Premature or Inappropriate Publication of Research Findings

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INTRODUCTION
There is a great need for objective and scientific valid information on drugs and pharmacotherapy. It is a joint responsibility of both scientists and the medical-pharmaceutical profession to provide this information and to take control over the quality and the timing of the information process. The quantity of the information flow appearing in the biomedical press suggests that the knowledge base doubles every ten years(1). Modern computer technology facilitates increasingly the access to and management of publications and other formats of scientific information. However, nobody is able to read, if not to judge the merits of all the available sources of biomedical information, both in the scientific, the professional and the lay press. The overburdened biomedical literature is a feature with strengths and flaws(2,3). The purpose of this paper is to discuss some pertinent characteristics of today’s publication system and to evaluate the consequences for the quality and timing of publication of research findings on drug treatment.

SCIENCE AND PUBLICATION PRESSURE
One major factor in the enormous increase in the flow of publications is the structure and reward system in science(2-5). The “product” of science is more than ever defined in terms of number and impact of publications. This means that the performance of scientists, their research funding, promotion opportunities, etc. are evaluated in terms of publication productivity. And these terms are becoming tighter and tighter. When the Nobel price winner “James D. Watson became an associate professor at Harvard, his résumé comprised 18 publications. Today, a similar position would dictate a candidate having published 50 up to 100-papers(2).

The pressure of producing an increasing number of papers is manifest and has raised questions on the quality and the timing of publication on research findings. In the publishing game, features like the “least published unit,” “salami science,” publishing the same study in different forms, and irresponsible co-authorship have drawn attention from editors and others committed to the scientific literature. The spectrum of concerns ends with speculations on fraud, e.g., plagiarism and fabrication of data(5-7).

SCIENCE AND THE PUBLIC DOMAIN
The relationship between science and the lay press has always been one of hate and love. Scientists frequently blame journalists about what they consider as an irresponsible search for sensation and turmoil, and are therefore
reliant to associate themselves with the public domain of the media. On the other hand, science, in particular in the biomedical field, needs press coverage in order to be visible and to attract research funds(1).

An important point in settling the relationship between science and the press are the guidelines on timing of publication of research findings in the lay press. It was the former editor of the New England Journal Medicine, Dr. Ingelfinger, who defined these guidelines(8). Most major medical journals have adopted the “Ingelfinger rule” which says that a manuscript is not considered for publication when the contents has been published elsewhere, unless under strict conditions. The main objective of this rule is to prevent public debate about new medical research findings before the formal scientific publication is available(8,9).

An interesting case of prior publication was a report in the 1985 April issue of the American Journal of Public Health dealing with the effects of preventive dentistry modalities applied in schools(9). The report was accepted for publication although the major results were already disseminated through an in-house press conference and brochure by the agency who sponsored the study. Because the press was intrigued with the findings of the study—the findings indicated that dental health prevention in schools was not effective, so that large amount of governments funds were being wasted—media coverage was widespread. In the same issue of the publication of the report, the editor of the Journal explained this particular form of violation of the “Ingelfinger rule” and defended the unusual editorial decision to accept the report for publication by making the point that an in-house publication should not substitute formal scientific journal publication: “To rely on in-house publication as a method of disseminating scientific information is to set the clock back three centuries and to return to the days before the birth of scientific journals when authors printed and promoted their own papers”(9).

**CASES OF “EARLY PROMISE”**

As said before, media coverage of biomedical research is an important factor in promoting certain research projects and to raise funds for future research. The concept of “early promise” should be understood in the context of the socio-political dynamics of science and from that perspective it is a lubricating vehicle of scientific progress. The flip-side of “early promise” is the risk of unduly claims of efficacy and safety of new drugs, being misleading to the medical community and patients. Two examples of “early promise” show how this type of inappropriate publication of research findings has its negative impact.

**AIDS Therapy**

AIDS holds a strong fascination for the media and claims of AIDS “cures” in the lay press give a constant impetus for being concerned about the negative impact of premature publications on patients’ well being(10-12). Making research visible and attracting funding in a very competitive area do play an important role here. However, “striking the happy media” in the AIDS area is a feature where both scientists and journalists loose control over their responsibilities(11).

A recent example of media manipulation was the paper of Chow et al. in the February 18 issue of Nature in 1993, presenting in vitro data on a multidrug strategy for the treatment of AIDS(13). The problem of drug resistance in AIDS therapy is well recognized as a threat for mankind and is waiting for a solution. The paper of Chow et al. attracted far more attention from the media than was responsible. New York tabloids showed headlines such as “Graduate Student Cures AIDS”(14). Their paper was also criticized by the scientific community and six months after the first publication Chow et al. had to send in a retraction of part of their work to Nature(15). An editorial in Nature told the story like this: “Whatever the outcome, the history of this article illustrates a problem now all too common in AIDS research but also in other fields. The paper by Chow et al. was carefully reviewed, and it was agreed that the results would be useful in planning strategies to manage AIDS. Such reports should obviously be published with speed so that beneficial knowledge may be snared more quickly. But, by the same test, retractions should also be speedy and full-throated. Publicity does not help; the scientific community is tolerant of admissions of honest error, but honest errors seem more grievous if they follow wide publicity. Sadly, there is no escape from that.”(14) However, the mounting pressure from AIDS advocates groups and the cut-throat world of AIDS research constitute a risky couple in a world full of greedy journalists(10).

**Treatment for Septic Shock**

In 1991 Ziegler et al. published a randomized controlled clinical trial showing a reduction of mortality of 37 percent in patients with gram-negative sepsis and receiving HA-1A (Centoxin)(16). The decision for treatment with Centoxin had to be on the basis of presumed diagnosis of gram-negative sepsis. The clinical implications of this and further studies with Centoxin were difficult to interpret because one cannot identify patients with gram-negative sepsis (when compared with gram-positive or fungal) at the onset of the septic syndrome. To test this it takes approximately 18 hours and the clinician cannot wait because he is prompted to act immediately.

Centoxin was marketed in 11 countries (e.g., U.K., The Netherlands) but its lifetime was short. In January 1993 the drug was suspended and several clinical trials were stopped. There was evidence that Centoxin might increase mortality in patients not having gram-negative sepsis. This data and several other factors (e.g., debate about the high price, unduly optimistic claims on efficacy, drug stock speculations) have contributed to the dramatic event of voluntary suspension of Centoxin(17). How did it happen that Centoxin could arouse such high and unjustified expectations? In the New York Times of February 12th 1993, Kolata stated: “The answer lies in a tale of highly touted scientific data that could not be replicated and of warnings from prominent researchers that went largely unheeded by many financial analyses and doctors.”(18)
CASES OF “TRIAL BY THE MEDIA”

At the other side of the spectrum of biomedical news lies “trial by the media,” which means heavy media coverage, frequently unfounded and unduly, with the result of inflated regulatory decision making. Two cases are striking examples of the “trial by the media” concept.

NSAID

Withdrawals from the market for safety reasons frequently comprise nonsteroidal antiinflammatory drugs (NSAID), e.g., benoxaprofen (U.K. and U.S.A. in 1982) and indomethacin in an osmotic slow-delivery system (U.K. and the Netherlands in 1983). In Table I three cases of NSAIDs under siege are shown and in all three cases “trial by the media” occurred. Benoxaprofen was successfully introduced in 1980 in a number of countries. In 1982, a cascade of (fatal) reports started a process of turmoil; political debate and consumer pressure followed, and in August 1982 the drug was withdrawn worldwide(19). Inman concluded: “The Opren affair was inflated by the media to the proportions of a thalidomide disaster but was, in reality, a comparatively minor and preventable accident. It led to a general cull of NSAIDs.”(20)

The same story happened with the 75 mg indomethacin Oros formulation (Indosmos in the Netherlands, Osmosin in the UK, Osmogit in the FRG), marketed by Merck Sharp & Dohme, and piroxicam (Feldene)(21,22). However, in case of the last example the FDA conducted a comprehensive analysis of spontaneous reports received concerning eight NSAIDs in the period 1974-1984. Several factors were identified which could have influenced the high crude numbers of side effects associated to piroxicam(23).

Halcion

The classic example of the “trial by the media” phenomenon is triazolam (Halcion)(24). In 1979 the Dutch psychiatrist Van der Kroef contacted the press with a number of cases of recipients of Halcion showing complex, difficult to interpret patterns of psychiatric symptoms. The impact of a television program was so significant that political pressure forced the Dutch regulators to take action, leading to a temporary withdrawal of the drug from the market. The scientific evidence for the decision was poor, at least at that moment.

DISCUSSION

There is no doubt about the value of sharing beneficial biomedical information as soon as possible. However, paper inflation, early promises and unduly turmoil in the media are sincere points of concern. They jeopardize the sound exchange of information within and outside the scientific and medical community. Transparency of research findings and evaluation of scientific performance on other grounds than crude listings of publications are needed. The scientific and professional community should be aware of the possible threats to the integrity in the provision of scientific information. Guidelines and codes of ethics can help, and schools in biomedical sciences should teach their students in professional publication performance. Pharmacists may contribute as gatekeepers and reviewers of publications in the biomedical and pharmaceutical press. They are in the position and have the knowledge to assure the quality of information on medicines and to warn physicians and their patients for premature and inappropriate publication of research findings.


References