Constructing "Sound Science" and "Good Epidemiology": Tobacco, Lawyers, and Public Relations Firms

The tobacco industry has attacked "junk science" to discredit the evidence that secondhand smoke—among other environmental toxins—causes disease. Philip Morris used public relations firms and lawyers to develop a "sound science" program in the United States and Europe that involved recruiting other industries and issues to obscure the tobacco industry's role. The European "sound science" plans included a version of "good epidemiological practices" that would make it impossible to conclude that secondhand smoke—and thus other environmental toxins—caused diseases.

Public health professionals need to be aware that the "sound science" movement is not an indigenous effort from within the profession to improve the quality of scientific discourse, but reflects sophisticated public relations campaigns controlled by industry executives and lawyers whose aim is to manipulate the standards of scientific proof to serve the corporate interests of their clients.

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THE TERMS "SOUND SCIENCE" and "junk science" have increasingly appeared in the media, medical literature,[1,2] and litigation.[3] Industries—those responsible for products ranging from silicone gel breast implants[4,5] to hormone-treated beef[6] to secondhand smoke[7]—claim to be victimized by lawsuits and regulations based on "junk science,"[2,8] while the scientific, public health, and regulatory communities claim their actions are based on "sound science."[9–12]

The tobacco industry has always contested the evidence that secondhand smoke endangers nonsmokers[13–17]; during the last decade the Philip Morris (PM) tobacco company appropriated the "sound science" concept to attack studies on secondhand smoke. To deal with the tobacco industry's lack of credibility, it developed "sound science" coalitions involving other industries opposed to regulation to support its position, similar to smokers' rights[18,19] and restaurant association[20,21] front groups. PM also mounted a sophisticated public relations campaign to promote "good epidemiology practices" (GEP) to shape the standards of scientific proof to make it impossible to "prove" that secondhand smoke—among many other environmental toxins—is dangerous.

We analyzed tobacco industry documents made public as a result of litigation in the United States and available on the Internet in an online repository to which documents are continually added as additional and unrelated legal cases are resolved. The documents cited in the reference list were originally accessed between January 2000 and May 2001. Search terms included "IARC," "TASSC," "sound science," "junk science," "GEP," and the names of key players. We did not use documents from a related depository covering British American Tobacco in Guildford, England, because of the depository's practical inaccessibility to researchers.[22] If we had used the Guildford documents, they probably would have contributed to a broader story.

PHILIP MORRIS'S "SOUND SCIENCE" ORGANIZATION IN THE UNITED STATES

PM began its "sound science" program in 1993 to stimulate criticism of the 1992 US Environmental Protection Agency (EPA) report,[23] which identified secondhand smoke as a Group A human carcinogen. Ellen Merlo (vice president, PM Corporate Affairs) wrote to William Campbell (chairman, PM USA):

> OBJECTIVES
> *Our overriding objective is to discredit the EPA report and to get the EPA to adopt a standard for risk assessment for all products.*
> Concurrently, it is our objective to prevent states and cities, as well as businesses from passing smoking bans.
> And finally, where possible we will proactively seek to pass accommodation legislation with preemption.
> STRATEGIES
> *To form local coalitions to help us educate the local media, legislators and the public at large about the dangers of "junk science" and to caution them from taking regulatory steps* before fully understanding the costs in both economic and human terms [emphasis added].[24]

In February 1993, PM and its public relations firm, APCO Associates, worked to launch a "sound science" coalition in the United States, with approximately $320 000 budgeted for the first 24 weeks.[24] Three months later, The Advancement for Sound Science Coalition (TASSC) had been formed.[25] TASSC described itself as "a not-for-profit coalition advocating the use of sound science in public policy decision making,"[26] even though APCO created it to help PM fight smoking restrictions.[27,28] TASSC's public positioning and media campaign were designed to minimize its connections with the tobacco industry[29,30]; TASSC's member survey mentioned only secondhand smoke among a list of other potential examples of "unsound, incomplete, or unsubstantiated science."[31]

A broad base of issues and members was necessary to provide credibility to the new organization. Charles Lister, a lawyer at the tobacco industry's Washington, DC, law firm, Covington & Burling, wrote, "No one would take seriously a meeting even partly sponsored by PM in which

EPA was more than one example among several. In any event, our points can be made more effectively and persuasively if EPA is discussed within a larger context."[32] Lister suggested that "foods, plastics, chemicals, and packaging would be natural candidates" in broadening the scope of TASSC's sponsors and issues beyond EPA and the tobacco industry.[32]

To develop TASSC into "a broad-based and diverse national coalition,"[33] more than 20 000 recruitment letters were mailed, with 100 letters mailed to "key scientists,"[34] signed by TASSC's chairman Garrey Carruthers (former Republican governor of New Mexico). The leadership and members, which included prominent scientists and policymakers[35–37] plus representatives from corporations,[37,38] would be provided PM's secondhand smoke agenda suggestions through APCO but made to feel the agenda was their own.[39]

PM hid its role[40] so successfully that when longtime tobacco industry consultant Gary Huber, then a professor at the University of Texas Health Center, received the letter inviting him to join TASSC, he contacted Tony Andrade of the PM law firm Shook, Hardy & Bacon (SH&B) to inform him that the organization might be helpful to the tobacco industry.[41] Andrade, also unaware of PM's role with TASSC, forwarded the information to PM, which subsequently "filled him in on TASSC."[41]

TASSC's overall effectiveness in serving PM's initial goal of discrediting the EPA report may not have met PM's expectations; by April 1994, Merlo expressed concern that, despite its $880 000 cost in 1994,[42,43] TASSC was not proving to be a "tool to affect legislative decisions"[28] to stem smoking restrictions.

Even so, by 1995, a TASSC Web site was being planned with PM to distribute scientific papers and polls to support PM's position.[44] TASSC and its Web site are now defunct, but its executive director Steve Milloy, an adjunct scholar at the Cato Institute (a libertarian think tank in Washington, DC, that has received funds from the tobacco industry[45]), now produces a "junk science" Web site.[46] Milloy's Web site continues TASSC's original work in criticizing and "debunking" the science behind public health and environmental issues, including secondhand smoke.[46]

THE EUROPEAN "SOUND SCIENCE" PROGRAM AND "GOOD EPIDEMIOLOGY PRACTICES"

PM also developed a "sound science" program in Europe to subvert[47] the effects of a large ongoing European epidemiologic study of passive smoking and lung cancer being conducted by the International Agency for Research on Cancer (IARC),[48] which the tobacco industry feared would stimulate smoking restrictions in Europe. PM sought to "develop a programme to generate support for 'junk science' and education on use and abuse of epidemiology, possibly through a coalition on bad science,"[49] which would prepare a skeptical environment for interpreting the study's results. PM used the public relations firms Burson-Marsteller and APCO[39,50–54] to address the need that "science must be managed according to clear, scientifically based criteria, e.g., good epidemiology,"[55] consistent with the industry's interests.

PM's interest in promoting "good epidemiology" developed after the Chemical Manufacturers Association (CMA) published its suggested "Good Epidemiology Practices" (GEP) in 1991 as a framework for "consumers of epidemiology" (policymakers and regulators) to determine the quality of a study and address poorly conducted studies.[56] The CMA's GEP promoted the "sound science" and "good epidemiology" concepts for each step in the conduct of an epidemiologic study.[57,58] Covington & Burling lawyer Charles Lister distributed the CMA's GEP to PM in February 1994:

> Their [CMA's] announced goals are essentially our own. The GEP Guidelines are intended to be analogous to Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP), both of which are expressly now endorsed and required by Community law.
>
> The GEP Guidelines themselves seem disappointingly vague to me.
>
> ...GEP is being pushed in Europe by a number of companies, including particularly Monsanto and ICI.
>
> ...I was informally told that DGV [European Union's Directorate General for Employment, Industrial Relations and Social Affairs] is quite interested in GEP, although reticent about proposing new legislation. Nonetheless, there seems to be a realistic prospect that they might be persuaded to issue a [European] Commission Communication or other policy document.[59]

PM saw the CMA's GEP as an opportunity to promote an official epidemiologic standard that would challenge the methodology of IARC's work.[60] Thomas Borelli (Director, PM Science and Environmental Policy), however, expressed concern that the CMA guidelines did not go far enough to meet the tobacco industry's needs because

> . . . it lacks teeth and as written it does not have enough meat to help us on ETS [environmental tobacco smoke, another term for secondhand smoke]. However setting up our own standards is a good project for us and our consultant's [sic] program. It would be good offensive strategy for our consultant's [sic] to be out there trying to fix epidemiology instead of being critical all the time.[61]

PM's scientific personnel agreed that PM could adapt GEP to include secondhand smoke studies and that PM's consultants, a network of scientists being financed by industry lawyers to contest the evidence that secondhand smoke caused disease,[47,62,63] should "fix" epidemiology proactively.[64,65] Mitch Ritter (PM Scientific Affairs) noted the obstacles, and appeal, of this approach: "It is difficult to imagine epidemiologists—or the health lobby in general—accepting this [CMA] initiative as it stands, though they will have to accept the principle of a set of good practices."[64,65] PM decided to appropriate the GEP movement by broadening its GEP support base to the scientific community, European government bodies, and other industries with similar concerns about low-level risks. PM's 1994 "Legislative Guidelines on GEP" included the following:

> Objective
> * Impede adverse legislation
>
> Strategy
> * Endorsement by scientific world
> * International gathering of world's top epidemiologists (October)
>
> Tool: GEP guidelines
> * Expand debate to EU [European Union] political targets
> * Political conference opportunities (DGV, STOA [EU Directorate General for Em-

ployment, Industrial Relations and Social Affairs; Science and Technology Office of Assessment])
* Legislative opportunities (EAC, Biomed, public health framework)
Tool: GEP resolution
* Motivate concerned industry sectors
* GEP lobby
Physical agents:
- Mobile phones, electricity (EMF)
- Computers (UV rays)
Chemical agents:
- Food (sugar, dairy, flavorings)
- Chemicals
- Metals
* Sound science lobby
Widen to
- Packaging
- Pharmaceutical
- Forestry/paper[66]

PM wanted GEP guidelines to be endorsed by the scientific community, a GEP resolution to be passed through European legislation, and a GEP lobby with other industries facing regulation and a broad-based "sound science" lobby. As with the initial "sound science" efforts, the tobacco industry's role would be minimized. The industry sought broad support of numerous endorsers on a variety of issues to provide credibility for PM's GEP objective—to avert increased smoking restrictions.

With the help of its legal, public relations, and scientific resources, PM began drafting a GEP resolution that would be "authored" by a "sound science" coalition. In June 1994, APCO drafted a potential TASSC-sponsored list of "17 Guiding Scientific Principles,"[67] which PM found "too vague" and not supportive enough of its GEP plans.[68] SH&B drafted GEP guidelines to be sponsored by an "Executive Committee of the Sound Science Coalition" (Table 1).[54] SH&B's GEP resolution[54] promoted the tobacco industry's position, subsequently advocated publicly by SH&B,[69] that odds ratios of 2 or less are highly questionable and that a statistically significant association is not strong enough evidence for causation to warrant regulatory action. (This concentration on odds ratios was not in the original CMA proposal.)

PM consultant Roger Walk restructured the GEP resolution, relying "heavily on the content of the [SH&B] drafts" to "look more like a 'scientist's' version of guidelines."[70,71] With the relative risk for lung cancer due to passive smoking at about 1.2,[17,23,48,72–75] and the relative risk for heart disease about 1.3,[74–76] this standard would prevent action to protect the public from lung cancer and heart disease caused by secondhand smoke.

To obtain scientific endorsement of PM's GEP, PM needed scientists to promote it to government bodies.[77] In June 1994, PM sought scientists to participate in a GEP seminar in Germany[54] and planned for a subsequent long-term coalition that would help criticize the IARC study.[78] Burson-Marsteller identified scientists interested in "sound science" and "good epidemiology," but found that some scientists were concerned that corporate sponsorship—especially sponsorship by PM—would limit their scientific independence, even though Burson-Marsteller had not mentioned PM.[79,80] In August 1994, Covington & Burling created a list of potential epidemiologists who might be approached for the GEP seminar, excluding "influential epidemiologists known to have strongly antitobacco views."[81]

The plan to use prescreened epidemiologists may have changed just as PM was ready to introduce GEP to them.[82] An October 1994 memo from Joanna

TABLE 1— Shook, Hardy & Bacon's Draft GEP Resolution for a "Sound Science" Coalition[54]

THE EXECUTIVE COMMITTEE RECOMMENDS that the members of the Sound Science Coalition adopt and actively promote in the scientific community at large and within their individual disciplines, appropriate and specific professional standards for epidemiological research, to be carried out by accredited individuals and institutions, reflecting the following principles:

1. The study design should clearly define all objectives and hypotheses. Possible problems in design and data interpretation should be described and the intended method for addressing each fully set out. Every effort should be made to address possible confounders to avoid the need for subsequent adjustments.

2. In case-control studies, special attention should be given to how the control group will be selected and what matching procedures will be utilized. Also, case selection should be explained with emphasis on efforts to ensure a high participation rate. A pre-calculation of required sample size should be carried out to ensure that the sample is sufficient to produce meaningful results.

3. Statements of study design should contain a description of statistical techniques. This should include underlying assumptions for distribution, variance, correlation and regression procedures. The degree to which violation of these assumptions would invalidate the analysis should be specified whenever possible.

4. Adherence to the study protocol should be as close as possible. Any deviations (e.g., errors in randomization, low participation rate, suspected confounders, possible misclassification) should be documented.

5. Special care should be given to the training and monitoring of those administering questionnaires and surveys; blinded techniques are preferred.

6. After the study is conducted, the results should be analyzed as specified by the study protocol. Two-sided hypothesis tests are encouraged. If a one-sided test is employed, this should be noted and the rationale for using it provided. The presentation of confidence intervals for the estimate of risk gives more information than a single point value with an associated p value. Generally, 95% confidence intervals are preferred.

7. An adequate description of the raw data should precede and complement formal statistical analysis. If the data are not supportive of the stated hypotheses, no further analysis is necessary. Subsequent treatment of the data should only be for hypothesis generating purposes.

8. Odds ratios of 2 or less should be treated with caution, particularly when the confidence intervals are wide. There is a likelihood that the odds ratio is artefactual and the result of problems with case or control selection, confounders or bias.

9. Meta-analysis and pooling techniques are best used for homogenous data gathered under a uniform pool.

10. Observations that are inconsistent with the main body of the data should not be excluded from the analysis.

11. Journal articles and scientific conferences are the appropriate forum for the presentation of research results. Every effort should be made to publish and report on all completed research, regardless of outcome. Only by such efforts can the entire sample of conducted research be made available to the scientific community and publication bias minimized.

12. Generally, hypotheses tests not specified by the study protocol should not be reported. When many hypotheses tests are performed on data from a single study, a number of positive results can be expected to arise by chance alone, creating serious problems of interpretation.

13. Recognizing that a statistically significant association does not in itself provide direct evidence of causal relationship between the variables concerned and that causation can only be established on nonstatistical grounds, particular care should be taken when comparing two variables that have changed over time. Such comparisons often produce apparent associations.

14. Graphic display of results and figures that show individual observations are to be encouraged. For example, when appropriate, fixed regression lines should be presented together with a scatter diagram of the raw data. Any complex statistical methods should be communicated in a manner that is comprehensible to the reader.

15. Rigorous scientific objectivity should be the standard when reporting on epidemiological results. Defects in study design, conduct and analysis should be frankly admitted. It is helpful for abstracts accurately to reflect any study deficiencies. Advocacy and objectivity rarely comfortably coexist.

Sullivan (PM Corporate Services Brussels) announced, "the GEP project would be halted as previously discussed because the [PM IARC] Task Force agreed that it could be counterproductive."[83] PM's planned long-term "sound science" coalition is now likely to be the Cambridge-based European Science and Environment Forum, which sought funding from tobacco companies in addition to PM for its 1996 inception and has actively criticized the IARC study.[47]

PM still sought official European Union endorsement of GEP, which other industries were already seeking,[59] and PM hoped it would contain "the necessary language to catch the IARC study."[77] In July 1994, PM had a draft of a possible European Union GEP resolution,[54] and Covington & Burling lawyer John Rupp drafted a European Council resolution about GEP for PM's consideration.[84] In early 1995, PM was considering holding a GEP seminar in Germany and introducing PM's GEP at an October 1995 conference on the use of science in public health regulations to be funded by the European Union's Directorate General V (Employment, Industrial Relations and Social Affairs) and the nonferrous metal industry.[85]

In September 1995, Joanna Sullivan (PMCS Brussels) wrote to Richard Carchman (director, Scientific Affairs, PM USA) stating that the SH&B GEP guideline revision[71] "should be given to Professor [Ernst] Wynder for passing onto Dr [Henriette] Chamouillet of DG V of the European Commission."[86] Wynder, whose early work linked smoking and cancer, had developed a financial relationship with the tobacco industry.[87–99] PM described Wynder as "being in favor of the [GEP] project" and helping PM organize a GEP conference.[100]

It is unclear whether Wynder and Chamouillet did indeed meet, but by late 1995, the European Union Data Protection Directive was adopted, stating that "the Commission shall encourage the drawing-up of codes of conduct [for studies involving the processing of medical data]" and that "the Commission may ensure publicity for [approved] codes."[101,102] This European Union directive led to a new GEP proposal, drafted in 1995, with limited distribution in 1997, by a group of European and American epidemiologists from industry and academia, in hopes of international review and subsequent European Union Working Group approval.[101] Despite PM's efforts, no European Union resolution on GEP had been produced as of mid-2000.

WORLDWIDE SEMINARS ON GOOD EPIDEMIOLOGY PRACTICES

From 1994 to 2000, seemingly independent seminars on GEP have been conducted by several organizations in the United States, United Kingdom, European Union, and China. In fact, PM is connected to all these events.

Federal Focus, Inc, a nonprofit foundation based in Washington, DC, that engages in research and education pertaining to federal government policy issues, conducted 2 seminars[103] on epidemiology and risk assessment that appear to have been part of PM's GEP program. In 1994, Federal Focus convened a 19-member panel in the United States that advocated uniform epidemiology principles.[104] In October 1995, a second 18-member panel met in London, England, and drafted the "Principles for Evaluating Epidemiologic Data in Regulatory Risk Assessment," or "London Principles,"[105] which pose a series of questions to guide a risk assessor about the overall quality of the data and its potential weight for a risk assessment. The panel comprised scientific representatives from academia and industry, including some who had received tobacco industry funding or served as tobacco industry consultants.[47,105,106]

The London Principles do not criticize relative risks of less than 2, but the Federal Focus leaders have, while working under contract with PM. Federal Focus received at least $200 000 from PM in 1993.[107] Federal Focus' chairman, Jim Tozzi of Multinational Business Services, was under contract with PM for $40 000 a month in 1993 and up to $610 000 in 1994.[108,109] Thorne Auchter, director of Federal Focus' Institute for Regulatory Policy, has testified to the US Occupational Safety and Health Administration Public Meeting on Standards Planning Process that "a determination needs to be made regarding the reliability of relative risks in the "weak association (RR<2.0–3.0) range."[110] In 1993 and 1994, Tozzi was to work with PM "to develop materials designed to intensify the debate on the need for scientific standards on meta-analysis and epidemiology such as electromagnetic fields, chlorinated water, and radon in water," with the purpose of "supporting legislative mandates on epidemiological standards" and "increasing debate on ETS risk assessment within EPA."[108]

PM, Covington & Burling, and Tozzi collaborated on 8 "Criteria for Epidemiology" of which "all guidelines for conducting epidemiological studies should incorporate consideration," including "[d]oes the relative risk fall into the realm of 'weak association' (RR<2.0–3.0) relative to background?"[111] In July 1995, Tozzi sought PM to discuss the Federal Focus "EPI Principles" from the "first conference" with NATO and IARC officials, as "EPA, through IARC and NATO, continues to market its indoor air quality program overseas."[112]

The Weinberg Group, a consultancy run by Myron Weinberg that testifies for the tobacco industry on clean indoor-air issues,[63] worked with PM to conduct "Good Risk Management Practices" conferences in Europe and Asia. An October 1997 European conference, "The Challenges of Responsible Good Risk Management Practices," included PM as one of 11 corporate supporters with official sponsorship by the European Union Commission.[113] The speakers included tobacco industry consultant Ragnar Rylander[63] (who has consulted for PM about GEP's utility,[114,115] stated that relative risks of less than 2 have severe methodological problems,[116] and advocated GEP at a 1996 scientific conference[117]) and the European Science and Environment Forum's executive director, Roger Bates.[113] Government administrators were session moderators, which Weinberg described to PM as a "valuable concept" because they were "the target of the expert presentations."[113] PM wanted to repeat a similar Weinberg seminar in Asia in 1998, to be endorsed by the Association of South East Asian Nations,[113] which PM expected to establish guidelines for risk assessment.[118] PM planned to commit $220 000[113] for a conference in Kuala Lumpur or Bangkok by

November 1998 and hoped for published journal articles or conference proceedings.[118]

The tobacco industry's Center for Indoor Air Research cohosted a July 1997 "International Workshop on Risk Assessment and Good Epidemiological Practices" in China with the Guangzhou Institute for Chemical Carcinogens and the Chinese Epidemiological Association.[119] (The Center for Indoor Air Research financed projects "specially reviewed" by tobacco industry lawyers, as opposed to its peer-reviewed projects; the former are more likely to conclude that secondhand smoke does not cause disease.[120,121]) The China conference brought together 100 lung cancer specialists within China[122] with a few scientists from outside China, including scientists funded by the tobacco industry.[47,63,106,123] This China GEP workshop was part of the tobacco industry's "Asia-specific IARC preparation,"[124] and PM hoped to produce GEP resolutions by Chinese science organizations.[125] An organizer of the conference coauthored a paper on GEP and the etiology of lung cancer[126] with industry consultant Joseph Wu,[106] who had been paid $235 000 in 1995 and 1996 to organize and conduct "Chinese projects" through SH&B.[127] Wu authored an accompanying editorial[128] on risk assessment and GEP in the *Chinese Journal of Epidemiology* that states that relative risks of less than 2 may be artifactual for secondhand smoke studies, and that scientists need to examine other factors, such as pollution and diet, for lung cancer.[128]

Several European epidemiologic societies have developed GEP guidelines, including the International Epidemiological Association (IEA),[129] the Danish Society of Epidemiology,[129] and the Association des Epidémiologistes de Langue Française (ADELF, Association of French-Speaking Epidemiologists).[130] PM may have sought to participate in these processes; John Rupp, the lawyer from Covington & Burling who had drafted a European Council GEP resolution for PM,[84] lobbied ADELF on GEP, as well as in Italy and Germany.[131,132] The ADELF and IEA epidemiologists who headed the GEP efforts for their organizations state that they had no idea that PM had such subversive intentions. The GEP guidelines developed by the epidemiologic societies do not discuss relative risks of less than 2, and the IEA guidelines emphasize the ethical conduct of epidemiologic studies.

CHANGES IN PHILIP MORRIS'S GOOD PRACTICE PROGRAM

By April 1998, PM began to scale back its GEP program. Ted Sanders (PM Worldwide Scientific Affairs), who was to inherit the GEP program, expressed concern about the GEP program's value to Cathy Ellis (senior vice president of research and development, PM USA):

> . . . the concept of GEP's was discussed in considerable detail in PM. *Corporate Affairs thought it was a wonderful idea, because at first they . . . felt that part of a code for Good Epidemiological Practices would state that any relative risk of less than 2 would be ignored. This is of course not the case. No epidemiological organization would agree to this, and even Corporate Affairs realizes this now* [emphasis added].[131]

Sanders describes PM's initial objective as to discredit epidemiologic results with relative risks of less than 2, but the company realized that no epidemiological organization would agree to such a standard. Sanders' memo also suggests that if PM had succeeded in securing a GEP code as initially planned, there was a good chance PM would not be able to criticize future errors in epidemiologic studies, and a better alternative would be to continue developing GEP with other companies. PM seems to have followed Sanders' advice; by July 20, 1998, "no further work was to be done on GEP's" by Rupp, who had continued his activities in France.[131]

GEP has most recently been a focus for Toxicology Forum, a nonprofit organization that fosters interaction between scientists in academia, government, and industry.[133] The 1999 Brussels conference included "Epidemiology in a Policy and Regulatory Context: Considering a Code of Good Epidemiology Practice," and the May 2000 Brussels conference discussed "Determinants and Structure of Guidelines of Epidemiological Practice."[133] (Note: When the referenced Web site was accessed on September 24, 2001, the title of the May 2000 conference had been changed to "Comparison of the Principles and Practice of Risk Assessment Performed at the Global and European Level," and the list of pending participants had been removed.) The May 2000 session speaker list included tobacco industry consultants.[63,133–135] PM, R.J. Reynolds, and the Tobacco Institute contributed $35 000 through Covington & Burling for a 1992 Toxicology Forum meeting[136] that included the session "Weak Epidemiological Associations and the Limitations of Meta-Analysis."[137] The international discussion of GEP continues, although the tobacco industry's interest in the 1999 and 2000 GEP Toxicology Forum conference remains unclear.

DISCUSSION

PM appropriated the "sound science" concept to shape the standards of epidemiology and to prevent increased smoking restrictions. The "sound science" coalition was viewed by PM and its public relations firms as a launching point to introduce the tobacco industry version of "good epidemiological practices" that would be accepted by the scientific community. The "sound science" coalitions are similar to other tobacco industry front groups used as third-party spokesmen without disclosing the tobacco industry's involvement.[18–21] PM's GEP was constructed by their lawyers and internal scientific resources. To gain support for its GEP programs and perspectives, PM capitalized on the concerns of other industries facing regulation and the good intentions of the scientific community, which sought to improve the conduct of epidemiology.

PM has gone beyond "creating doubt"[63] and "controversy"[120,121] about the scientific evidence that demonstrates that active and passive smoking cause disease, to attempting to change the scientific standards of proof. PM's higher level of activity in Europe with GEP reflects the reason for this strategy shift. PM sought to establish a tactically advantageous scientific and policy-making environment before a scientific threat materialized in Europe, whereas in the United States, PM was reacting against an already damaging scientific government publication. The versions of GEP PM

and its allies promoted discount relative risks below 2 and would set the standard in such a way that would make it impossible to conclude that secondhand smoke, as well as many other environmental toxins, is dangerous.

This approach ignores the fact that a comprehensive assessment of risk involves considering all the evidence related to a toxin, not just the epidemiology. This distinction was highlighted in the response to a news article in *Science*,[138] which represented several epidemiologists as concluding that there was a high threshold for a relative risk's being worth considering.[139] One of the epidemiologists quoted in the article responded that the news story

> . . . writes that I have expressed the view that only a fourfold risk should be taken seriously. That is correct, *but only when the finding stands in a biological vacuum or has little or no biological credibility.* We all take seriously small relative risks when there is a credible hypothesis in the background. Nobody disputes that the prevalence of boys at birth is higher than that of girls (an excess of 3%), that men have a 30% higher death rate compared with women of the same age, or that fatality in a car accident is higher when the car is smaller [emphasis added].[140]

The risks mentioned are similar in magnitude to (or smaller than) the risks associated with secondhand smoke.

The industry's strategy for dealing with secondhand smoke may be shifting again. In 2000, PM released a Web site that acknowledges that many scientific studies report a small increased risk in disease with secondhand smoke exposure, but also claims that "exposure levels outside the home are lower than regulators have generally assumed."[141]

These claims of inconsequential exposures are based on tobacco industry–funded studies of dubious accuracy that were carried out within the same construct as the GEP efforts and other efforts to subvert the scientific process. Indeed, the pilot studies for these exposure studies have been demonstrated in government proceedings to be unreliable.[47]

As greater understanding of the tobacco industry's subversive operations accumulates, scientists and policymakers face the question of whether or not to include the tobacco industry in their discourses. Pros and cons of publishing any material funded by the tobacco industry have been debated, and some journals and organizations have rules to exclude those who are funded by the tobacco industry.[142]

The World Health Organization's tobacco control effort is the most prominent global case to observe in the near future, as the WHO deals with both the scientific and policy-making worlds and has been targeted by the tobacco industry. The WHO recently published a special inquiry on the tobacco documents, which concluded that the tobacco industry views the WHO as one of its leading enemies and strategized to "contain, neutralise, reorient" WHO's tobacco control initiatives.[143] The WHO is also conducting hearings, which include the tobacco industry, for its international Framework Convention on Tobacco Control. (Uncannily similar to projects of the TASSC and to Junkscience.com, a Web site for Guest Choice Networks, which claims to represent more than 30 000 restaurant and tavern owners in promoting consumer choice, proclaims the WHO's Framework Convention as "Junk Science Goes Global."[144])

Publicly, the tobacco industry is now shifting to a campaign touting responsible corporate citizenship[145,146] and nominal efforts purportedly to discourage youth smoking prevention.[147] The industry's many past efforts—beginning with the "Frank Statement" advertisement and creation of the Tobacco Industry Research Committee in the United States in 1954[63(pp32–44)]—to publicly reinvent itself, while privately doing everything it can to protect itself from meaningful regulation and maximizing sales and profits, suggest that the WHO (and other government and scientific bodies) maintain an arm's-length relationship with the tobacco industry until it visibly reduces its aggressive efforts to promote tobacco use, whether to children or adults, worldwide.

Because the US Supreme Court is allowing judges more freedom to decide whether to admit or exclude scientific evidence,[148,149] the question of what work constitutes "junk science" or "sound science" comes to the forefront in discussions of the health effects of industry products and activities. Discussions of how to improve epidemiology should be ongoing, although there is continued debate as to the necessity for epidemiologic guidelines.[150,151] While every practicing scientist agrees that scientific work should be rigorously done, the scientific, public health, and regulatory communities need to be more aware that the "sound science" and "GEP" movement is not simply an effort from within the profession to improve the quality of scientific discourse. This movement reflects sophisticated public relations campaigns controlled by industry executives and lawyers to manipulate the scientific standards of proof for the corporate interests of their clients. ■

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Passive Smoking, Coronary Heart Disease, and Meta-Analysis

META-ANALYSIS — the formal combination of the research results from multiple studies — is widely used, but with little general understanding of its limitations and uncertainties. There is something quite appealing about collecting all the available research on some question and reducing it to a single figure or a single confidence interval. When properly used, this approach can be useful. However, there is broad evidence that the results of meta-analyses are often not very reliable. LeLorier et al.[1] have shown that many meta-analyses do not agree with the results of subsequent large, randomized trials, and there is little reason to believe that those trials are consistently wrong.

In a review published a few years ago[2] I cited five meta-analyses that produced conclusions that were questionable for a variety of reasons. These included lack of understanding on the part of the meta-analysts of the scientific subject in question or, conversely, lack of understanding on the part of the experts in the scientific subject of the procedure for meta-analysis; failure to consider a host of relevant covariates; and frank bias on the part of the meta-analysis team. Another common problem is lack of homogeneity. When an effect exists, its size may vary substantially from one population to another, such that no combined estimate can have much meaning. (For example, if the rate of some disease is 5 percent among men and 1 percent among women, does it make sense to find that the rate is 3 percent for a person of "average" sex?)

Finally, research studies are not all of high quality, and there is no good way to adjust meta-analyses for variations in quality. Some authors have prepared checklists that can be reduced to a quality score. Studies are commonly weighted according to their quality scores, but the practice is not universal, and even when formal scoring systems are used, poor studies are often weighted too heavily. If some reports are given a quality score of 95 or 100 (of a possible 100), does it make sense for a meta-analysis to include studies scored as 50 and give them 50 percent of the weight given to a nearly perfect study?

Meta-analysis is commonly designed as a series of operations. First, the problem must be stated in terms that can be studied (this sometimes is the hardest step). Second, all the available sources of potentially relevant data must be found and the reports collected. Third, each report is evaluated and an individual summary measure derived (for example, the incidence rate of a disease or an odds ratio). Fourth, the collection of summary measures is interpreted, and a single "best estimate" is derived. Finally, the findings of the meta-analysis are presented. Of these, the fourth step is the most controversial, and because of its limitations, it is sometimes omitted.

In this issue of the *Journal,* He et al.[3] report a meta-analysis of epidemiologic studies of the relation between coronary heart disease and passive smoking (also known as exposure to environmental tobacco smoke). With regard to this important subject, there is no reliable substitute for epidemiologic research, for several reasons: responses in animals may not be like those in humans, laboratory studies involving human subjects must necessarily be of short duration, and reports of clinical series are subject to a range of serious biases. Can meta-analysis of epidemiologic studies on this topic provide a more reliable conclusion than a thoughtful review of the usual type? There are reasons to think that it cannot.

The first reason is the quality of the data. He et al.[3] found an association between coronary heart disease and environmental tobacco smoke, but most studies of lung cancer and this risk factor have likewise reported a positive association, and those findings have been received with some skepticism because of concern about the quality of the data. Among the reasons for concern are a possible tendency of nonsmokers with lung cancer to look for some external reason (for instance, smoking by a spouse or coworker) for an otherwise inexplicable disease, inaccuracies in the reporting of exposure to environmental tobacco smoke, and reluctance to report a personal history of smoking. He et al. gave little consideration to such possible problems with the quality of the studies they analyzed. Surely not all those studies were perfect.

A second reason for concern is the procedure for meta-analysis itself. The published literature on some topics may reflect the greater likelihood of publication of positive results than of negative results. When study-to-study randomness is considered, the lack of publication of negative studies can sometimes be inferred by analyzing the probability distribution of the results of the studies that have been published. If only the positive part of the probability distribution is represented in the literature, it can be inferred that small negative studies may not have been reported. He et al.[3] examined this matter and obtained a P value that did not indicate statistical significance but that did not exclude the possibility of publication bias. The absence of proof of such bias

is not proof of its absence. Analysis of a total of 18 studies, as in this case, can hardly provide much statistical power to detect publication bias.

The authors do not comment on the remarkable uniformity of the findings of the 18 studies, despite the large variations in study design, methods, and populations. For example, if environmental tobacco smoke causes coronary heart disease, why are estimates of this effect from studies that include exposure in the workplace about the same as those from studies that do not? Figure 1 in the report by He et al. shows that study-by-study "best estimates" of the relative risk of coronary heart disease associated with environmental tobacco smoke ranged from slightly over 1.0 to about 2.2. This seems to be a very small range, considering the random variations present in the samples, most of which were small; the large differences in both the methods and the populations examined; the likelihood of confounding, for which there was no adjustment; and the failure to consider the "dosage" of environmental tobacco smoke. A great deal of uniformity among the results of independent studies of a particular phenomenon is not necessarily good: it can suggest consistency in bias rather than consistency in real effects.

Interpretation of Figure 2 in the article is difficult because the reported "linear trend" apparently included analysis of data from persons with zero exposure to environmental tobacco smoke. In view of the potential sources of bias noted above, and in view of the possibility that the never-exposed group had a disproportionally high percentage of persons from population segments generally more careful about health-related behavior (including some religious groups), these data would be more convincing if they showed a significant trend of higher risk with higher degrees of exposure, without including the never-exposed groups.

The authors compared the risk of coronary heart disease in exposed and nonexposed persons in terms of relative risks, but they did not defend their use of that statistical measure or show that it is compatible with their findings. This approach implies a multiplicative model (in which risk factors are multiplied rather than, say, added), but why should we expect a complex biologic relation to follow this type of model rather than a model that is linear, or otherwise not multiplicative? In general, mathematical convenience is a common but weak reason for studying relative risks (or odds ratios, their surrogates) or any other specific mathematical model.

Perhaps the most troubling aspect of these results is the size of the effect reported. Is an increase in the incidence of coronary heart disease of 25 percent associated with passive smoking compatible with the generally reported increase of about 75 percent among active smokers (a threefold difference)? I find it hard to understand how environmental tobacco smoke, which is far more dilute than actively inhaled smoke, could have an effect that is such a large fraction of the added risk of coronary heart disease among active smokers. Some estimates of the relative risk of lung cancer in association with environmental tobacco smoke are also about 25 percent, but the risk among active smokers is increased by about 1200 percent over that among nonsmokers. This finding leads to the more plausible conclusion that the added risk of lung cancer that is due to environmental tobacco smoke may be about 2 percent of the risk associated with active smoking.

The clear effects of active smoking on coronary heart disease give us good reason to think that passive smoking might have a similar but much smaller effect. The meta-analysis reported by He et al.[3] meets the accepted technical criteria for meta-analysis, but it suffers from problems inherent in the method, such as deficiencies in the data analyzed. Therefore, I regretfully conclude that we still do not know, with accuracy, how much or even whether exposure to environmental tobacco smoke increases the risk of coronary heart disease.

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MEDICAL EDUCATION AND MANAGED CARE

STUDENTS, residents, faculty members, and deans at medical schools in the United States don't like managed care. In this issue of the *Journal*,[1] Simon et al. report the results of a 1997 telephone survey of a national sample of medical students, residents, department chairs, directors of residency training, and deans to determine their views of managed care. Fee-for-service medicine was rated better than managed care in terms of the access of patients to care, minimizing ethical conflicts, the quality of the doctor–patient relationship, the continuity of care, care at the end of life, and care for patients with chronic illness. Medical school faculty members criticized managed care for decreasing the amount of time they

platin is unreasonable. The median duration of treatment in our study was 9 weeks (63 days).[5] The durations of treatment in the treatment groups were similar, suggesting that the survival benefit was due to the addition of cisplatin chemotherapy. In the study by Morris et al., a treatment time of less than 8 weeks was prescribed, and the actual median duration was 58 days.[7] Again, the cisplatin chemotherapy plus radiation therapy was superior to radiation therapy alone.

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Passive Smoking and Coronary Heart Disease

To the Editor: In their meta-analysis of passive smoking, He et al. (March 25 issue)[1] analyzed 10 cohort and 8 case–control studies and concluded that nonsmokers exposed to environmental tobacco smoke had an overall relative risk of coronary heart disease of 1.25. I want to point out several problems with their analysis. For the cohort studies they analyzed, each adjusted relative risk shown in Figure 1 of their article is higher than the corresponding crude relative risk that can be calculated from the data given in the figure. For example, in the study by Garland et al.[2] the crude relative risk can be calculated as 3.5, and the relative risk reported by He et al. is 14.9, whereas the adjusted relative risk was reported by Glantz and Parmley as 2.7.[3] However, the most dramatic difference occurs in the study by Steenland et al.[4] for which the crude relative risk is 0.54 and the relative risk reported by He et al. is 1.2.

It is often instructive to compare the crude relative risk with the adjusted relative risk to ascertain the influence of the adjustment. With use of the meta-analytic methods of He et al., the overall crude relative risk is 0.84 for the 10 cohort studies. Thus, the conclusion as to whether exposure to passive smoke is harmful or helpful appears to depend on an adjustment process that is often imprecise and ambiguous.

Interpretation of the case–control studies may be even more difficult. Because in a case–control study the relative risk cannot be calculated directly, the odds ratio is used as a surrogate when the disease is rare. However, if the disease is not rare in the particular group being studied (even if it is rare in the general population), then the odds ratio overestimates the actual relative risk.[5] This can yield an exaggerated effect. Furthermore, in a case–control study, what is actually estimated is the relative probability of exposure, given that a person has heart disease. Since heart disease has multiple causes, it is not logical to argue a relative probability (relative risk) of heart disease given that a person is exposed to a particular risk factor. Therefore, the case–control studies should be excluded from the meta-analysis, or at least the cohort and case–control studies should be analyzed separately.

Of course, these considerations would not be relevant if the reported effect of passive smoking were large. It is because the effect is so small that these issues must be taken into account in the final interpretation.

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To the Editor: He et al., in their Methods section, erroneously assume that the data presented by Steenland et al.[1] concern American Cancer Society Cancer Prevention studies I and II, when in fact they concern only study II. Because of this error, results from study I were not included in their meta-analysis, a serious omission in view of the large number of cases of heart disease and the lack of relation with passive smoking seen in that study.

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To the Editor: Bailar's editorial[1] on the article by He et al.[2] deserves rebuttal. Most of Bailar's concerns about

meta-analyses of passive smoking and coronary heart disease have been addressed elsewhere in the literature. Specifically, results in male and female patients are sufficiently homogeneous to allow their combination.[3,4] The various studies can be, and were, given meaningful quality scores.[3,4] The questions of misclassification of smoking status and exposure status have been adequately dealt with, as has publication bias.[3] Adjustment has been made for potential confounders,[3,4] and positive trends with dose were found for 16 of 22 studies without the inclusion of the nonexposed group.[4]

Bailar is also worried that the pooled relative risk of coronary heart disease associated with passive smoking is large as compared with the risk associated with active smoking. The ratio of excess risks, active to passive, is about (1.93−1)÷(1.24−1), or 3.9, when the risk for active smokers is measured against that for nonexposed persons who have never smoked. This is not unusual for an anatomical site that is not in direct contact with tobacco smoke and for which the dose–response curve is convex upward.[5] For comparison, the best study we have on breast cancer and active and passive smoking[6] found an active-to-passive ratio of excess risks of only (3.0−1)÷(2.3−1), or 1.6. Although the data are fewer, similar low ratios appear to hold for other noncontact cancer sites, such as the cervix, liver, and brain, and for lymphoma and leukemia. Relative risk ratios are low because so many of the carcinogens in environmental tobacco smoke that cause coronary heart disease and cancer are in the vapor phase[7]; they therefore are deposited more completely in the lung and are harder to clear than particle deposits. The toxins must be cleared into the body fluids, where they can circulate to distant sites, such as the heart or breast.

Bailar appears to prefer a "thoughtful review of the usual type."[1] If so, he should read the review by Kritz et al.,[8] which covers the same ground as the study by He et al.[2] and others,[3,4] but without the meta-analysis. Of course, Kritz et al. also conclude that environmental tobacco smoke causes coronary heart disease.

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To the Editor: Many readers would dispute Bailar's conclusion that "we still do not know . . . whether exposure to environmental tobacco smoke increases the risk of coronary artery disease." The evidence available to mid-1997 on this topic was reviewed by Australia's National Health and Medical Research Council (NHMRC).[1] The NHMRC considered 22 analyses from 16 studies; 17 of the 22 analyses indicated some increase in the risk of coronary events among nonsmokers with exposure to environmental tobacco smoke, and in 8 of them the results were statistically significant. Rather than undertake a quantitative meta-analysis, the NHMRC summarized the data in terms of a median relative risk and corresponding interquartile range. The median estimate of 1.24 (interquartile range, 1.02 to 1.62) is entirely consistent with the pooled estimate of 1.25 (95 percent confidence interval, 1.17 to 1.32) derived by He et al. and was supported by findings of excess risks of mortality from all causes in seven of eight prospective studies of passive smoking.

The report from the NHMRC also examined the relation between passive smoking and coronary heart disease in light of the criteria proposed by Hill[2] and concluded that "all the evidence put together is reasonably coherent."[1] Like Bailar, the NHMRC drew attention to the relatively large excess risk of coronary heart disease associated with passive smoking as compared with the risk attendant on active smoking, but it cited evidence that platelet function in nonsmokers is particularly sensitive to exposure to environmental tobacco smoke.[3]

Whatever the limitations of meta-analysis, the abundant evidence that passive smoking causes harm to health can no longer be ignored.

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To the Editor: In his editorial, Bailar uses several flawed arguments. His concern about reporting bias might be appropriately applied to the case–control studies, but not to the cohort studies (10 of the 18 studies analyzed). Moreover, when the two types of studies were analyzed separately by He et al., the conclusions were strikingly similar. The possibility of publication bias was also raised. This is often a valid criticism of meta-analyses, but it appears misdirected in this instance. Specifically, of the 18 studies reviewed, 7 found a significant association and 11 did not. If anything, the bias here is likely to be very small. In addition, random reporting errors, also mentioned by Bailar, are likely to attenuate and not spuriously strengthen these associations.

Bailar considers the range of relative risk of about 1.0 to 2.2 in He et al.'s study to be "very small." He believes that uniformity in results is "not necessarily good." Such comments are only his opinion, and not facts. Finally, Bailar criticizes the use of a "multiplicative model," but meta-analysis must use the models of the original studies and

may not choose others. Bailar does not show in any way that the particular model in this case produces a bias.

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To the Editor: Bailar questions whether a 25 percent increase in the incidence of coronary heart disease associated with passive smoking, as reported by He et al., is compatible with the generally reported increase of about 75 percent among active smokers. Bailar finds it more plausible that the added risk of lung cancer from passive smoking may be about 2 percent of the risk associated with active smoking. That view ignores the fact that the mechanisms causing lung cancer and coronary heart disease are different. Tobacco smoke induces lung cancer through chemical carcinogenesis, whereas none of the mechanisms of coronary heart disease resemble chemical carcinogenesis. These different underlying mechanisms may explain how environmental tobacco smoke causes a larger increase in the incidence of coronary heart disease than in the incidence of lung cancer.

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The authors reply:

To the Editor: Swanson's estimation of crude relative risks for the 10 prospective studies presented in our meta-analysis is erroneous because he used the number of persons rather than person-years of exposure as the denominator for his calculations. Contrary to his claim, there is not a large discrepancy between crude and adjusted relative-risk estimates.

Denson expresses concern because we excluded the American Cancer Society Cancer Prevention Study I from our meta-analysis. We did this because LeVois and Layard[1] failed to provide details of their analytic approach. Moreover, their findings in the data from the Cancer Prevention Study II conflict with Steenland et al.'s more rigorous assessment.[2]

In his editorial, Bailar criticizes both the methods and conclusions of our meta-analysis. We are surprised that he believes meta-analysis does not yield a more reliable conclusion than "a thoughtful review of the usual type," because it is generally considered to be the most objective means to gain an overview of evidence from different studies. This is especially true in the identification of a small increase in relative risk that may have important public health implications. Bailar suggests that the relation between passive smoking and coronary heart disease may reflect the desire of sick patients to identify a cause for their illness (recall bias), but this would not explain the findings of the 10 prospective studies in which exposure was assessed before the onset of disease. Bailar worries about the failure of journals to publish negative findings, but our analysis did not suggest this bias, and the inclusion of three unpublished studies did not change the estimate of relative risk.

Bailar asserts that the consistent pattern of association we observed in studies with different designs, methods, and populations may "suggest consistency in bias rather than consistency in real effects." Most epidemiologists believe that consistency suggests the presence of a causal association.

The relative risk (or odds ratio) is a widely used measure of association. Elsewhere, Bailar states that "findings must be expressed on a common scale (often as odds ratios)" in a meta-analysis.[3] Bailar's suggestion that dose–response relations be studied without the inclusion of an unexposed reference group is interesting but unconventional.

There are many potential mechanisms by which passive smoking may result in coronary heart disease, and they are different from those by which cigarette smoking may cause lung cancer. Why should we expect the same pattern of relative risk in association with active and passive smoking for lung cancer as we do for coronary heart disease?

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To the Editor: I am grateful to these correspondents for raising several issues that need discussion. However, their conclusions are mistaken. In my editorial, I did not deny that there is a relation between passive smoking and coronary heart disease, but I noted that the evidence presented to support a relation is not convincing. It is likely that such a relation exists, but more work will be needed to confirm it, and still more to estimate its strength with much precision.

We must examine evidence that seems to support a favored hypothesis with even more care than we would examine evidence against it. Single-minded dedication to a specific proposition may be useful once other work has clearly shown a need for action, but not before. Furthermore, a well-informed scientist can come up with a plausible explanation for almost any set of research findings. To describe a mechanism by which environmental tobacco smoke might increase coronary artery disease is not to show that it operates in the real world.

Exposure–response relations for toxic agents (excluding many carcinogens) are generally concave upward — that is, the effects of successively smaller exposures decrease more rapidly than the dose itself, and often something close to a threshold may be found at low doses. The levels of exposure to specific constituents of environmental tobacco smoke are not fully understood, but I do not know of any for which exposures among nonsmokers are as high as one third of those among smokers. This is further rea-

son for caution in concluding that an increase in risk induced by environmental tobacco smoke among nonsmokers is one third or more of the excess risk among smokers.

Other evils of environmental tobacco smoke are well known, and even without coronary artery disease there is strong reason to protect the nonsmoking public. I understand the urge to "pile it on," perhaps in the hope of generating stronger action sooner, and there may be reasons related to public health and public policy for taking action before the evidence is complete. Those reasons are not advanced by overstatement.

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Acute Myocardial Infarction after the Use of Sildenafil

To the Editor: A 70-year-old man came to his physician with acute myocardial infarction after self-administration of sildenafil (Viagra) and nitrates, a case highlighting a new trigger for acute myocardial infarction. He had a history of hypertension and hypercholesterolemia, and atypical chest pain had developed a few weeks previously. A thallium exercise test revealed neither angina nor evidence of ischemia at a heart rate of 146 beats per minute, and exercise capacity was normal for his age. Two weeks after the exercise test, another episode of chest pain occurred, [illegible] hours after he took sildenafil that had been provided by a friend. Fifteen minutes after the onset of chest pain, the patient took two sublingual nitroglycerin tablets given to him by his mother. His chest pain continued for eight hours despite the use of aspirin and acetaminophen. He then presented to his physician's office, where an electrocardiogram revealed new right bundle-branch block, Q waves in leads V_1 through V_4, and 1-to-2-mm elevation of the ST segment with upward sloping in leads V_2 through V_6, indicating recent anteroseptal myocardial infarction. Elevated serum troponin I and creatine kinase levels were found, confirming the diagnosis of acute myocardial infarction.

Emergency coronary angiography revealed 95 percent occlusion of the mid–left anterior descending artery and 60 percent occlusion of the posterior descending artery. An intracoronary stenting procedure of the left anterior descending artery was then performed without complications.

The use of sildenafil presents a risk of acute myocardial infarction in patients who have hypotension as a result of drug regimens (such as nitrates) or low blood volume. Sildenafil produces a transient reduction in blood pressure.[1,2] On the basis of his coronary angiogram, it is likely that this patient had preexisting coronary artery disease, despite the absence of perfusion defects on his exercise test. Thus, the use of sildenafil, in combination with nitroglycerin, may have led to a critical lowering of blood pressure that exacerbated his ischemia and resulted in acute myocardial infarction.

The Food and Drug Administration has reported 128 nonviolent deaths in the United States among men who received prescriptions for sildenafil. Of these deaths, 34 percent occurred within four or five hours after sildenafil was used, and approximately 70 percent of the men who died had risk factors for cardiovascular or cerebrovascular disease.[3]

Sildenafil is widely available through the Internet without contact with a physician and through unregulated, illicit trade. Patients who are reluctant to reveal erectile dysfunction to their physicians can easily self-administer the drug. Therefore, men should be warned of the risks of taking sildenafil and nitrates concurrently if they have received a prescription for only one or the other. Also, online medical care must be fully investigated, and guidelines should be established regarding the prescription of drugs over the Internet.

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Subaortic Obstruction after Sildenafil in a Patient with Hypertrophic Cardiomyopathy

To the Editor: Recently, the American College of Cardiology and the American Heart Association released an expert consensus document on the use of sildenafil (Viagra) in patients with cardiovascular disease.[1] The recommendations focused on patients with coronary artery disease, but little is known about the effect of sildenafil on patients with other cardiac disorders.

We report on a 54-year-old man with hypertrophic cardiomyopathy. Echocardiography performed in 1994 showed no gradient at rest and only mild obstruction of the aortic outflow tract after inhalation of amyl nitrite. The patient was treated with 40 mg of verapamil twice daily and was asymptomatic. He also had erectile dysfunction and was given a prescription for sildenafil. After taking his first pill, he felt lightheaded and had the perception of an irregular pulse. He had an episode of near syncope two hours after taking sildenafil and came to the emergency room of a local hospital.

On admission, his symptoms had resolved, and the house officer noted a heart rate of 88 beats per minute, blood pressure of 135/70 mm Hg, and a harsh grade 3/6 systolic murmur. The electrocardiogram was noteworthy only for occasional isolated ventricular premature beats. The patient was referred to a cardiologist, and 24-hour Holter monitoring was performed the next day.

Echocardiography was performed while the patient was receiving 120 mg of verapamil twice daily (the dosage had been increased after his visit to the emergency room), two hours after the administration of a single dose of sildenafil.