Public health

Tobacco industry efforts subverting International Agency for Research on Cancer's second-hand smoke study

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Scientific reports on second-hand smoke have stimulated legislation on clean indoor air in the USA, but less so in Europe. Recently, the largest European study, by the International Agency for Research on Cancer (IARC), demonstrated a 16% increase in the point estimate of risk in lung cancer for nonsmokers, a result consistent with earlier studies. However, the study was described by newspapers and the tobacco industry as demonstrating no increase in risk. To understand the tobacco industry's strategy on the IARC study we analysed industry documents released in US litigation and interviewed IARC investigators. The Philip Morris tobacco company feared that the study (and a possible IARC monograph on second-hand smoke) would lead to increased restrictions in Europe so they spearheaded an inter-industry, three-prong strategy to subvert IARC's work. The scientific strategy attempted to undercut IARC's research and to develop industry-directed research to counter the anticipated findings. The communications strategy planned to shape opinion by manipulating the media and the public. The government strategy sought to prevent increased smoking restrictions. The IARC study cost $2 million over ten years; Philip Morris planned to spend $2 million in one year alone and up to $4 million on research. The documents and interviews suggest that the tobacco industry continues to conduct a sophisticated campaign against conclusions that second-hand smoke causes lung cancer and other diseases, subverting normal scientific processes.

In 1978, a confidential study for the US Tobacco Institute concluded that public concern about second-hand smoke, also referred to as environmental tobacco smoke (ETS) and "passive smoking", was "the most dangerous threat to the viability of the tobacco industry that has yet occurred".[1] The industry's concern was borne out as three landmark reports concluded that second-hand smoke did cause lung cancer and other diseases,[2–4] leading to legislation on smoke-free environments in the USA.[5,6] Few such studies had been done in Europe,[7] and European countries have been slower to implement smoke-free measures.[8]

This European situation was poised for change when the International Agency for Research on Cancer (IARC), a research branch of the World Health Organization (WHO), undertook, from 1988, the largest European epidemiological study on lung cancer and second-hand smoke.[7] Consistent with earlier studies (panel 1),[2–4,9–12] IARC[7] observed a 16% increase in risk for nonsmoking spouses of smokers (95% CI 0·93–1·44), and a 17% increase for nonsmokers' exposure in the workplace (95% CI 0·94–1·45).[7] The study was too small to detect, with 95% confidence, an increase in risk of around 16%, the sample size having been selected to have enough power to detect a relative risk of 1·3. The October, 1998 issue of the *Journal of the National Cancer Institute* published the study with an editorial concluding that the new study data, plus previous evidence, presented "an inescapable scientific conclusion . . . that ETS is a low-level lung carcinogen".[13]

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This journal publication was not, however, the first the public had heard of the IARC study. On March 8, 1998, the London *Sunday Telegraph* reported that WHO was withholding a study that not only failed to show that passive smoking caused lung cancer but also might even demonstrate a protective effect.[14] British American Tobacco (BAT), which had held private media briefings[15] to ensure "balanced" coverage of the forthcoming study, was suspected to have fuelled the story.[16] BAT responded that it knew of IARC's preliminary results from earlier conferences and IARC's biennial report,[17] which had reported the study's progress by providing results but no conclusion. Despite press releases from WHO[18] and

Panel 1: **IARC and major summaries evaluating risk of lung cancer in passive smokers**

Organisation	Year	Country	Relative risk (and 95% CI)
IARC[7]	1998	Europe†	1·16 (spousal) (0·93–1·44) 1·17 (workplace) (0·94–1·45)
Scientific Committee on Tobacco and Health[9]	1998	UK	1·20–1·30(N/A)
California Environmental Protection Agency[10]	1997	USA	1·20 (N/A)
National Health and Medical Research Council[11]	1997	Australia	1·32 (1·10–1·69)
US EPA[4]	1992	USA	1·19 (1·01–1·39)
National Research Council[3]	1986	USA	1·34 (1·18–1·53)
Surgeon General[2]	1986	USA	1·53 (N/A)

*Confidence intervals are two-tailed 95%, except US EPA which is one-tailed 95% (two tailed 90%).
†Seven European countries.
N/A=not applicable.

Glossary: **Abbreviations**

BAT	British American Tobacco
CIAR	Tobacco industry's Center for Indoor Air Research
EPA	US Environmental Protection Agency
ESEF	European Science and Environment Forum
ETS	Environmental tobacco smoke
GEP	Good Epidemiological Practices
IARC	International Agency for Cancer Research, Lyon, France
IEMC	International ETS Management Committee
NHANES	National Health and Nutrition Examination Survey
PM	Philip Morris tobacco company
PMCS	Philip Morris Corporate Services
RJR	R J Reynolds tobacco company
TASSC	The Advancement of Sound Science Coalition
WHO	World Health Organization
WRA	PM's Worldwide Regulatory Affairs

IARC[19] noting that the study still awaited peer-review publication and calling the *Sunday Telegraph* interpretation of statistical significance "false and misleading",[19] the allegations quickly spread around the world, from Australia[20] to Zimbabwe.[21]

To understand the industry's strategy towards the IARC study, we examined previously confidential tobacco industry documents that reveal how Philip Morris (PM) spearheaded an extensive inter-industry effort to stop, affect the wording of, delay, and counteract the IARC study.

Data sources

The tobacco industry documents are among 32 million pages made public as part of the settlement of the 1998 legal case of State of Minnesota and Blue Cross/Blue Shield of Minnesota *vs* Philip Morris Inc, et al. These documents are deposited in Minneapolis and each tobacco company has a searchable website archive. Search terms included IARC, IEMC, WRA, GEP, TASSC, NHANES (see glossary), "confounders," and the names of key players. Most of the documents referred to here are on PM's website.* We also asked IARC investigators (see acknowledgments) to describe their experience with the industry and to confirm information about themselves reported in certain documents.

Initial fears and organisation

The 1992 US Environmental Protection Agency (EPA) report[4] provided a comprehensive evaluation of second-hand smoke's health effects that stimulated clean indoor air laws in the USA.[6] As similar legislation increased worldwide, PM began monitoring research internationally to prevent further restrictions. By 1993, Philip Morris Corporate Services in Brussels expressed concern that the IARC study would become "Europe's EPA". PM also feared that IARC would produce, for tobacco smoke, one of its authoritative monographs reviewing and classifying carcinogens. The global respect for IARC's work led the chairman of the public relations firm Burson-Marsteller to advise PM:

"Let's assume for a moment that IARC 'confirms' EPA that ETS is a probable low risk carcinogen. There is no way we can convince the world that they are wrong. The critical regulatory issues is what the world will do about [it]".

PM decided on a proactive response rather than simply reacting after publication. The 1993 "IARC Objectives" were to:

" • Delay the progress and/or release of the study
• Affect the wording of its conclusions and official statement of results
• Neutralize possible negative results of the study, particularly as a regulatory tool
• Counteract the potential impact of the study on government policy, public opinion, and actions by private employers and proprietors"

These objectives formulated the beginnings of a coordinated strategy for scientific, communications, and government relations issues related to IARC. R W Murray (chairman of PM Companies) was presented with these details in 1993, and PM's board of directors was informed of the proactive measures to deal with the study in 1995.

By September, 1993, PM had established a high-level, multidisciplinary task force with representatives from legal, research and development, science and technology, and corporate services departments (figure 1). The initial leader was Matthew Winokur of PM's Worldwide Regulatory Affairs (WRA), a department created in July, 1993 for "the strategy and coordination of activities relating to environmental tobacco smoke and the social acceptability of smoking". WRA's 1994 budget was $66·1 million, with $2 million earmarked for the IARC plans. The IARC study is estimated to have cost $1·5–3·0 million over ten years.

PM also organised the industry worldwide, as Winokur (chair, PM IARC Task Force) reported on Jan 17, 1994: "PM initiated and chairs an industry-wide task force to manage both the IARC monitoring and scientific intelligence gathering process and the development of a global communications/government relations plan to address [the] impact of the [IARC] study". Besides PM, the group included R J Reynolds (USA), Rothmans (UK), Imperial (UK), BAT (British American Tobacco), and Reemtsma (Germany). The group's objective was to "coordinate plans and resources among the companies and in conjunction with National Manufacturers Associations". This industry-wide task force is the International ETS Management Committee (IEMC).

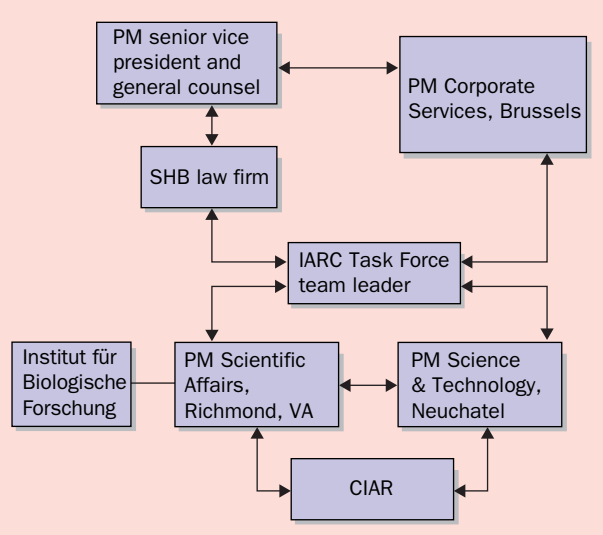

Figure 1: **Philip Morris' IARC Task Force structure**
CIAR, responsible for producing studies to offset the IARC study, would communicate with PM Europe Science and Technology and PM USA Scientific Affairs. These scientific departments would report to PM's IARC Task Force team leader, who would communicate with the legal resources, PM Corporate Services in Brussels, and PM senior management.
Source=adapted from Bates 2023897132 at www.pmdocs.com

*www.pmdocs.com; on this website the documents are identified by "Bates number" and *Lancet* readers will find a list of the same documents used in this article attached to the version freely available on www.lancet.com. Some non-PM websources are also referenced.

Panel 2: **Philip Morris' approach on IARC methodology**

"1 To ascertain a range of information on the study objectives, status, parameters, predisposition of IARC team/collaborators, timing, likely results, etc.

2 To brief the country collaborators and the IARC team on the industry perspective on ETS and to make them mindful of the weaknesses of epidemiology that rely on survey questionnaires. We recognise that there is [sic] down side to this in that our input could help them improve the quality of the study. However, it is considered that the benefits outweigh the risks if the collaborators can be persuaded that the IARC methodology is inadequate (it does not take into account confounders or measure actual exposure leading to misclassification)."

National tobacco monopolies were also recruited. France's Seita financially contributed to the IEMC-funded research, Japan Tobacco had a response plan to the IARC study by 1997, and Indian Tobacco Company and Korean Ginseng and Tobacco Research Institute were kept informed of the IEMC's Asia-specific IARC preparations.

Scientific strategy

IARC study

In early 1993 PM had asked Covington and Burling "through their consultants, to try and uncover as much information as possible on the current status, etc, of the IARC study" and requested "all those who receive a copy of this memo to use whatever internal and external resources they may have or may know about to help us get more information on the IARC study as quickly as possible". Covington and Burling, the industry's Washington, DC based law firm, had established a network of sympathetic scientific consultants in Europe a few years before, known as "Project Whitecoat", to help the industry "produce research or stimulate controversy". These consultants systematically approached the IARC investigators, reporting back to the tobacco industry on the study's design, questionnaire, progress and authors' scientific viewpoints. Such efforts allowed PM to compile a picture of the IARC study and to begin assessing the study design for weaknesses.

Unaware of PM's coordinated plans, IARC investigators were nonetheless cautious about discussing the results with industry representatives, but the consultants did not always disclose their industry affiliations. For example, PM obtained its most detailed intelligence about IARC in 1993–94 from the Italian consulting firm SCR Associati. One anonymous report described a meeting between the IARC investigators that recorded specific confidential results, including expected relative risks from different centres participating in the IARC study. The name of the consultant is not disclosed. The IARC investigators were not aware of a consultant's presence. SCR Associati's source of information in additional consultant reports about IARC was the late Giuseppe Lojacono (former professor of health economics, University of Perugia). Lojacono visited IARC several times in his role as a journal editor and inquired about the IARC study, without disclosing his relationship with the tobacco industry.

PM's objectives in contacting the investigators went beyond tracking the study's progress; a PMCS Brussels report describes its objectives (panel 2). PM was not contacting the investigators to help them improve the study but to promote the industry's perspective about the study's inadequacies.

Panel 3: **Philip Morris' 1994 plan to influence potential IARC monograph**

"1 Encourage re-evaluation of IARC monograph priorities
Budgetary constraints of funders (US Cancer Institute, WHO, EU).
Funders have been identified. Possibility for influence agreed as extremely limited.

Competing interests (within IARC) for other monographs
Contact envisaged direct with IARC via S&T [PM Science & Technology], C&B [Covington & Burling law firm] and SHB [Shook, Hardy, and Bacon law firm] consultants + CIAR.

2 Encourage balanced perspectives among experts in IARC Monograph Working Group
It is expected that invitations will be issued by IARC to both [Peter] Lee [industry consultant] and a SHB consultant.
Efforts are ongoing to encourage IARC invitations to other "objective" scientists by encouraging them to be vocal on the issue now . . .

3 Try to obtain observer status in IARC Monograph Working Group
Coffee precedent. Procedure to get observer status known.
Need to identify best industry representative(s)."

The executive director of the industry's Center for Indoor Air Research (CIAR) visited the IARC head investigators, who did not understand at the time that CIAR was funded by the tobacco companies. Winokur listed ideas on how to use CIAR to engage IARC: assisting IARC with future studies, encouraging IARC to include an industry consultant in designing analysis protocols, recruiting IARC investigators for CIAR-sponsored studies, and granting the senior IARC co-head-investigator funding or an advisory board position. IARC decided not to collaborate with CIAR. The industry did try to recruit individual investigators for a CIAR-sponsored study and one IARC-affiliated investigator did undertake a CIAR-funded study.

IARC monograph

In 1994, PM examined its options in influencing the outcome of a potential IARC monograph reviewing the health effects of second-hand smoke (panel 3).

If PM could not shelve the monograph outright by redirecting financial or institutional priorities it would try to participate in the process and produce a "balanced perspective". The inquiry into redirecting IARC's priorities extended to the new IARC director, who, PM anticipated, would "be dealing with a strangled budget". To its disappointment, PM later reported that the new IARC director was a "'fervent antismoker' who believes that 'passive smoking is more dangerous than active smoking'". Regarding the memorandum's reference to the industry's "balanced perspective", the industry has sponsored and promoted "special reviewed" (not peer-reviewed) research projects awarded by industry executives,[22] review articles,[23] and symposium publications[24,25] that generally conclude that second-hand smoke is not harmful. The reference to a "coffee precedent" refers to the preparation of an earlier IARC monograph, when Covington and Burling's consultants "were able to give General Foods [a division of Philip Morris] considerable information about IARC's evaluation of coffee as a possible risk factor for cancer".

Anticipating the IARC study and monograph , IEMC funded research "to expose the weakness of epidemiology" through CIAR. PM commissioned two types of study in the same countries in which IARC

Panel 4: **Philip Morris' communication stratey**

"Develop a communications programme to build appropriate public/policy climate in advance of the study results (PMCS, S&T, Legal).
Develop a contingency plan, should the preliminary results be leaked.
Assemble a crisis communications team/plan to manage the impact of the release of the study . . .
Evaluate the pros and cons of conducting journalist briefings prior to the release of the study.
Prepare pre/post public and leadership opinion surveys to evaluate the impact of the findings on public attitudes towards ETS and the need for smoking restrictions.
Develop a programme to generate support for 'junk science' and education on use and abuse of epidemiology, possibly through a coalition on bad science . . .
Develop a communications programme to mute/neutralise smoking bans/excessive restrictions . . ."

conducted its study and projected the cost at $4 million. The CIAR studies were to be finished before publication of the IARC study. PM sought "to develop means of providing IARC with relevant data so they will either consider it in their report [monograph], or if they don't, we will be in a position to ask them why".

The first type of study monitored nonsmokers' second-hand smoke exposure using personal air samples. Pilot studies were done by the US Oak Ridge National Laboratory[26,27] and UK Hazleton Laboratory;[28] Hazleton subsequently did studies in the same countries as IARC,[29–36] as well as in Asia and Latin America. Despite the reluctance of Hazleton's parent company, PM was eager to promote an interpretation of the studies' findings; later, the Aug 16, 1998, *Sunday Telegraph* reported that the studies demonstrated that "real-life levels" of second-hand smoke probably do not cause fatal diseases.[37] The pilot studies were shown to be unreliable sources of data on second-hand smoke exposure at the US National Toxicology Program;[38] results for salivary cotinine (a nicotine metabolite)[39] were far below what was expected for the reported air nicotine levels. The industry's prominent role in collecting the data may account for this result. RJR and its marketing research firm conducted all of the US study's operations, with the author simply analysing industry-provided data;[40] Rothmans drafted Hazleton's protocols and questionnaires for the European studies, which would also use the industry's second-hand smoke personal exposure monitors.

The second type of study analysed the nonsmoking population for confounding factors other than second-hand smoke exposure that might explain a risk for cancer. Genevieve Matanoski and her colleagues' analysis of a US nutritional survey was funded by CIAR.[41] PM also planned to analyse similar large databases in Japan, Hungary, Germany, UK, Sweden, and Switzerland. PM also commissioned confounder studies from industry consultant Ragnar Rylander (University of Gothenburg)[42,43] and worked with the German Verband (similar to the industry's US Council for Tobacco Research) and the GESOMED research institute. As of 1999, an IARC investigator (Francesco Forastiere) was also conducting a CIAR-funded confounder study. Matanoski and Forastiere both acknowledged CIAR funding.

Communications strategy

PM planned a variety of programmes to deliver and reinforce the industry's perspective on second-hand smoke, described in the September, 1993 "Action Plan" (panel 4).

The industry implemented these programmes before the IARC study's release. Besides the programmes that were internally conducted, PM used third-party vehicles that recruited other participants and funders and expanded its "sound science" discussion to issues beyond second-hand smoke, masking the industry's role as the initiator or sponsor of these programmes.

From 1993 to 1994, PM and public relations firm APCO Associates worked to launch The Advancement of Sound Science Coalition (TASSC), a "grassroots" organisation advocating "sound science" in policy decision making. PM wanted a similar organisation in Europe at the end of 1994, with potentially sympathetic European scientists invited to a conference hosted by TASSC. However, Burson-Marsteller research indicated that potential European members wanted independence from any corporate sponsors; two people specifically mentioned PM as typical of questionable corporate sponsors. It appears that the outcome was the European Science and Environment Forum (ESEF), established in 1996,[44] whose executive director sought funding from the tobacco companies. In December, 1997, ESEF and TASSC issued a joint press statement, in which both organisations have identical descriptions.[45] ESEF now states[46] that its funding only comes from sales of its working papers, one of which criticises IARC and the evidence on second-hand smoke. ESEF's medical demographer, Lorraine Mooney, published a *Wall Street Journal Europe* opinion piece stating that the IARC study's possibly "trivial or nonexistent" true risk ratio demonstrated the overstated health risks of second-hand smoke.[47]

Continuing the "sound science" theme, PM expanded the promotion of "Good Epidemiology Practices" (GEP), a guideline standardising the conduct of epidemiological research. The Chemical Manufacturers Association had originated GEP in 1991 and the idea was being pushed in Europe by chemical companies. However, PM found those guidelines inadequate, as PM's Thomas Borelli commented: " . . . It lacks teeth and as written it does not have enough meat to help us on ETS. However setting up our own standards is a good project for us". It would be "good offensive strategy" for their consultants to be "out there trying to fix epidemiology instead of being critical all the time".

GEP was "urgently needed" to challenge the methodology of the IARC study and monograph review. PM drafted revised guidelines, covering IARC, for endorsement by a sound science coalition and planned a GEP seminar with members of European government bodies interacting with selected epidemiologists, screened out for anti-tobacco views. A European Council resolution on GEP was drafted by John Rupp of Covington and Burling. Seminars on good risk assessment and GEP were conducted by PM-sponsored Federal Focus Inc in the USA and UK,[48] industry consultant Myron Weinberg's The Weinberg Group in Europe, and CIAR in China.

The industry sought to manage and monitor the public's perception of the IARC study's results. European sentiment towards smoking restrictions was not reflected in legislative action: a 1989 PM survey in ten European countries concluded that "both smokers and non-smokers in Europe desire more rules in the future against smoking

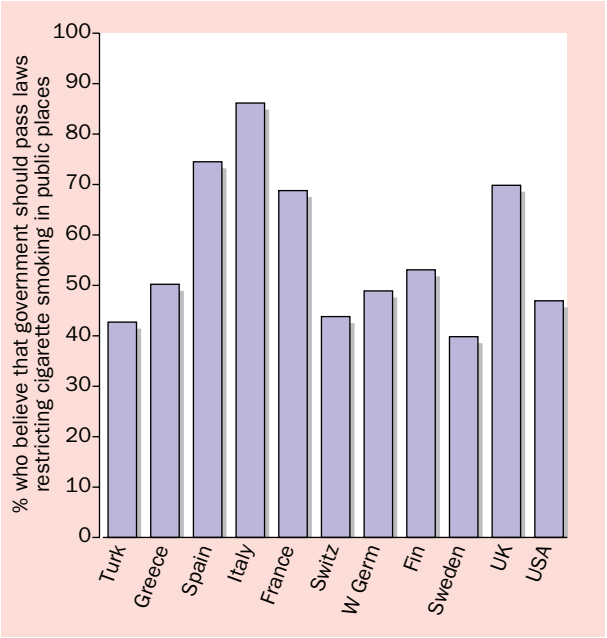

Figure 2: **Results of large multinational survey, conducted by PM International, of public opinion on regulation of smoking**
1989 survey in 10 European countries with a random sample representative of each population using 1000 smokers and 1000 nonsmokers, in each country.
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in public places" and that Europeans are less opposed to government involvement with smoking than Americans (figure 2). Public relations firm Burson-Marsteller wrote a 13 page "Preparedness plans for the announcement of the IARC study", and organised IEMC members into three teams for a coordinated interindustry response, to be delivered within 48 hours, to IARC's findings, and PM management held "IARC simulation" response exercises.

PM realised that the tobacco industry had little credibility in Europe, and it turned to the media to promote its messages. PM had even considered producing its own journal to critique "the objective validity of statements claimed to be scientific—and therefore their technological or policy usefulness". BAT instigated the March, 1998, press articles about the IARC study. A comprehensive press package included a prerecorded interview with BAT, background material on IARC and statistical results of second-hand smoke studies, and surveys of irritating behaviours. Winokur reported that the "publicity generated by BAT" started with the March, 1998, *Sunday Telegraph* story and continued with promotions in the USA, Australia, Brazil, and other markets. BAT Bangladesh sent the *Sunday Telegraph* articles to a Bangladesh newspaper that refuses cigarette advertisements.[49] Winokur noted that the timing of the *Sunday Telegraph* story seems to have been designed to precede the release of the UK's Scientific Committee on Tobacco and Health report[9] on passive smoking three days later.

Government relations strategy

In September, 1993, PM planned to develop a lobbying plan before and after the IARC study's release. PM sought "key international government influence points" in the IARC donor countries for "generating pressure for reorientation/reprioritisation of IARC priorities/budget allocations", and planned to lobby regulatory bodies and secure preemptive legislation against smoking restrictions. In 1994, PM developed a "briefing book" about the IARC study for the industry's messengers, allies, and government contacts to provide a standardised resource to support PM's plans. The table of contents indicates that the book assesses possible bias by the investigators, criticises the study design, questions the role of epidemiology as a basis for policy, and drafts arguments for sympathetic allies and industries.

Besides the industry's traditional concept of lobbying, the GEP programme was to become a lobbying tool, presumably to convince the EU to adopt a standard that would discredit the study. Indeed, the Commission of the EU sponsored the Weinberg-organised seminar, which had "the valuable concept of administrators being moderators, and hence, the target of the expert presentations in breakout sessions". These moderators included representatives from the EU's Directorates General V (Employment, Industrial Relations, and Social Affairs) and XII (Science, Research, and Development), the UK's Environmental Agency, and Sweden's EPA. PM planned to commit $220 000 to repeat the conference in Asia with the Association of Southeast Asian Nations.

The industry now cites the IARC study to government and regulatory bodies as evidence that second-hand smoke does not cause cancer, contrary to IARC's conclusions,[7] or that it has numerous flaws. Examples include Imperial Tobacco's (a Canadian BAT subsidiary) published stance for legislators about smoking-related issues,[50] the Tobacco Institute submission about a tobacco bill to the South African Parliament's Portfolio Committee on Health,[51] and PM's submission and testimony to the US National Toxicology Program review of second-hand smoke.

Discussion

The massive effort launched across the tobacco industry against one scientific study is remarkable. Whereas over ten years (1988–98) the IARC study is estimated to have cost $1·5–3·0 million, PM alone budgeted at least $2 million for "IARC" plans for just one year (1994) and proposed $4 million for studies to help discredit IARC's work. The elaborate plans were developed by PM's top management, implemented by an elite task force, and designed to coordinate the international tobacco industry. The complex plan relied on third-party vehicles that did not reveal the extent of the industry's efforts to shape the scientific, communications, and government relations issues of secondhand smoke on a worldwide basis. Such long-term programmes, from scientific consultants to "sound science" coalitions to GEP seminars, were instituted to influence the scientific basis of policymaking and public perception on second-hand smoke more in favour of the industry. BAT's March, 1998, media event represented only the first public manifestation of the industry's effort. BAT took advantage of IARC publishing the study's results without an accompanying conclusion in its biennial progress report, and timed its efforts to undermine the credibility of the UK Scientific Committee on Tobacco and Health report on second-hand smoke, which was released a few days later.

BAT's media misrepresentation was not the first time the industry misrepresented a second-hand smoke study's results as showing no risk. In 1981, Lawrence Garfinkel

of the American Cancer Society published a paper[52] which, like the IARC study, reported an increase in risk (relative risk=1·27) that did not reach statistical significance (95% CI, 0·85–1·89). Garfinkel noted this failure might have been related to methodological problems. The US Tobacco Institute ran advertisements in major US newspapers and magazines claiming that the Garfinkel study demonstrated an "insignificant"[43,53,54] and "very little, if any" effect[55] on lung cancer and nonsmokers. Finally, three years later, in 1984, Garfinkel protested in a letter to the *New York Times* that the industry had taken his work out of context and distorted the results.[55] After the Tobacco Institute of Australia ran a similar advertisement in 1986, the Australian Federation of Consumer Organisations successfully sued the Tobacco Institute of Australia on the grounds that the advertisement was false and misleading.[56]

The IARC and Garfinkel examples demonstrate how the tobacco industry has been trying to shape the scientific debate on the statistical interpretation of second-hand smoke studies. The industry imposes a one-sided interpretation of confidence intervals, focusing the entire discussion on whether the lower bound of the 95% CI for a relative risk includes 1. By definition, if the lower bound exceeds 1, then the risk is statistically significantly raised (with p=0·05). Whether or not there is anything magic about 95%, the true risk is equally likely to be anywhere inside the 95% CI, including values above the point estimate. In environmental and health and safety regulation, it is common to take the health-protective approach of basing public policy on the upper 95% confidence limit (1·44 and 1·45 for the IARC study[7]). The industry's discussions of the risks of passive smoking ignore the upper end of the confidence interval.

The IARC study's results did not reach statistical significance, and the IARC investigators noted that this was due to the study's low power. The IARC study was originally designed to have a statistical power of 80% to detect a relative risk of 1·3,[7] rather than a more realistic expected risk of around 1·2. Detecting this lower risk with 95% confidence would have required a larger sample size than the study used (because it was powered based on the higher presumed risk of 1·3). Hence, despite a point estimate above 1 for the risk in the study, this low power produced a wide confidence interval, too wide for statistical significance. The industry has represented the fact that the increase in risk observed did not reach statistical significance as indicating that the study did not find any increased risk.

The IARC study may, in fact, have underestimated the true relative risk of lung cancer associated with second-hand smoke. An industry statistical criticism, given much consideration by IARC and others, relates to the misclassification of smokers as nonsmokers. Such a misclassification error would incorrectly raise the numerator in the risk ratio because active smoking increases the risk of lung cancer. This error, however, has been repeatedly shown to be small,[4,57–59] including in the IARC report itself.[7] In contrast, another misclassification error, never mentioned by the industry, arises if people in the "unexposed" group are actually exposed to background second-hand smoke. This error biases results towards the null, leading to systematic underestimates of the effect of second-hand smoke. Repace, for example, estimated the effects of background exposure to secondhand smoke and found that properly correcting the Garfinkel study[52] for background levels increases the point estimate of the relative risk from 1·2 to 1·7.[60] The study validating the IARC study's questionnaire included results suggesting that women are exposed to a background level of secondhand smoke not reflected in the questionnaire.[61] The IARC lung cancer study[7] only adjusted for the industry's form of misclassification bias in the relative risk ratio's numerator and did not similarly adjust the denominator. The true point estimates of risk of lung cancer in the IARC study may very well be above the reported 1·16 and 1·17.

Scientists and policy makers need to understand that they function in an environment that is heavily influenced by covert tobacco industry efforts to subvert the normal decision-making processes. The industry has in the past submitted material to major scientific evaluations similar to the potential IARC monograph in New Zealand,[62] USA,[63] Australia,[11] and UK,[64,65] when these countries were evaluating the health effects of second-hand smoke.[4,9,11,66] The industry has filed lawsuits over scientific decisions to exclude this material.[11,67,68] However, each report's conclusions that second-hand smoke causes lung cancer and other diseases remains unchanged.

Contrary to the tobacco industry's fears, IARC has not yet decided to prepare a monograph on the health effects of second-hand smoke. Public attention has been focused on lung cancer, but it is important to remember that heart disease, not lung cancer, kills most passive smokers. Moreover, second-hand smoke's health effects range from asthma in children to sudden infant death syndrome, with recent research suggesting breast cancer as another possible health effect.[69] The strenuous effort mounted by the industry to subvert the IARC study and prevent an IARC monograph is probably the most compelling justification for IARC to prepare such a publication that considers not just lung cancer but all the diseases that second-hand smoke causes.

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References

1 Roper Organization. A study of public attitudes toward cigarette smoking and the tobacco industry in 1978, vol I. New York: Roper Organization, 1978.
2 US Department of Health and Human Services. The health consequences of involuntary smoking: report of the Surgeon General (DHHS Pub No (PHS) 87-8398). Washington, DC: DHHS, 1986.
3 National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: NRC, 1986.
4 US Environmental Protection Agency. Respiratory health effects of passive smoking: lung cancer and other disorders. Washington, DC: EPA, 1992.
5 Manley M, Pierce J, Gilpin E, Rosbrook B, Berry C, Wun L. Impact of the American Stop Smoking Intervention Study on cigarette consumption. *Tobacco Control* 1997; **6** (suppl 2):S12–16.
6 Glantz S. Back to basics: getting smoke-free workplaces back on track. *Tobacco Control* 1997; **6:** 164–66.
7 Boffetta P, Agudo A, Ahrens W, et al. Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. *J Natl Cancer Inst* 1998; **90:** 1440–50.
8 Chapman S, Bower H, Macready N, et al. Bans on smoking in public become more commonplace. *BMJ* 1998; **316:** 727–30.
9 Scientific Committee on Tobacco and Health. Report of the Scientific Committee on Tobacco and Health. London: Department of Health, 1998 (www.official-documents.co.uk/document/doh/tobacco).
10 California Environmental Protection Agency. Health effects of exposure to environmental tobacco smoke. Sacramento: California EPA, 1997.

11 National Health and Medical Research Council. The health effects of passive smoking. Canberra: Australian Government Publishing Service, 1997.
12 National Health and Medical Research Council. Effects of passive smoking on health. Canberra: Australian Government Publishing Service, 1986.
13 Blot W, McLaughlin JK. Passive smoking and lung cancer risk: what is the story now? *J Natl Cancer Inst* 1998; **90:** 1416–17.
14 Macdonald V. Passive smoking doesn't cause cancer—official. *Sunday Telegraph* 1998, March 8.
15 Sweet M. Tobacco companies try to sow seeds of doubt. *Sydney Morning Herald* 1998, Feb 3.
16 Simpson D. BAT attacks. *Tobacco Control* 1998; **7:** 119–20.
17 Proctor C. BAT has not tried to discredit data on passive smoking. *BMJ* 1998; **317:** 349.
18 World Health Organization. Passive smoking does cause lung cancer: do not let them fool you. Geneva: WHO, 1998.
19 International Agency for Research on Cancer. Passive smoking and lung cancer in Europe. Lyon: IARC, 1998.
20 Le Grand C. Anti-smokers blown away by study. *Australian* 1998, March 10.
21 WHO rejects smoking link with lung cancer. *Zimbabwe Independent* 1998, Oct 23.
22 Barnes D, Bero L. Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research. *J Health Politics Policy Law* 1996; **21:** 515–42.
23 Barnes D, Bero L. Why review articles on the health effects of passive smoking reach different conclusion. *JAMA* 1998; **279:** 1566–70.
24 Bero L, Galbraith A, Rennie D. Sponsored symposia on environmental tobacco smoke. *JAMA* 1994; **271:** 612–17.
25 Barnes D, Bero L. Scientific quality of original research articles on environmental tobacco smoke. *Tobacco Control* 1997; **6:** 19–26.
26 Jenkins R. Determination of personal exposure of non-smokers to environmental tobacco smoke in the US. *Lung Cancer* 1996; **14** (suppl 1): s195–s213.
27 Jenkins R. Exposure to environmental tobacco smoke in 16 cities. *J Exp Anal Envir Epidemiol* 1996; **6:** 473–502.
28 Phillips K, Howard D, Browne D, Lewsley J. Assessment of personal exposures to environmental tobacco smoke in British nonsmokers. *Environ Int* 1994; **20:** 693–712.
29 Philips K, Bentley M, Howard D, Alvan G. Assessment of air quality in Stockholm by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. *Scand J Work Environ Health* 1996; **22** (suppl 1): 1–24.
30 Phillips K, Bentley M, Howard D, Alvan G, Huici A. Assessment of air quality in Barcelona by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. *Environ Int* 1997; **23:** 173–96.
31 Phillips K. Howard D, Bentley M, Alvan G. Assessment of air quality in Turin by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. *Environ Int* 1997; **23:** 851–71.
32 Phillips K, Bentley M, Howard D, Alvan G. Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Prague using personal monitoring. *Int Arch Occup Environ Health* 1998; **71:** 379–90.
33 Phillips K, Bentley M, Howard D, Alvan G. Assessment of air quality in Paris by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. *Environ Int* 1998; **24:** 405–25.
34 Phillips K, Howard D, Bentley M, Alvan G. Measured exposures by personal monitoring for respirable suspended particles and environmental tobacco smoke of housewives and office workers resident in Bremen, Germany. *Int Arch Occup Environ Health* 1998; **71:** 201–12.
35 Phillips K, Howard D, Bentley M, Alvan G. Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Basel by personal monitoring. *Atmos Envir* 1999; **33:** 1889–904.
36 Phillips K, Howard D, Bentley M, Alvan G. Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Lisbon by a personal monitoring. *Environ Int* 1998; **24:** 301–24.
37 Matthews R, Macdonald V. Passive smokers inhale six cigarettes a year. *Sunday Telegraph* 1998, Aug 16.
38 Repace J. Secondhand smoke is a human carcinogen: National Toxicology Program Board of Scientific Counselors' meeting of nominations for listing in or delisting ETS from the 9th report on carcinogens. Dec 2, 1998. Research Triangle Park, NC: National Institute of Environmental Health Sciences.
39 Benowitz N. Cotinine as biomarker of environmental tobacco smoke exposure. *Epidemiol Rev* 1996; **18:** 188–204.
40 Jenkins R. US Occupational and Safety Health Administration. Jan 5, 1995. Public Hearing on proposed standard for indoor air quality. Washington, DC: US Department of Labor.
41 Matanoski G. Kanchanaraksa S, Lantry D, Chang Y. Characteristics of nonsmoking women in NHANES I and NHANES I epidemiologic follow-up study with exposure to spouses who smoke. *Am J Epidemiol* 1995; **142:** 149–57.
42 Thomas H, Gagliardi J. Smoking guns. *South China Morning Post* 1999, Jan 18.
43 Glantz S, Slade J, Bero L, Hanauer P, Barnes D. The cigarette papers. Berkeley: University of California Press, 1996.
44 Gelbspan R. The heat is on: the high stakes battle over Earth's threatened climate. Reading, MA Addison-Wesley, 1997.
45 PR Newswire. 500 physicians, scientists oppose climate treaty. 1997, Dec 3.
46 European Science and Environment Forum. 1999, April. www.esef.org
47 Mooney L. Smoking out bad science. *Wall Street J* 1998, March 19; A18.
48 Federal Focus, Inc. August 1999. www.fedfocus.org
49 Simpson D. Bangladesh: not a cigarette paper (news analysis). *Tobacco Control* 1998; **7:** 228–29.
50 Imperial Tobacco. Imperial Tobacco's position on smoking-related issues. Montreal, Canada: 1999. www.imperialtobacco.com/c/newsroom/stand
51 Tobacco Institue of Southern Africa. TISA submission index for portfolio, Committee on Health meeting, Oct 19, 1998. Capetown, South Africa: TISA, 1998.
52 Garfinkel L. Time trends in lung cancer mortality among non-smokers and a note on passive smoking. *J Natl Cancer Inst* 1981; **66:** 1061–66.
53 Glantz S. Tobacco industry response to the scientific evidence on passive smoking. In: Proceedings of 12th World Conference on Tobacco and Health (Winnipeg, Canada, 1983): 287–92.
54 Barnes D, Hanauer P, Slade J, Bero L, Glantz S. Environmental tobacco smoke. *JAMA* 1995; **??:** 248–53.
55 Garfinkel L. Cancer society aide's words with tobacco concern's twist. *New York Times* 1984, June 5.
56 Tobacco litigation: AFCO v TIA, the case against passive smoking. Redfern, Australia: Legal Books, 1991.
57 Wells A, English P, Posner S, Wagenknecht L, Perez-Stable E. Misclassification rates for current smokers misclassified as nonsmokers. *Am J Public Health* 1998; **88:** 1503–09.
58 Riboli E, Haley N, Tredaniel J, Saracci R, Preston-Martin S, Trichopoulos D. Misclassification of smoking status among women in relation to exposure to environmental tobacco smoke. *Eur Respir J* 1995; **8:** 285–90.
59 Fontham E, Correa P, Reynolds P, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. *JAMA* 1994; **271:** 1752–59.
60 Repace J, Lowrey A. A qualitative estimate of nonsmokers' lung cancer risk from passive smoking. *Environ Int* 1985; **11:** 3–22.
61 Riboli E, Preston-Martin S, Saracci R, et al. Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study. *Cancer Causes Control* 1990; **1:** 243–52.
62 New Zealand Department of Health (prepared by J Teinken). Through the smokescreen: a critique of environmental tobacco smoke; a review of the literature by the Tobacco Institute of New Zealand. Wellington: TINZ, 1990.
63 Bero L, Glantz S. Tobacco industry response to a risk assessment of environmental tobacco smoke. *Tobacco Control* 1993; **2:** 103–13.
64 Environmental tobacco smoke and lung cancer: an evaluation of the risk: report of a European working group. Trondheim: Trondheim European Working Party, 1996.
65 Davey Smith G, Phillips A. Passive smoking and health: should we believe Philip Morris's "experts"? *BMJ* 1996; **313:** 929–33.
66 New Zealand Department of Health. Creating smokefree environments. Wellington: NZ Department of Health, 1998.
67 Schlesinger J. Secondhand-smoke study ruled invalid: federal judge says EPA overstated cancer link; agency likely to appeal. *Wall Street J* 1998, July 20.
68 Dyer C. Tobacco firms win a hearing. *Guardian* 1998, July 7.
69 Lash T, Aschengrau A. Active and passive cigarette smoking and the occurrence of breast cancer. *Am J Epidemiol* 1999; **149:** 5–12.

THE LANCET

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Resisting smoke and spin

The Lancet endured an unwelcome shock in 1998 when legal documents placed on the internet revealed that a letter about environmental tobacco smoke, published in *The Lancet* during the 1990s, was part of a project sponsored by the tobacco industry to blur the issues surrounding risks of passive smoking. Unknown to the editors of the time, there was a campaign to seed the medical literature with pro-tobacco misinformation.

Only now has the extent of that campaign become clear. Elisa Ong and Stanton Glantz (see p 1253) describe how the tobacco industry worked to undermine the conclusions of an International Agency for Research on Cancer (IARC) report on passive smoking. The IARC found an increased relative risk of both spousal lung cancer and lung cancer among those exposed to smoke in the workplace. This European study was too small to show statistically significant differences but the results were in line with previously published reports.

When the existence of this research became known, Philip Morris established a multidisciplinary task force across the tobacco industry to explore, in conjunction with a public relations company and a firm of lawyers, the potential impact of the IARC report and ways to "stimulate controversy" around it. Philip Morris alone devoted US$2 million to this work. Consultants sympathetic to the tobacco industry were recruited to find out more about the IARC report, often by hiding their industry links while seeking information from IARC investigators. One aim of the task force was to criticise IARC's epidemiological methods by promoting the notion of "Good Epidemiological Practice". Another was to commission new research that might be more favourable to the tobacco companies' position. In sum, Ong and Glantz conclude that "Scientists and policy makers need to understand that they function in an environment that is heavily influenced by covert tobacco industry efforts to subvert normal decision making processes".

All Ong and Glantz say may be true. But a curious downside of the industry's strategy was that it made it harder for fair criticism to be made of the IARC study by truly independent scientists. Yet the IARC study was underpowered to detect reliably relative risks smaller than 1·3, and the tobacco industry was quick to exploit this methodological weakness. Moreover, good epidemiological practice is a sensible goal. The fact that it has partly originated from tobacco manufacturers may taint and therefore slow its successful attainment.

This week's *Lancet* report comes at a time when tobacco control has received a further important setback in the USA. Last month, the US Supreme Court ruled, in a 5-4 decision, that the Food and Drug Administration lacked authority to regulate tobacco products. Not surprisingly, tobacco companies were delighted, calling the FDA's attempt to protect public health "politically expedient". As industry stock prices rose, a programme of random checks to prevent retailers selling cigarettes to teenagers came to an end. The Supreme Court has recklessly and shamefully harmed efforts to stop smoking behaviour from creeping into ever-younger age groups. It is not without perverse irony that Mark Smith, a spokesman for the tobacco company Brown and Williamson, noted how US businesses "ought to breathe a sigh of relief" at the Court's decision.

While the US Congress now contemplates tougher restrictions on tobacco manufacturers, the dirty war of misinformation in academic and more public settings is likely to continue. Journal editors are especially vulnerable to being duped since we have limited powers to discover sources of funding support other than merely inviting disclosure from authors. And, as Ong and Glantz observe, even European Union officials were drawn into the web.

Tobacco is not the only aspect of medicine open to twisted corporate communications strategies. A 1998 study reported that published opinions on safety of calcium-channel blockers were related to the financial rewards bestowed by pharmaceutical companies on those giving such opinions. All policymakers must be vigilant to the possibility of research data being manipulated by corporate bodies and of scientific colleagues being seduced by the material charms of industry. Trust is no defence against an aggressively deceptive corporate sector. Meanwhile, IARC should now add passive smoking to its respected monograph series on substance carcinogenicity.

The Lancet

COMMENTARY

Pathophysiology and treatment of microscopic-colitis syndrome

The term collagenous colitis was coined by Lindstrom in 1976 to describe the histological findings of subepithelial fibrosis and inflammation in the rectal mucosa of a woman with chronic watery diarrhoea whose mucosa looked normal on proctoscopy.[1] Several years later Read and colleagues introduced the term microscopic colitis to describe the histological findings of mucosal inflammation (without fibrosis) in patients with chronic diarrhoea whose colonic mucosa looked normal on colonoscopy.[2] Yardley and colleagues subsequently introduced the term lymphocytic colitis to emphasise the presence of intraepithelial lymphocytosis in this form of microscopic colitis.[3]

The relationship between lymphocytic colitis and collagenous colitis has not been clear from the start. Since their clinical presentations are so similar and their histological appearances differ only in the presence or absence of a thickened subepithelial collagen table, current usage now includes lymphocytic colitis and collagenous colitis as histological subtypes of microscopic colitis syndrome. This clinical syndrome is characterised by chronic watery diarrhoea, a normal or near-normal gross appearance of the colonic mucosa, and specific microscopic changes of lymphocytic-plasmacytic inflammation in the lamina propria and intraepithelial lymphocytosis with or without thickening of the subepithelial collagen table.[4]

Microscopic-colitis syndrome is a fairly common cause of chronic diarrhoea of obscure origin at referral centres. Where I work this syndrome occurs in 10% of patients with chronic diarrhoea, with an even division between lymphocytic and collagenous subtypes.[5] The keys to diagnosis are remembering to take a biopsy sample of normal-appearing colonic mucosa in patients presenting with chronic watery diarrhoea and having a skilled pathologist to review the biopsy slides.[4]

The cause or causes of microscopic-colitis syndrome remain unknown. Dogs and cats have a similar disorder that resolves with a hypoallergenic diet.[6] However, in human beings with microscopic-colitis syndrome ingestion of an elemental diet for 3 weeks did not improve colonic histopathology (K D Fine, personal communication, June 1999). Bacterial antigens in the colonic lumen might be of importance. Transgenic rats genetically engineered to express HLA-B27 routinely develop a picture identical to lymphocytic colitis, but only if the animals have bacteria in the colon.[7] Whether bacterial toxins or constitutive antigens produce this effect is not clear. A relevant point is that antibiotics have been reported to help some patients with microscopic-colitis syndrome.[8]

Microscopic colitis in human beings is not linked to HLA-B27, but has been associated with other HLA loci. The most fascinating linkage is with HLA-DQ2 and HLA-DQ1,3 (including the HLA-DQ1,3 subtypes, HLA-DQ1,7, DQ1,8, and DQ1,9).[9] These loci are tightly linked with the occurrence of both lymphocytic and collagenous colitis and are also tightly linked with coeliac sprue, which suggests the possibility that similar immune mechanisms are involved. Gluten is almost certainly not the antigen involved since many patients with coeliac disease treated with a gluten-free diet have histological evidence of lymphocytic colitis. The association of many autoimmune diseases with microscopic-colitis syndrome also suggests an immune cause.

Whatever the cause of the inflammation, clearly mucosal inflammation is, to a large extent, the cause of the diarrhoea of microscopic-colitis syndrome. Perfusion studies have shown that absorption of water and salt is impaired in lymphocytic colitis and collagenous colitis.[10,11] Colonic water absorption correlates inversely with the cellularity of the lamina propria, but not with thickness of the collagen table. However, net secretion of water and salt is not noted frequently.

K-A Ung and colleagues have recently suggested that bile-acid malabsorption is an important pathophysiological factor in collagenous colitis.[12] They found that patients with this disorder had a high prevalence of bile-acid malabsorption as measured by the selenohomocholyltaurine test (SeHCAT) and a good chance of responding clinically to bile-acid-binding resins, even if the test was normal. However, bile-acid malabsorption is unlikely to be the cause or the main pathophysiological mechanism of collagenous colitis. First, although administration of bile-acid binders produced a clinical response, there is no evidence that there was an improvement in mucosal inflammation. Second, other disorders that are associated with bile-acid malabsorption, such as ileal disease or resection, are not associated with microscopic inflammation in the colon. Third, many chronic diarrhoeal diseases are associated with bile-acid malabsorption, probably because of diarrhoea-induced changes in rate of ileal flow or concentration of bile acids.[13] Co-existing bile-acid malabsorption might aggravate diarrhoea in some patients but is unlikely to be causative in most cases. Finally, the improvement with bile-acid-binding resins might be due to the binding of substances other than bile

acids that might have a more direct influence than the acids on the disease process.

Nevertheless, should bile-acid binders be the first line of therapy in patients with microscopic-colitis syndrome, as Ung and colleagues suggest?[12] Certainly the high response rate and low toxicity that they found favours such an approach. However, treatment with bile-acid binders would have to be continued permanently to maintain the effect, so these agents may not be such a good choice.

What about other therapeutic choices, such as 5-aminosalicylates or corticosteroids? Although no controlled trial has been conducted, experience with these agents has not been good.[4] Sulfasalazine and the newer 5-aminosalicylate drugs produce a clinical response in up to 40% of patients, but relapse is frequent once the drug is withdrawn. Prednisone must be used in high doses (typically 60 mg daily) to induce a response and must be tapered slowly to maintain the response. Older patients with microscopic-colitis syndrome may be intolerant of corticosteroid therapy, and side-effects at this dose level may be limiting, even in younger patients.

At present, the best choice for initial therapy in patients with microscopic-colitis syndrome is bismuth subsalicylate. This bismuth compound has antibacterial, anti-inflammatory, and antidiarrhoeal effects that could produce a clinical response. In an open-label trial of bismuth subsalicylate in 12 patients with microscopic colitis who took eight 262-mg chewable tablets in divided doses daily, the diarrhoea stopped in 11 and the mucosal inflammation resolved in eight over an 8-week course of therapy.[14] Diarrhoea did not recur after completion of treatment. The preliminary results of a placebo-controlled trial suggest that three 262-mg chewable tablets three times a day were more effective than placebo and as effective as bismuth was in the open-label trial.[15] Should clinical experience continue to be favourable, this well-tolerated agent will be the drug of choice for microscopic- colitis syndrome. Bile-acid-binding resins, 5-aminosalicylate drugs, and corticosteroids would then be used only when bismuth subsalicylate does not produce a response.

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1 Lindstrom CG. "Collagenous colitis" with watery diarrhoea: a new entity? *Pathol Eur* 1976; **11:** 87–89.

2 Read NW, Krejs GJ, Read MG, Santa Ana CA, Morawski SG, Fordtran JS. Chronic diarrhea of unknown origin. *Gastroenterology* 1980; **78:** 264–71.

3 Lazenby AJ, Yardley JH, Giardiello FM, Jessurun J, Bayless TM. Lymphocytic (microscopic) colitis: a comparative histopathologic study, with particular reference to collagenous colitis. *Hum Pathol* 1989; **20:** 18–28.

4 Schiller LR. Microscopic colitis syndrome: lymphocytic colitis and collagenous colitis. *Sem Gastrointest Dis* 1999; **10:** 145–55.

5 Fine KD, Seidel RH, Do K. The prevalence, anatomic distribution, and diagnosis of colonic causes of chronic diarrhea. *Gastrointest Endosc* 2000; **51:** 318–26.

6 Nelson RW, Stookey LJ, Kazacos E. Nutritional management of idiopathic chronic colitis in the dog. *J Vet Intern Med* 1988; **2:** 133–37.

7 Rath HC, Herfarth HH, Ikeda JS, et al. Normal luminal bacteria, especially *Bacteroides* species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rats. *J Clin Invest* 1996; **98:** 945–53.

8 Bohr J, Tysk C, Eriksson S, Abrahamsson H, Jarnerot G. Collagenous colitis: a retrospective study of clinical presentation and treatment in 163 patients. *Gut* 1996; **39:** 846–51.

9 Fine KD, Lafon G, Ogunji F. The genetic and histopathologic relationship of microscopic colitis and celiac sprue or refractory sprue. *Gastroenterology* 1999; **116:** A879.

10 Lee E, Schiller LR, Fordtran JS. Quantification of colonic lamina propria cells by means of a morphometric point-counting method. *Gastroenterology* 1988; **94:** 409–18.

11 Lee E, Schiller LR, Vendrell D, Santa Ana CA, Fordtran JS. Subepithelial collagen table thickness in colon specimens from patients with microscopic colitis and collagenous colitis. *Gastroenterology* 1992; **103:** 1790–96.

12 Ung K-A, Gillberg R, Kilander A, Abrahamsson H. Role of bile acids and bile acid binding agents in patients with collagenous colitis. *Gut* 2000; **46:** 170–75.

13 Schiller LR, Bilhartz LE, Santa Ana CA, Fordtran JS. Comparison of endogenous and radiolabeled bile acid excretion in patients with idiopathic chronic diarrhea. *Gastroenterology* 1990; **98:** 1036–43.

14 Fine KD, Lee EL. Efficacy of open-label bismuth subsalicylate for the treatment of microscopic colitis. *Gastroenterology* 1998; **114:** 29–36.

15 Fine KD, Ogunji F, Lee E. Randomized, double-blind, placebo-controlled trial of bismuth subsalicylate for microscopic colitis. *Gastroenterology* 1999; **116:** A880.

Blood or marrow?

See page 1231

Interest in the use of cytokine-mobilised peripheral-blood stem cells (PBSC) instead of marrow from normal allogeneic donors evolved from the remarkably good effects of PBSC on engraftment observed with autologous transplantation.[1] PBSC samples contain not only more progenitor cells than do marrow samples but also, on average, one log greater numbers of lymphocytes.[2] Although larger numbers of lymphocytes might provide benefits such as facilitation of engraftment, faster immune reconstitution, and antileukaemic effects, they were also expected to increase likelihood of acute and chronic graft-versus-host-disease (GVHD). Early phase II studies largely confirmed the faster engraftment but, surprisingly, there were no differences in acute GVHD.[3–5] The issue of chronic GVHD was much less clear. Several phase II studies showed either an increased or similar frequency of chronic GVHD when PBSC recipients were compared with historical controls who had received marrow.[6–8] Although there is little information on relapse and survival, which are more important endpoints than engraftment and GVHD, one retrospective study from Germany suggests that the use of PBSC is associated with a lower risk of relapse in patients transplanted for chronic myeloid leukaemia.[9] Data from a large registry analysis suggest a survival advantage with the use of PBSC in patients with advanced leukaemias.[10]

Clearly, phase III, prospective, randomised trials comparing PBSC with marrow are needed to resolve these issues. A prospective, randomised study of a size similar to the one reported by Ray Powles and colleagues in today's *Lancet* showed faster platelet recovery, equivalent frequency of acute GVHD and of survival, but more extensive chronic GVHD with PBSC.[11] According to a preliminary report by the European Bone Marrow Transplant Group, based on partial accrual to a randomised study in patients with early-stage leukaemia, there were no major differences in engraftment, acute GVHD, or survival.[12] A third randomised study of about 100 patients with early-stage leukaemia showed a higher incidence of chronic GVHD with PBSC but no differences in relapse or survival.[13] Thus, these three prospective studies have not resolved the issue of whether use of PBSC instead of marrow influences the frequency of chronic GVHD, relapse, or survival.

Powles and colleagues' prospective, randomised study comparing PBSC with marrow was double blinded.