



## Neglected Diseases of Global Importance

Nathan Ford; Els Torreele; Gregory K. Folkers; et al.

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## Does Right Heart Catheterization Prevent Perioperative Complications?

**To the Editor:** In their observational study, Dr Polanczyk and colleagues<sup>1</sup> found an increased incidence of congestive heart failure (CHF) in patients receiving perioperative right heart catheterization (RHC) for noncardiac surgery. They state that “diagnosis of perioperative CHF was obtained from progress notes recorded by clinicians involved in the patients’ care.” They do not indicate, however, whether the diagnosis of CHF was made in light of data obtained from RHC. It is possible that an elevated pulmonary capillary wedge pressure (PCWP) would have resulted in a diagnosis of CHF and thus resulted in medical therapy, which would then have been classified as a complication. If a certain level of postoperative PCWP was diagnostic of CHF, monitored patients who received RHC would be more likely to have this so-called complication. It is common knowledge that the clinical examination is less sensitive than RHC at detecting an abnormally high PCWP.

The pertinent question is not whether RHC is needed in all patients, but whether interventions in response to information obtained from the catheter altered the outcomes in these observational studies. Absence of proof is not proof of absence.

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1. Polanczyk CA, Rohde LE, Goldman L, et al. Right heart catheterization and cardiac complications in patients undergoing noncardiac surgery: an observational study. *JAMA*. 2001;286:309-314.

**To the Editor:** The study by Dr Polanczyk and colleagues<sup>1</sup> of postoperative complications associated with RHC emphasizes the lack of randomized controlled trials (RCTs) of this serious intervention. In 1980, I urged that such trials be completed before “the genie gets out of the bottle.”<sup>2</sup> The genie has escaped. Wholesale commitment to RHC on faith alone has made performing RCTs of this technology difficult. For instance, in a Canadian trial,<sup>3</sup> 35% of patients were excluded because their physicians considered it unethical not to insert a catheter. Similarly, in the original Coronary Artery Surgery Study trial of coronary artery bypass, two thirds of the patient refusals were at the behest of their personal physicians.<sup>4</sup> The actual breach of ethics is in *not* performing RCTs, which give the earliest candidates a 50-50 chance not to get new and unproved procedures.<sup>4</sup>

As was true in our original case-control study<sup>5</sup> and several similar subsequent studies, Polanczyk et al found that patients who received RHC consistently fared worse than those who did not, even after matching for disease severity.

Thus, an RCT is long overdue. An additional refinement of such a trial could not only assess the safety of RHC but also reveal for which patients it is indicated and for which it is not. Most clinicians remain convinced that RHC has some legitimate applications. Its use in every patient for whom it seems clinically indicated, however, has not been scientifically established.

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**To the Editor:** Dr Polanczyk and colleagues<sup>1</sup> concluded that, after controlling for disease severity, postoperative cardiac events and outcomes were no different in patients who received RHC vs those who did not. It is debatable, however, whether these are suitable end points for studying an intervention such as RHC, which has 2 functions. First, it can be used as a diagnostic tool, such as in differentiating the etiology of shock. Second, it can be used to guide therapy with fluids or vasoactive drugs. However, RHC itself is not therapeutic.

The outcome measures used in this study are typically used to assess therapies or therapeutic devices. It is possible that a diagnostic device capable of positively affecting outcomes will fail to demonstrate a mortality benefit because of errors in measurement or interpretation of the data it yields. A study of the accuracy of measurements and of how physicians interpret, pro-

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**Letters Section Editors:** Stephen J. Lurie, MD, PhD, Senior Editor; Jody W. Zylke, MD, Contributing Editor.

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cess, and use the data provided by RHC would be the most enlightening study in terms of outcomes.

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1. Polanczyk C, Rohde L, Goldman L, et al. Right heart catheterization and cardiac complications in patients undergoing noncardiac surgery: an observational study. *JAMA*. 2001;286:309-314.

**To the Editor:** Dr Polanczyk and colleagues reported that RHC did not reduce complication rates in patients undergoing noncardiac surgery. In this case-control study, the authors matched patients by using a propensity score for RHC and type of procedure. Even though the patients seem to be matched, we question the authors' method. In contrast to a randomization procedure that balances groups for all known and unknown confounding factors, matching groups by using a propensity score takes into account only selected factors, which is illustrated by the large disparity in the duration of surgical procedures (5 hours in RHC patients vs 3.9 hours in non-RHC patients,  $P < .001$ ), despite similar propensity scoring.

Also, the severity of the associated diseases was not adequately taken into account. For example, patients with a history of chronic bronchitis may include those with chronic cough as well as those with severe respiratory disease. Similarly, a history of diabetes can range from moderate hyperglycemia to complicated diabetes with end-organ damage. This gradation in the severity of the disease is one of the most important factors in a physician's decision to perform RHC. It is likely that physicians decided to perform RHC in patients with the most severe forms of these diseases and that patients in the matched group had less severe forms. Despite a similar propensity score, patients in the RHC group may have been more severely ill than those in the other group. Hence, important intergroup differences caused by confounding factors were not taken into account, and these factors may interfere considerably with the outcome.

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1. Polanczyk C, Rohde L, Goldman L, et al. Right heart catheterization and cardiac complications in patients undergoing noncardiac surgery: an observational study. *JAMA*. 2001;286:309-314.

**In Reply:** Dr Myla raises the issue of detection bias—that is, the possibility that the use of RHC might simply improve diagnosis of CHF by providing data on PCWP. Such a bias would not explain the significantly increased odds of our combined end point of major cardiac events, which included pulmonary edema as well as less severe heart failure, or the increased length of stay among patients who underwent RHC.

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We agree with Dr Spodick on the need for trials to identify patient subsets for whom RHC is beneficial. As Dr Trzeciak and colleagues point out, such trials are especially challenging because they must evaluate not only the accuracy of data obtained from RHC, but also how the data are used to guide interventions. Thus, any RCT should include guidelines for the clinical response to specific findings from RHC. In response to Dr De Backer and colleagues, we noted that the potential for incomplete adjustment for confounding was noted in our article and we called for trials that would address this issue.

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## Exercise and Glycemic Control in Diabetes

**To the Editor:** The results of the meta-analysis by Mr Boulé and colleagues<sup>1</sup> support a widely held assumption that exercise improves glycemic control in patients with diabetes. The main outcome of the meta-analysis was a 0.66% reduction in glycosylated hemoglobin (HbA<sub>1c</sub>) in the exercise group. This effect is much smaller than the nearly 2-fold reduction in all-cause mortality observed by Wei et al.<sup>2</sup> Potential reporting flaws in the original data may have led Boulé et al to underestimate the effect.

The authors state that "HbA<sub>1c</sub> reflects average blood glucose concentration from the previous 8 to 12 weeks." In Table 1, 10 of the 16 trials lasted 13 weeks or less. It is unlikely that the postintervention HbA<sub>1c</sub> reflected the full effect of the intervention. In order for the HbA<sub>1c</sub> to capture the intervention's full effect, the intervention needs adequate time to reach a steady state.<sup>3</sup> We have previously tried to capture the effect of non-pharmacological diabetes interventions when multiple intraintervention and postintervention HbA<sub>1c</sub> values are reported.<sup>4</sup> We would like the authors to clarify the timing of postintervention HbA<sub>1c</sub> values reported in their meta-analysis.

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**In Reply:** Drs Ellis and Elasy suggest that inclusion of studies lasting less than 13 weeks would result in underestimation of the effect of exercise on glycemic control. To address this concern, we performed 2 analyses. First, among the 11 exercise vs nonexercise control comparisons, we performed a subgroup analysis comparing the 6 studies lasting 8 to 12 weeks

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with the 5 studies lasting more than 12 weeks. The weighted mean differences in HbA<sub>1c</sub> were almost identical in the 2 groups of studies (−0.65% [*P*=.005] and −0.67% [*P*=.004], respectively). Second, we performed a meta-regression analysis regressing postintervention difference in HbA<sub>1c</sub> on study duration and found no significant association (*r*=0.07, *P*=.84). Therefore, the inclusion of studies lasting just 8 to 12 weeks did not result in an underestimation of the effects of exercise on HbA<sub>1c</sub>. Had we excluded these briefer studies, our results would have been unchanged but statistical power would have been reduced.

Ellis and Elasy argue that the postintervention HbA<sub>1c</sub> difference of 0.66% we found was too small to be consistent with the significantly lower mortality among physically active subjects compared to inactive active subjects in a cohort study.<sup>1</sup> Our results would only be inconsistent with a major mortality reduction if one assumed that the benefits of exercise on mortality were mediated exclusively through glycemia. We believe that improved glycemic control is only part of the explanation for the lower mortality in diabetic men who exercise. Exercise might also protect against mortality through mechanisms such as increased high density lipoprotein cholesterol, decreased plasma triglycerides, decreased blood pressure, decreased systemic inflammation, or improved fibrinolysis. Metformin is another example of a therapy causing greater mortality reduction than would be expected based on glycemia alone. In UK Prospective Diabetes Study (UKPDS) subjects randomized to intensive glycemic control with metformin, HbA<sub>1c</sub> was only 0.6% lower than with conventional treatment but there was a 42% reduction in diabetes-related deaths. This mortality reduction was very close to the 45% reduction in mortality found by Wei et al in physically active diabetic men.<sup>2</sup> Therefore, our results are not inconsistent with a major beneficial effect of exercise on mortality.

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## Antibiotic Treatment of Adults With Sore Throat

**To the Editor:** Drs Linder and Stafford<sup>1</sup> found that a large number of adults are treated with antibiotics for acute pharyngitis, although the overall rate is declining. However, they also found that the number of prescriptions for inappropriate prescriptions appears to be increasing. We disagree with the authors that extended macrolides such as clarithromycin or azithromycin are necessarily inappropriate.

Penicillin should remain the first choice for streptococcal pharyngitis. However, when the patient is allergic to penicillin, the choice between erythromycin and other macrolides should be made by primary care physicians according to individual patient characteristics. Although many physicians are aware of the guidelines recommending erythromycin for group A streptococcal pharyngitis, they may choose extended macrolides because of less frequent dosing, fewer adverse effects, and less interaction with other medicines. Including extended macrolides with penicillin or erythromycin as recommended antibiotics in this analysis would increase overall use from 23% to only 27%. Furthermore, the decline in use of recommended antibiotics throughout the 11 years the study analyzed would be reduced except in 1999 (15% in 1999 vs 28% in 1998).

There is complete cross-resistance to erythromycin, azithromycin, and clarithromycin among resistant gram-positive organisms<sup>4</sup>; thus, the rate of resistant group A streptococcus infection will not change if any one of these 3 agents is chosen, although the resistance in colonized gram-negative organisms may increase, such as *Haemophilus influenzae*. Azithromycin is much more expensive than penicillin, as discussed by the authors (\$39.32 vs \$2.31). However, azithromycin does not cost much more than erythromycin (about \$27.00 for 1 g of erythromycin estolate for 10 days).<sup>5</sup>

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1. Linder JA, Stafford RS. Antibiotic treatment of adults with sore throat by community primary care physicians: a national survey, 1989-1999. *JAMA*. 2001;286:1181-1186.
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**In Reply:** We agree that erythromycin estolate suspension is relatively expensive, but the retail cost of 10 days' worth of erythromycin-base tablets, a form more commonly used in adults, is \$11.20. Penicillin costs \$6.80. In contrast, a 5-day course of azithromycin is \$41.52, and a 10-day course of clarithromycin is \$74.40.<sup>1</sup> As implied by Drs Iwata and Blum, clarithromycin and azithromycin have an unnecessarily broad spectrum of activity for the treatment of group A β-hemolytic streptococci (GABHS). Additionally, erythromycin base can be given to adults in dosages of 500 mg twice daily.

Penicillin remains the drug of choice in the treatment of pharyngitis caused by GABHS. It is inexpensive and well tolerated, reduces symptoms,<sup>2</sup> and is the only antibiotic proven to prevent rheumatic fever. There is no resistance to penicillin among

GABHS, and penicillin can be used in convenient regimens (500 mg orally 2 or 3 times daily).<sup>3</sup> Despite being the drug of choice, the low and decreasing rate of penicillin use we noted—from 17% in 1989 to 6% in 1999—is difficult to explain on clinical grounds. It seems unlikely there was an 11% absolute increase in the rate of penicillin allergy in the United States throughout the study period. It is more likely that nonclinical factors, such as promotional efforts, were responsible for changes in antibiotic choice. Of greater concern than specific antibiotic choice for adults with pharyngitis is the overall high rate of antibiotic use. Five to 10% of adults with pharyngitis treated by primary care physicians will have positive culture results for GABHS.<sup>3</sup> Even in the last year of our study, 1999, which had the lowest proportion of antibiotic use for any year, an antibiotic was prescribed in 57% of visits. Our conclusion that antibiotics are overprescribed for adults with pharyngitis should prompt physicians to use accepted criteria in evaluating patients with pharyngitis<sup>4,5</sup> and bolster efforts to limit inappropriate antibiotic use for upper respiratory tract conditions.

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## Neglected Diseases of Global Importance

**To the Editor:** We agree with Mr Folkers and Dr Fauci that the success of acquired immunodeficiency syndrome research over the last 2 decades shows what can be achieved if enough financial and human resources are provided.<sup>1</sup> There was serious commitment from Western governments as well as major investments from the pharmaceutical industry that anticiated a hugely profitable market in developed countries.

But many infectious diseases that continue to be the leading cause of death in poor countries do not affect industrialized countries. Without enlightened self-interest by Western governments and a profitable market for industry, drug development has ground to a virtual standstill<sup>2</sup>: only 1% of the 1393 new drugs approved between 1975 and 1999 are for tropical diseases,<sup>3</sup> which account for almost 10% of the global disease burden. Exacerbating this neglect, drug resistance is reducing the effectiveness of many available drugs.

Recently, the Drugs for Neglected Disease Working Group and the Harvard School of Public Health questioned the world's

top 20 pharmaceutical companies on their research and development activities for malaria, tuberculosis, sleeping sickness, Chagas disease, and leishmaniasis.<sup>3</sup> Eleven companies responded (representing \$117 billion of the \$406 billion worldwide pharmaceutical market.). Of these, 7 reported spending less than 1% of their research and development budget over the last fiscal year on any of the 5 diseases; 8 spent nothing on the 3 most neglected diseases (ie, sleeping sickness, Chagas disease, and leishmaniasis).

The public sector, increasingly focusing research along profitable avenues, is also failing. Experts estimate that annual public funding for drug research and development on these same 5 diseases is less than \$75 million.<sup>3</sup>

Governments are ultimately responsible for ensuring that people's health needs are met. Global liability and moral obligation must be the driving force behind research efforts. Governments could frame a compulsory research obligation that would require industry—highly profitable thanks to increasing levels of patent protection<sup>4</sup>—to reinvest a percentage of pharmaceutical sales into research and development for neglected diseases, either directly or through public programs. Such mandates, framed in a global treaty, would correct the imbalance between private sector rights and obligations under current international agreements and provide legal options to make drugs for neglected diseases global public goods. Ultimately, not-for-profit drug development initiatives should be explored, to take drug research and development for neglected diseases out of the marketplace altogether.

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**In Reply:** We agree with Mr Ford and Dr Torrelee that research and development of therapies for “neglected” diseases is an urgent priority. Innovative approaches to facilitate the development of drugs and vaccines for diseases that predominantly affect the developing world will require commitment by (and partnerships between) government, industry, academia, nongovernmental organizations, and philanthropies.

At the National Institute of Allergy and Infectious Diseases (NIAID), research into parasitic and tropical diseases has been an important focus for more than 50 years, in intramural laboratories, at grantee institutions, and through global health research networks such as the International Centers for Tropical Disease Research.<sup>1</sup> Government-sponsored research in pathogen genomics, as well as efforts to identify metabolic pathways, receptor-ligand interactions, and other potential targets

for intervention, sets the stage for the development of new drugs and vaccines against infectious diseases. In this regard, it is incumbent that government agencies and others continue to pursue innovative ways to collaborate with industry to fight diseases that are not addressed by market forces. One example is the NIAID Challenge Grants Program, in which NIAID provides matching funds to companies that will commit their own dollars and resources toward developing new drugs and vaccines for diseases of global health importance.<sup>2</sup>

We recently convened a meeting focused on the perspectives of industry and academia with regard to the barriers to the development of drugs for infectious diseases and the criteria used in selecting products for development.<sup>3</sup> Participants from several institutes at the National Institutes of Health, other government agencies, academia, private foundations, and approximately 30 large and small pharmaceutical and biotechnology companies participated. As a result of this meeting, NIAID has implemented several new programs for partnering with industry on new interventions against diseases that currently are not a high priority of industry or that may be too financially risky. Clearly, this dialogue must continue and further initiatives developed to address the imbalance in the burden of infectious diseases between rich and poor countries.

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1. National Institute of Allergy and Infectious Diseases. *Global Health Research*. Available at: <http://www.niaid.nih.gov/dmid/global>. Accessibility verified November 15, 2001.
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### When Should the Public Be Informed of the Results of Medical Research?

**To the Editor:** In their discussion of THE JOURNAL's policy on prepublication release of information,<sup>1</sup> Dr Fontanarosa and Ms Flanagan<sup>2</sup> used an inappropriate example to defend a flawed policy that attempts to squelch public discussion of medical research.

Restrictions on the prepublication dissemination of research results are invoked in the name of good patient care, yet the THE JOURNAL's policy fosters an environment in which sketchy research abstracts presented at scientific meetings may be widely disseminated by the news media, while more thorough discussion that could improve the quality and accuracy of such journalism is harshly discouraged. Indeed, almost every health or medical journalist can recount cases of researchers too terrified to share even basic clarifications or explanations of their work with reporters, for fear that their papers would be banished from consideration by THE JOURNAL, resulting in serious harm to their reputations and careers.

Certainly there are important differences between brief reports at scientific meetings and peer-reviewed journal articles. Journalists, researchers, and public relations staff have a responsibility to weigh carefully those distinctions when deciding how and whether to disseminate research results through the news media. But the fact is that the news media are a leading source of medical information for patients and physicians alike. It is difficult to understand how patient care is served by a policy that even in the setting of a professional meeting hinders the ability of journalists and scientists to engage in full discussions of medical research. By digging deeper into the data and interpretations presented to them, journalists can do a better job of informing the public.

Moreover, both the public and individual patients lose when a paper is rejected due to prepublication release of the results. Such papers are rejected not because of any scientific or clinical shortcomings, but simply because researchers have spoken more freely than journal editors would prefer. Such punitive actions create an impression that editors are placing the prestige of their journals ahead of the free flow of medical research results.

Other peer-reviewed medical journals do not find it necessary to wield sanctions against authors in their efforts to bolster the quality of discussions of medical research.<sup>3</sup> THE JOURNAL should join them.

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1. Fontanarosa PB, Flanagan A, DeAngelis CD. THE JOURNAL's policy regarding release of information to the public. *JAMA*. 2000;284:2929-2931.
2. Fontanarosa PB, Flanagan A. Prepublication release of medical research. *JAMA*. 2000;284:2927-2929.
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**To the Editor:** Dr Fontanarosa and Ms Flanagan<sup>1</sup> cautioned about release of preliminary information to the public prior to its publication in scientific journals. We strongly agree with their concerns and offer an example of how premature dissemination of study results can lead to both misinterpretation of the scientific inferences and inappropriate public reaction.

A presentation<sup>2</sup> at the 13th International AIDS Conference (Durban, South Africa, July 9-14, 2000) described preliminary data from a study of nonoxynol-9 and human immunodeficiency virus (HIV). The researchers reported that sex workers using a gel containing nonoxynol-9 had a higher risk of acquiring HIV than those using the placebo vaginal moisturizer (15.5 infections vs 10.1 per 100 person-years). The relative risk increased with adherence to the use of either product, thus supporting a causal inference. Armed with this interpretation, press around the world proclaimed that products containing nonoxynol-9 are dangerous. For example, *JAMA's* own Medical News and Perspectives headline<sup>3</sup> implied that spermicides might be dangerous for all women in all circumstances. Other media were even stronger in their messages implying that nonoxynol-9 caused harm.

However, this simplistic message obscured the complexities of these preliminary data. Major problems existed with both the internal and the external validity of the study. Internally, at least 3 plausible interpretations exist for these findings. First,

nonoxynol-9 could have produced an increased risk of male-to-female HIV transmission. The irritating effect of nonoxynol-9's detergent-like action on vaginal mucosa, and the greater risk of genital lesions in this group, support this interpretation. Second, the placebo vaginal moisturizer could have reduced transmission risk by either preventing genital trauma during intercourse or by favorably affecting vaginal flora. The hyperviscosity and lower pH of the vaginal moisturizer support this interpretation. Third, both interpretations could be correct, thus producing the relative risk initially found.

Externally, the main problem is with the study's generalizability. The sex workers averaged 3.6 coital acts a day, with a mean of 70 sexual episodes a month. This level of sexual activity is highly atypical for the vast majority of women worldwide, and severely limits generalizing the conclusions outside the study. In the United States, most women using nonoxynol-9 products for contraception have much lower levels of coital activity.<sup>4</sup>

Three previous trials of nonoxynol-9, all of which were conducted in sex workers, have yielded conflicting results.<sup>5-7</sup> While the 4 studies all had different strengths and weaknesses, taken together they provide a "consistently inconsistent" picture, indicating neither a harmful nor a protective effect.

Unfortunately, the release of the preliminary data in Durban has led to a variety of premature actions. A congressman called on the US General Accounting Office to investigate the safety of spermicidally coated condoms. A manufacturer decided not to include nonoxynol-9 in a vaginal lubricating agent. Some clinicians have advised low-risk patients not to use nonoxynol-9 as an adjunct to diaphragm use. Quite possibly, more unintended pregnancies may result. Until there are further data on the risks of nonoxynol-9 in typical settings, we feel that women currently using nonoxynol-9-containing spermicides for contraceptive purposes should not be discouraged from doing so.

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**In Reply:** It appears that Mr Holtz may have misinterpreted our policy regarding release of information to the public,<sup>1</sup> as it applies to research abstracts presented at biomedical meet-

ings. As we noted in our Editorial, research presentations and discussions at biomedical meetings are an integral part of the orderly progression of scientific communication and scholarly discourse. However, these presentations are designed as a preliminary exchange of information among physicians, other health care professionals, and other researchers.

THE JOURNAL's policy does not, as Holtz suggests, preclude researchers from sharing "basic clarifications or explanations of their work with reporters," but advises authors not to provide additional data or information beyond that covered during the course of their presentation and its ensuing discussion.<sup>1</sup> We request authors of papers submitted to or accepted by *JAMA* to forgo participation in formal press conferences before publication, so their preliminary study results will not be provided only to selected reporters before the release of our embargo, when the full study results are available equally to all news media. Our approach is consistent with recommendations of the International Committee of Medical Journal Editors.<sup>2</sup>

In addition, one need look no further than the information presented by Dr Cates and colleagues for an example of the potential for misinterpretation and the possible ramifications of widespread news dissemination of preliminary research reported at scientific meetings. Given the promising and compelling nature of some research findings, it is not surprising that some presentations of abstracts at scientific meetings receive substantial news attention. However, the data for most research presentations at most scientific meetings have undergone limited peer review, and a substantial proportion of abstracts presented at biomedical meetings are never published as full reports in peer-reviewed scientific journals.

Moreover, while Holtz acknowledges the important differences between reports at scientific meetings and peer-reviewed journal articles, he fails to note the important differences between peer-reviewed journal articles and news media reports, some of which have been shown to vary in terms of accuracy, completeness, sensationalism, and quality of coverage.<sup>3,4</sup> In our view, the best way to communicate medical research findings is not by advocating widespread dissemination of preliminary research reports based on presentations at meetings, but rather by ensuring that published research articles have undergone rigorous peer review and careful editorial evaluation, and that these articles present complete findings, provide objective interpretation of the results, include appropriate caveats and limitations, and discuss the results in context with other research.

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## RESEARCH LETTER

### Persistent Macrocytosis Following Abstinence From Chronic Alcohol Use

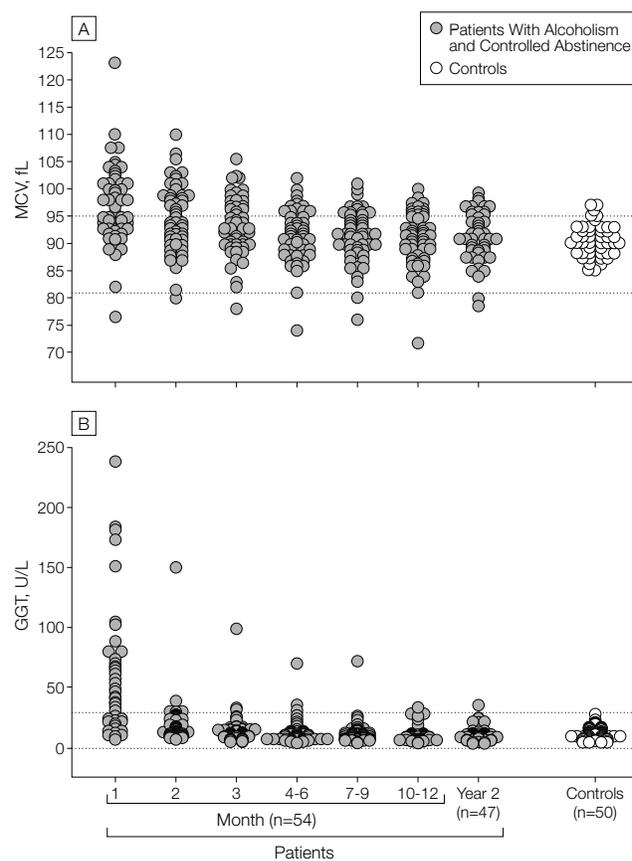
To the Editor: Because the mean corpuscular volume (MCV) of red blood cells may be elevated in as many as 89% of patients with chronic alcohol use<sup>1</sup> this test is often used as a marker of ongoing alcohol abuse.<sup>2</sup> It is not known, however, whether the MCV returns to normal after cessation of chronic alcohol use.

**Methods.** Subjects were 54 otherwise healthy patients (46 men, 8 women) with a history of chronic alcoholism, who were followed-up for 10-25 (median, 21) months of strictly controlled abstinence. Their median age was 42.5 (range, 26-63) years and they had been alcohol dependent (according to *DS-MIV* criteria) for 15 (range, 6-37) years with an average daily consumption of 300 (range, 120-900) g of pure alcohol. After an inpatient detoxification period, subjects participated in a 2-year outpatient program that included counseling and use of disulfiram.<sup>3</sup> Abstinence was confirmed by frequent urine tests. A control group comprised 50 healthy volunteers without a history of alcohol abuse, who were matched with regard to sex, age, and cigarette use. Blood samples for MCV and  $\gamma$ -glutamyltransferase (GGT) were obtained at least monthly during the first 3 months and then every 3 months during the first year of abstinence. Samples were also obtained from 47 of the 54 subjects during the second year of abstinence. For all subjects, serum folic acid and vitamin B<sub>12</sub> concentrations were determined during the first 3 months of abstinence.

**Results.** Macrocytosis (MCV >95 fL) was observed in 27 of 54 (50%) subjects during the first month of abstinence (ie, baseline) (FIGURE). After 4 to 6 months of abstinence the MCV returned to the normal range in 41 of the 54 (76%) subjects with alcoholism. The remaining 13 of these subjects had ongoing macrocytosis throughout the first year and in 12 of them it persisted through the second year of abstinence. Only 3 of the 50 healthy control subjects (6%) had macrocytosis. Serum GGT rapidly returned to normal levels (Figure). Persistent macrocytosis was associated with significantly higher initial MCV values (102.5 fL vs 94 fL;  $P < .001$ ) and a longer history of alcohol dependence (20 y vs 13 y;  $P < .001$ ). Patients with persistent macrocytosis (MCV >95 fL after 10-12 months of abstinence) did not differ significantly from other patients with regard to sex, age, cigarette use, daily amount of alcohol, and preferred alcoholic beverages (Mann-Whitney U test). Average folic acid and vitamin B<sub>12</sub> serum concentrations were normal and were not statistically different between the 2 groups.

**Comment.** A significant number of subjects in our study had persistent macrocytosis after more than 3 months of abstinence from alcohol, which suggests a prolonged ethanol-induced impairment of erythropoiesis and erythrocyte dysfunction. This could be related to the cumulative amount of alcohol consumed before entry in the study, as persistent macrocytosis was associated with a longer duration of alcohol dependence in this sample. Because macrocytosis can persist even

**Figure.** MCV Values and GGT Activity of Abstinent Alcoholics vs Healthy Controls



A, Mean corpuscular volume (MCV) values of abstinent alcoholics compared with those of healthy controls. Reference range (dotted lines), 81-95 fL. B,  $\gamma$ -glutamyltransferase (GGT) activity of abstinent alcoholics throughout abstinence compared with that of healthy controls. Reference range (dotted lines), <29 U/L.

under conditions of strictly controlled abstinence from alcohol, an elevated MCV should not be used as a clinical indicator of relapse or continuation of alcohol use.

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