20th Anniversary

Physicians' Health Study

The PHS Turns Twenty!

On September 20,1982, a computer-generated random number assigned a Florida physician to a daily combination of aspirin placebo and active beta-carotene. That brief event signaled the official start of the Physicians' Health Study. This randomized trial (PHS-I), under the direction of Charles H. Hennekens, M.D., definitively evaluated the role of aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer. A new trial (PHS-II), under the direction of J. Michael Gaziano, M.D., is now doing the same for beta-carotene, vitamin E, vitamin C, and a multivitamin. And thanks to your ongoing commitment and support, the Physicians' Health Study has evolved into one of the largest and longest-running observational cohort studies in America.

The initial letter inviting physicians to join a randomized trial of aspirin and beta-carotene struck a nerve. Almost half of the 260,000 U.S. physicians who received the invitation responded to it. A number of physicians who were older than the initial age limit argued so persuasively that the study shouldn't be limited to younger men that the upper age limit was raised. Not only did physicians *want* to take part in the trial, but they stuck with it. The rates of pill taking and questionnaire return—both of which are crucial for the validity of all trials—have been excellent.

Why this interest and commitment? Physicians said they wanted to take part in the Physician's Health Study to "improve the profession I love" or to "give something back to medicine." Those joining PHS-II have cited similar reasons.

Such responses are gratifying, and important. If we want clear answers to critical questions about how best to prevent cardiovascular disease, cancer, and other chronic conditions, we need people who are willing and committed to join clinical trials. Having so many physicians answer the call sends a powerful message—that taking part in such trials is the right thing to do. It also sets a wonderful example for patients.

Solid findings

When it comes to results, every trial should be as blessed as the Physicians' Health Study. The main findings on aspirin and beta-carotene have clearly influenced both medical practice and the direction of future research (see Key Findings).

The annual questionnaires you fill out and the blood samples submitted by almost two thirds of the participants are a treasure trove of information that is advancing medical knowledge far beyond the focus of the randomized trial. Data from these valuable resources are providing insights into associations between lifestyle factors such as alcohol use or physical activity and cardiovascular disease; into novel risk

▶ continued on page 3

Dear Doctor,

This fall marks the 20th anniversary of the Physicians' Health Study!

As we hope you know, your participation in this landmark study has helped change the way American physicians and the public approach the prevention of cardiovascular disease, cancer, and a host of other chronic conditions.

Numerous results from the original study continue to appear in the *New England Journal of Medicine*, *JAMA*, and other leading medical journals. A new trial now underway promises to have a similar impact.

None of this would have been possible without your efforts. To thank you for your participation in and commitment to the Physicians' Health Study, we have enclosed a small token of appreciation. We hope you wear your PHS tie with pride.

This 20th anniversary newsletter offers a snapshot of the study: a little history, some of the study's achievements, where the PHS stands today, and what lies ahead, sprinkled with interesting facts about the participants and the study.

We hope you enjoy the newsletter, and we thank you for your participation in the Physicians' Health Study.

J. Michael Gaziano

Julie E. Buring

PHS Timeline

1978-80	1980	1981	1982	1984	1988	1995	1997	1997	2001	2007
Initial planning	NIH funding	First invitation letters	First physician randomized	Last physician randomized	Aspirin arm stopped early	Beta-carotene arm ended	PHS-II begun	First PHS-II physician randomized	Last PHS-II physician randomized	Expected end of PHS-II

Key Findings of the PHS

If one of your reasons for joining the PHS was to make a difference in how physicians approach prevention, rest assured that you have succeeded. Results from this trial have been translated into clinical practice. You can't ask for much more.

Selected highlights of the study's findings are listed below. A complete list of nearly 200 publications from the PHS with links to Medline abstracts is available on the Physicians' Health Study Web site (http://phs.bwh.harvard.edu).

Aspirin and Beta-carotene

Perhaps the most important finding from the PHS so far emerged from the trial's aspirin arm. As reported in the July 20, 1989 *New England Journal of Medicine*, aspirin reduced the risk of first myocardial infarction by 44% (P <0.00001). There were too few strokes or deaths upon which to base sound clinical judgment regarding aspirin and stroke or mortality.

If laid end to end, the forms completed by PHS participants so far would stretch from Boston to New York.

Results from the beta-carotene arm were equally important. As reported in the May 2, 1996 *New England Journal of Medicine*, 13 years of supplementation with beta-carotene produced neither benefit nor harm. These results demonstrated that beta-carotene alone wasn't responsible for the health benefits seen among people who ate plenty of fruits and vegetables.

Risk factors for cardiovascular disease and cancer

Another important avenue of investigation in the PHS has been the evaluation of risk factors for cardiovascular disease and cancer. These range from dietary factors such as consumption of fish or dairy products to biomarkers such as insulin-like growth factor-1.

Alcohol consumption and mortality. Data from the PHS-I Enrollment Cohort suggest that the shape of the alcohol consumption/mortality curve is probably U-shaped, not J-shaped—men who reported moderate alcohol intake were less likely to have died than nondrinkers or heavy drinkers. This was largely driven by reductions in cardiovascular-related mortality. *Journal of the American College of Cardiology 2000; 35:96-105.*

Insulin-like growth factor-1 and prostate cancer. Insulin-like growth factor-1 (IGF-1) is a mitogen for prostate epithelial cells. In a nested case-control study, men in the highest quartile of IGF-1 levels had a 4-fold increased risk of prostate cancer compared with men in the lowest quartile, independent of baseline prostate-specific antigen levels. *Science 1998; 279:451-566.*

Pills sent: 223,000,000

Address changes each year: 4,000

Other endpoints

Although the initial focus of the Physicians' Health Study was squarely on cardiovascular disease and cancer, data you have supplied have significantly broadened the study's scope. PHS investigators have looked at endpoints such as cataract, T-cell mediated immunity, and renal function.

Exercise and the prevention of type 2 diabetes. Preventive measures are urgently needed to stem the rapid increase in the incidence of type 2 diabetes. Data from the PHS pointed to exercise. Study participants who exercised almost every day were half as likely to have developed type 2 diabetes than those who rarely exercised. The association was particularly pronounced among overweight men. *JAMA 1992; 268:63-67.*

Analgesic use and renal function. Data from the PHS may help answer a nagging clinical question: Does the use of aspirin and other nonsteroidal anti-inflammatory agents increase the risk of chronic renal disease? Over 14 years of follow-up, both mean creatinine levels and creatinine clearances were similar among PHS participants who did not use analgesics and those who did, even at total cumulative intakes of 2500 or more pills. *JAMA 2001; 286:315-321.*

Smoking and macular degeneration. During seven years of follow-up, PHS participants who smoked a pack or more per day had a 2.5-fold higher risk of macular

degeneration than never smokers; past smokers had a slightly higher risk. *JAMA 1996;276:1147-1151.*

New and novel risk factors

New hypotheses constantly arise about the factors that influence the onset or progression of chronic disease. Information collected over the course of the Physicians' Health Study has been used to test a number of these.

C-reactive protein and total cholesterol. Although C-reactive protein (CRP) had been identified as a sensitive marker of inflammation, and elevated levels had been linked with future risk of myocardial infarction, little was known about whether its measurement helped define, or refine, cardiovascular risk. In the PHS, the 5-fold relative risk of future myocardial infarction among men with high levels of both CRP and total cholesterol were greater than the product of the individual risks associated with isolated elevations of either CRP or total cholesterol. This suggested that an individual's CRP level adds to the predictive value of lipid parameters in determining the risk of a first myocardial infarction. *Circulation 1998; 97:2007-2011.*

Homocysteine and heart disease. When Boston pathologist Kilmer McCully proposed in 1968 that elevated levels of homocysteine were associated with cardiovascular disease, his hypothesis was dismissed. Data from the PHS helped focus more attention on homocysteine, which is now being considered as a risk factor for cardiovascular disease. Men with the highest 5% of serum homocysteine levels were 3.1 times more likely to have had a myocardial infarction than those in the bottom 90%. *JAMA 1992; 268:877-881*

Genetics of cholesteryl ester transfer protein. Blood samples supplied by PHS participants are providing a unique database for genetic analysis. (As with all PHS studies approved by the Institutional Review Board, participants are never identified and their information is held in the strictest confidence.) One recent genetic analysis examined mutations in the gene coding for cholesteryl ester transfer protein, such as the TaqIB polymorphism, that are associated with higher plasma HDL. Although the B2B2 genotype was associated with higher HDL levels than levels in men with the B2B1 and B1B1 genotypes, the risk of a myocardial infarction wasn't significantly different across the genotypes. *Atherosclerosis 2002; 161:469-74*

Methodology

As mentioned in *Setting Trends (to the right),* the Physicians' Health Study has helped pioneer the use of the large, simple trial to efficiently answer pressing clinical questions. Dozens of publications about the study's methodology offer "lessons learned" that investigators have applied to the design and execution of other large, simple trials.

As described in a 1990 report, the study's factorial design, its use of a pre-randomization run-in phase, and the collection of blood samples before randomization were important strategies for ensuring long-term follow-up at a fraction of the usual cost of large-scale trials of primary prevention. *Statistics in Medicine 1990; 9:29-33.*

Physicians' Health Study Staff

20 YEARS—continued from page 1

factors for cardiovascular disease and cancer, particularly prostate cancer; and into genetic markers for a range of chronic diseases.

Setting trends

Most clinical trials are complex operations. The PHS has taken a different tack. It helped pioneer a new kind of epidemiologic study—the large, simple clinical trial conducted entirely by mail. Physicians were a perfect population for testing such a method by accurately reporting medical conditions and other health information on annual follow-up questionnaires. Physicians have also been excellent about sticking with their assigned treatments. As a result, the Physicians' Health Study was, and is, conducted at a fraction of the cost of most primary prevention trials.

The National Institutes of Health and investigators around the world now look to the Physicians' Health Study as a model for this kind of trial. Thanks for helping "write the book" on conducting a large, simple clinical trial.