of these previous nonrandomized trials and observational studies indicates that the apparent benefits of HRT reflected confounding by socioeconomic and lifestyle factors such as alcohol consumption and exercise.^[7] In other words, women who had chosen to receive HRT tended to have lower risks for cardiovascular disease and possibly fractures compared with women not using HRT. Thus, the benefits observed in previous nonrandomized studies reflected these underlying health differences, not intrinsic benefits of HRT itself.

Despite this sobering lesson in the persistent value of large randomized controlled trials, clinicians should not lose heart over the loss of HRT from the therapeutic armamentarium available for disease prevention in postmenopausal women. As pointed out by an editorialist,^[8] well-established evidence supports the use of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, "statins") for preventing CHD events and ischemic stroke in postmenopausal women. More recent randomized trials have also demonstrated the benefits of drugs such as alendronate and, more recently, raloxifene^[9] for the prevention of fracture in women with a history of fracture or low bone mineral density. Thus, clinicians can reassure patients inquiring about HRT that other well-established medical therapies (not to mention lifestyle interventions) provide substantial benefits in reducing cardiovascular risk and lowering the risk of osteoporotic fractures, without increasing the risk of adverse events such as cancer and thromboembolism.