Thyroid Storm

To study, to finish, to publish.

—Benjamin Franklin

I stopped a flawed study that would have put millions of patients at risk.

—Carter Eckert

In this issue of THE JOURNAL, we are publishing a report[1] of work that started 9 years ago, was concluded in December 1990, and the data from which were published in another journal in July 1995. Given that we at *JAMA* like to keep up-to-date and that we try never to republish what others have already put in print, the reader might well ask what is going on. The story necessary to answer this question provides a cautionary tale that illustrates the sharply differing views of research taken by the university researcher and the company sponsoring that research, if the company's product is at stake. At a time when an increasing proportion of research funding is provided by private companies,[2] the story holds lessons for both, as well as for university faculties, administrators, regulatory agencies, and for physicians who prescribe on the basis of evidence.

See also pp 1199, 1205 and 1224.

In this Editorial, I shall be discussing events that took place at the University of California, San Francisco (UCSF), which is where the West Coast office of *JAMA* is situated. I should make it plain that until *JAMA* became involved, I did not know, and had never had contact with, any of the research workers involved.

Background

The issue of the potency, reliability, and bioequivalence of levothyroxine preparations has continued to raise controversy.[3] Natural thyroid extracts were marketed before the regulations of 1938 and so were exempted from amendments to the Food, Drug, and Cosmetic Act requiring that drugs be proved safe and effective. Synthroid, the first synthetic version, had come to dominate a $600 million a year market[4] that was essentially unregulated because the Food and Drug Administration (FDA) had no approved standards for bioavailability and bioequivalence and no mechanism to evaluate them, and there were no adequate well-controlled trials. Such dominance was unusual, given that other competing formulations of levothyroxine had been available for years, and it was greatly assisted by the manufacturer's claims that other preparations were not bioequivalent.

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In 1987, to establish that Synthroid was truly more effective than competing preparations, Flint Laboratories, then the manufacturers of Synthroid, approached Betty J. Dong, PharmD, at UCSF. This seemed a good choice because in 1986, Dong et al[5] had published a letter showing that the levothyroxine content of different thyroid products, 2 brand-name products and 7 generic, differed widely. They noted that the 2 brand-name preparations, 1 of them Synthroid, were the preparations of choice. Flint and Dong signed a lengthy protocol/contract to finance comparative studies of the bioequivalence of Synthroid and 3 other preparations, and both sides expected the study to show that Synthroid was superior (letter from B. J. Dong to N. M. Kurtz, March 31, 1994). The contract detailed the experimental design and analysis of the data. Representatives of Flint, and after their takeover, Boots Pharmaceuticals Inc, made regular site visits, about 3 a year, to satisfy themselves that the work was being done properly. During these visits small problems were ironed out, but there was no hint of any bigger cloud.

In January 1989, at a time when there was a move to add a competitor's preparation to the Massachusetts formulary,[4] Boots, in the first of their site visits, began asking for the preliminary results of a parallel in vitro study in which tablets were compared, and because this would have meant breaking the masking code and therefore invalidating that particular study, Dong et al refused to comply. By the end of 1990, the major in vivo study was finished, and Dong sent all the results to Boots: it was clear that all 4 preparations were bioequivalent.

Over the next 4 years, Boots waged an energetic campaign to discredit the study and prevent publication of the drafts Dong and her colleagues sent to them for comment, claiming that the study was seriously flawed. Boots cited scores of purported deficiencies, including failure to carry out procedures not called for in the protocol. They alleged deficiencies with patient selection criteria and compliance, with assay reliability, with study administration, with measuring bioequivalence, and with the statistical analysis. Boots also cited unspecified ethical problems and demanded disclosure of any financial conflicts of interest, past, present, or future. Dong answered the catalog of complaints in a detailed letter (to N. M. Kurtz, March 31, 1994), noting her "serious objections to the allegations made" by Boots and agreeing to meet.

Boots also sent their complaint to the chancellor, all the vice chancellors, and several department heads at UCSF. Two investigations by the university found nothing but the most minor and easily correctible problems (letter from J. E. Goyan to N. M. Kurtz, June 5, 1992; memo from S. Fields to B. J. Dong, June 2, 1992). The company's interactions with Dr Dong were considered "harassment" to prevent publication of results the company did not like (memo from L. Z. Benet to J. E. Goyan, September 9, 1992). Dr Leslie Benet, then chairman of the Department of Biopharmaceutical Sci-

ences, characterized the company's representatives as "deceptive and self-serving."[6] UCSF found the study to be rigorously conducted in a way that complied fully with the contract. Minor deviations, made with the full knowledge of Boots, met clinical and ethical standards, and there were no violations of human subjects' procedures. Furthermore, the statistical procedures Boots criticized had been agreed on by Boots and had been performed well.

Boots had alleged numerous breaches of research ethics, but when asked by UCSF to make specific allegations that UCSF could formally investigate, Boots did not respond. Noting that all records and data had been open to Boots, who had monitored the study closely, UCSF told Boots, in August 1994, that there was no reason to suppress the manuscript and to do so would be an unprecedented intrusion upon academic freedom (letter from P. Lurie and S. M. Wolfe to D. A. Kessler, May 29, 1996). Later, they agreed to meet again with Boots, but suggested that this time it should be in the presence of officials from the FDA. That meeting never took place. Dong et al made numerous changes in their manuscript to accommodate Boots, but finally decided they would publish.

JAMA Becomes Involved

We at *JAMA* knew none of this when, in April 1994, *JAMA* received a manuscript, "Bioequivalence of Generic and Brand Levothyroxine Products," by Dong and 6 other coworkers at UCSF. The paper reported a 4-way crossover trial comparing 2 generic (Geneva Generics and Rugby) and 2 brand-name levothyroxine preparations, Synthroid (Boots) and Levoxine (renamed Levoxyl, Daniels Pharmaceuticals Inc, now Jones Medical Industries) in hypothyroid patients. The patients received the 4 preparations in a random sequence to ensure that potential carryover effects from the previous formulation would introduce no systematic bias. Each preparation was given for at least 6 weeks, and the primary investigators, including the statisticians, were blinded to the preparation. They looked at 3 aspects of bioequivalence (area under the curve, peak serum concentration, and time to peak concentration), measured for 3 indexes of thyroid function (thyroxine [T_4], triiodothyronine [T_3], and free T_4 index), and concluded that for these patients with primary hyothyroidism the 4 formulations were bioequivalent according to the FDA's general criteria for oral preparations and were therefore interchangeable. The authors calculated that if the generics or the other brand-name preparation were substituted for Synthroid, $356 million might be saved annually.

With the manuscript came a letter explaining that the work had been funded by Boots. It went on: "Boots Pharmaceutical Company has been very critical of this study despite our numerous meetings with them. . . . we have sent them all the data, including a copy of this manuscript." The letter also mentioned individuals who were paid consultants to Boots, and asked that they not be reviewers, and some who the authors thought, not always correctly, were free of such ties.

The manuscript was sent out to 5 expert reviewers, some revealing themselves as consultants to Boots. It was revised and was accepted for publication under a revised title in November 1994. Proofs were circulated and a publication date set for January 25, 1995, when, on January 13, 1995, we received a letter from Dr Dong abruptly withdrawing the manuscript from publication. She gave as their reason "impending legal action by Boots Pharmaceuticals, Inc against the University of California, San Francisco and the investigators." When I inquired, Dr Dong explained to me that in the protocol/contract she had signed back in May 1988, there was a restrictive covenant which read: "All information contained in this protocol is confidential and is to be used by the investigator only for the conduct of this study. Data obtained by the investigator while carrying out this study is also considered confidential and is not to be published or otherwise released without written consent from Flint Laboratories, Inc." They did not have this permission, and she had just been told by a UCSF attorney that because of this clause, the university advised her to withdraw the paper, saying it would not defend the authors if a suit was brought by Boots.

Knowing that the University of California forbids such restrictions on the right to publish, I asked how she had managed to sign such an agreement. She said that she had assumed the clause to be routine. It was in fact common, partly because until 1993, there was no general requirement for centralized review of such contracts, and the university attorney was told only after the fact. Dr Dong had not previously informed *JAMA* because she had been reassured by the university lawyers that such contracts had never before prevented publication, and she had repeatedly informed the company that she intended to publish. UCSF was now convinced that the company would forbid publication. The senior author claimed to have been twice threatened with the possibility of lawsuit should sales of Synthroid suffer as a consequence of publication. The company has vigorously denied making such threats.[4]

The Position at the University

At the University of California, "Freedom to publish is fundamental to the university and is a major criterion of the appropriateness of a research project."[7] At the most, the sponsor could be allowed 30 days for comment and, where a patent application was to be filed, an extra 60 days. Dong had in fact signed a clause giving a sponsor veto rights over publication, which somehow failed to receive the requisite administrative review. Despite this, the university counsel whom she consulted advised her that, though it was improper of Dong to have signed a contract with this restrictive clause, not least because she would be in breach of their contract with the university which states that "the University will undertake research or studies only if the scientific results can be published or otherwise promptly disseminated,"[8] there was unlikely to be a problem.

When Dong and her colleagues finally decided that the company's scientific concerns were spurious delaying tactics and that they should publish, the university, now with a new lawyer, was faced with a difficult choice. The university knew the financial stakes had risen because of an impending takeover of Boots, and they had to consider "the possibility of significant damages the company might claim by virtue of publication of the article."[9] Extensive negotiation failed to change the university's opinion that the contract superseded any general right of a member of the faculty to publish, or considerations of science or the public health.

Boots/Knoll

At this time the pharmaceutical manufacturing arm of Boots was indeed being considered for purchase, and information on

the comparative bioequivalence of its most important drug, Synthroid, might affect its price. In March 1995, the company was bought by BASF AG, for $1.4 billion, and is now part of their Knoll Pharmaceutical subsidiary. In May 1995, *JAMA* and a number of other journals received a letter from Dr Gilbert Mayor at Boots/Knoll, who had been monitoring the work of Dong et al, disparaging both the study and Dr Dong, and saying that the journals should "be concerned about publishing [the paper]." Meanwhile, Boots/Knoll had hired firms of investigators to look, among other things, into possible conflicts of interest on the part of the UCSF researchers (of which they had none).

Unable to publish their paper and receiving calls from their acquaintances asking about the firms' inquiries, Dong and her colleagues were further mortified when Mayor et al,[10] employees of Boots/Knoll, not only published the results of the study by Dong et al in a 16-page article without any acknowledgment to the people who did the study, but did so in a reanalysis that reached the opposite conclusion and threw doubt on the work at UCSF. Indeed, the article contains a table showing 18 "major study limitations." Using the UCSF data, Mayor et al agreed that bioequivalence of all the preparations was the same, but if correction was made for baseline values (something Dong et al did not do because they thought it inappropriate, partly as it produced negative values for levothyroxine), the preparations were "therapeutically inequivalent." The effect would, of course, be at the same time to strengthen the position of Synthroid and make it impossible for any journal to publish Dong's paper. The article by Mayor et al was published in a new journal, the *American Journal of Therapeutics*, of which Mayor was an associate editor.

Publicity

The issue came to the attention of the public when, on April 25, 1996, the *Wall Street Journal* published a meticulously researched account of the story, written by Ralph King. The Boots/Knoll position was best summarized by Carter Eckert, president of Boots/Knoll, who was quoted as saying: "I stopped a flawed study that would have put millions of patients at risk."[4]

Food and Drug Administration

On August 26, 1994, the FDA wrote to Boots (letter from A. M. Reb to R. F. King) saying that an article published in 1992 by 2 Boots researchers, Berg and Mayor,[11] on work done at IBF Research Corporation, Scarborough, Ontario, to support the position that Synthroid was pharmacokinetically superior to other preparations was misleading and should not be disseminated by Boots. This article showed that in normal volunteers studied over 48 hours (the half-life of levothyroxine is 7.6 days), there was a difference in absorption between Levoxine (now Levoxyl) and Synthroid.

Boots replied (letter from K. F. King to A. M. Reb, September 20, 1994), arguing that the study by Berg and Mayor[11] was designed not to test bioequivalence but to identify bio*in*equivalence. And a later letter from Knoll (letter from B. A. Buhler to P. C. O'Brien, July 12, 1995) quoted the Berg and Mayor article as saying that to determine bioequivalence "would require a more complex design involving chronic administration in a well-controlled hypothyroid population with the measurement of several endpoints, including thyroid-stimulating hormone." The Knoll letter further stated that "Knoll can state unequivocally that it is aware of no study that has been published or even conducted that satisfies these criteria," though the Berg and Mayor article cited 4 published ones the authors considered to be deficient. For the first time the company mentioned the unpublished work done by Dong et al, which Mayor and the company had known about for 3 years before the Berg and Mayor article came out. The letter cited it as the "upcoming" paper by Mayor et al,[10] and dismissed the work on which it was based as worthless.

Despite this, on November 7, 1996, the FDA wrote to Knoll concluding that Knoll had violated the Federal Food, Drug, and Cosmetic Act, 21 USC §331(a) by misbranding Synthroid (letter from M. Baylor-Henry to R. Ashworth). The FDA letter continues: "[T]he endpoints evaluated were the rate and extent of absorption over a relatively short period of time (less than one half-life) following supra-therapeutic doses of levothyroxine sodium [in normal volunteers]. . . . [T]he authors noted that to show similarity, 'a more complex design involving chronic administration in a well-controlled, hypothyroid population with the measurement of several endpoints' [11] would be required."

The letter noted that Knoll was in possession of the results of the study by Dong et al, which the company had not disclosed. The FDA wrote that the article by Dong et al was "a study with just such a more complex design involving administration of thyroid replacement products in a hypothyroid population with the measurement of several endpoints, including thyroid stimulating hormone." And, of course, the manuscript written by Dong et al reached opposite conclusions: namely, that Synthroid was bioequivalent with the other preparations.

Knoll Changes Its Mind

Under pressure from the FDA, and perhaps realizing that the public perception was so negative, Knoll began negotiations with the university. Eventually, this resulted in the current president of Knoll, Carter Eckert, and a board member, Louis Sullivan, MD (former secretary of the US Department of Health and Human Services), meeting with the chancellor of UCSF on November 25, 1996. Knoll agreed not to block publication of the manuscript by Dong et al, while still insisting that its conclusions were not supported by the data.

JAMA is now publishing the manuscript set into proof 2 years ago[1]; none of the content has been changed. *JAMA*'s mission is the public health, and we try hard to select the best papers we are sent. We do not claim that we are publishing a perfect study, just one of the best, made as good as expert review can make it. Experience has taught us that there are very few studies in which some reviewers cannot find flaws, and so it may be here. For example, though mean values of thyrotropin (TSH), the important long-term measure, were similar, individual values differed. Because this may make a difference to individual patients when switching therapy, some clinicians may feel that bioequivalence might not be the clinically relevant parameter when switching, as opposed to starting, therapy. However, it is our belief that this is a good study carried out by highly competent workers following a sensible design that tried to answer an important question. It is hard to believe that the sponsors would have made such extraordinary efforts to delay and block publication of the

study for such a very long time and for such an extraordinary number of specious reasons if the results had shown Synthroid to be better.

At the same time, we are publishing a letter from Knoll apologizing for blocking the manuscript,[12] and another objecting to its conclusions,[13] as well as rebuttals from Dong et al.[14,15] Given that Knoll has already made an extraordinary preemptive strike by publishing its lengthy criticisms of the study by Dong et al at a time when it looked as though the latter would never see the light of day, we do not think Knoll requires more space.

What Are the Lessons?

For Researchers and Faculty.—Even if researchers have been approached by sponsors, investigators should not assume that the sponsors will encourage publication of unfavorable results and should never allow sponsors veto power. Dr Dong was naive, but faculty members are the last line of defense against industry interference, and she and her colleagues deserve credit for standing up for their academic rights.

Given that this is an issue basic to their freedom to publish, the reaction of faculty at UCSF has been mixed. Many seem to have considered, reasonably enough, that Dr Dong had brought this upon herself and her colleagues by foolishly signing the contract and did not realize it could be challenged. But I believe that other considerations have been at work. Some faculty, perhaps hoping for commercial success, might have imagined the view from the commercial side of the fence and sympathized with the company. Or perhaps they were worried lest Dong and her coworkers might, by their stance, have spoiled things for others hoping for pharmaceutical company sponsorship and fearing that potential sponsors would be driven to friendlier universities or to commercial drug-testing shops.

The answer starts with the realization that when something like this happens, everyone loses, from researcher, to sponsor, to patient. But none stands to lose more than the faculty and the university. When it is revealed that its faculty can be bullied and kept quiet by their sponsor, yet the university has failed to back them fully on this basic issue, the university's reputation inevitably suffers. When there is no outcry, the faculty is seen as willing to cede its freedoms.

For the University.—All academic research institutions should forbid such clauses. But the problem would never have arisen had the university set up a system to screen them out. The university, handicapped by its faculty's signature on this restrictive clause, investigated charges against, and cleared, the researchers, while encouraging them to publish. Then, overawed by the amount of money they thought might be at stake, the university suddenly switched its position and told the researchers they would be at great personal jeopardy if they were to publish because the university would not defend them.

There are 2 views of the clause in the contract giving the company veto power. One, the narrower, holds that Dr Dong, without permission of the university and against its regulations, signed her publication rights away. She was bound by the letter of the contract, and any attempt to get out of it would have been legally doomed. In this view, the university had to advise against publication. If the researchers had gone ahead against its advice, the university would be freed from its statutory duty to indemnify and defend its faculty, and the researchers would have been on their own. This is the view that prevailed.

The other view, and that taken by the UCSF attorney who originally advised Dr Dong, was that when the company approached her they knew she did not work at a commercial drug-testing laboratory, but at a university, where she had a duty to publish, and where a high premium was placed on publication. The restrictive clause was incompatible with university regulations and the purpose of university research and was at odds with the purpose of the rest of this research contract.

The university, well aware of the importance of publication and the refusal of Boots/Knoll to consent to it, could have taken the case to court by filing for a motion for declaratory judgment, whereby a judge would be asked to rule on the meaning of the contract, particularly the reasonableness of the restrictive clause. With a ruling in their favor, Dong et al would have been free to publish. However, UCSF apparently failed to threaten to do so to Knoll's legal counsel, and when UCSF put this idea to the researchers, the plan died because the faculty was under the impression that this would require them to engage in a lengthy court battle and because the faculty was still afraid of being left to fend for themselves in any suit after publication.

In my view, an academic principle of the highest priority was at stake and recognized as such in the university's policies, and this principle should have been immediately and staunchly defended, notwithstanding the language of the contract. If the university had advised publication and stood behind its faculty, I doubt whether any suit would have resulted, if only because of the consequent adverse publicity to the company.

A university must above all things support the rights of its faculty. Indeed, California law requires UCSF to defend its employees, of whom Dong was one. The failure to do so seriously threatens academic freedom by creating an impression that the university will not back its faculty's right to publish or even to use results for other purposes, for example, teaching. This should be pondered by all segments of the institution if it is intent on encouraging academic-industry partnerships. Pharmaceutical companies come to researchers because they wish to form mutually beneficial cooperative relationships in developing and testing their products. And they come to places like UCSF because of its extraordinarily high reputation, hoping that some of the prestige of the university and its researchers will carry through to influence the FDA and the prescribers. Commercial sponsors are most likely to take their business elsewhere when the best people leave. And if the university, lawyers, and faculty cannot be trusted to defend faculty on such a key issue, why should they feel confident about staying?

For the Company.—I am relieved that the company president has said, in response to a highly critical editorial in *Science*,[16] that Knoll is "committed to strong industry academic partnerships."[17] A skeptic might ask whether the company's change of heart came in order to appease the FDA after the company had successfully delayed the bad news several years to maintain the market position of Synthroid and to increase the purchase price of Boots. Nevertheless, I congratulate them on belatedly seeing that neither academics nor the public are likely to commend their heavy-handed

tactics. I suggest that it is in the long-term interests of companies intending to sponsor research to be careful not to include such restrictive clauses if they wish to attract the best investigators.

Companies should realize that even if, as in the present instance, they select researchers whose results have favored the company's product in the past, the results may go against them. Sponsors must understand that researchers at universities have a duty to publish and a self-interest in publication. It may seem that the short-term interests of a company will be served by suppression of the results, but the public revelation of bullying tactics and spurious charges will ultimately damage the name of the sponsor in the eyes of the profession, the FDA, and the public.

For the FDA.—Thyroid preparations were grandfathered in by the 1938 Food, Drug, and Cosmetic Act, which required demonstration of safety, and the 1962 amendment, which required that drugs be shown to be effective. As is the case with other preparations of levothyroxine, Synthroid, introduced in 1958, could reasonably be regarded as a reformulation. The FDA has the authority to designate important pre-1938 drugs that have been reformulated as "new" drugs and require a New Drug Application (NDA). The FDA has taken this course in the cases of, for example, theophylline, phenytoin, quinidine, and digoxin. With levothyroxine, the issue is not so much safety and efficacy, but the requirement that its bioavailability be demonstrated. This itself would require specific standards to be set for levothyroxine, which would then allow bioequivalence to be measured and therefore generic substitution. One advantage of pursuing the NDA route is that it would finally let the practitioner and the public know whether substitution with cheaper formulations was appropriate and would dispel the confusion surrounding present claims of bioequivalence. It is, however, an arduous route to take merely to straighten this out for a drug that is good and one relied upon by millions.

A simpler and possibly more fruitful approach to setting standards for both bioequivalance and clinical interchangeability might be for scientific organizations with the best expertise in this area, such as the American Association of Pharmaceutical Scientists, the American Society for Clinical Pharmacology and Therapeutics, and the American Thyroid Association, to establish guidelines by consensus, which they could then publish for the benefit of all.

For Professional Societies.—The research community is getting progressively more entangled with industry, as became evident to me when I found it hard to find thyroid experts to review the paper who did not have financial ties with Boots/Knoll. This is a reflection, perhaps, of the extraordinary market dominance of Synthroid and, associated with this, the munificent scale of research and educational grants given by Boots/Knoll. But there is an inverse side which is dependence. Recently, for example, the American Thyroid Association, which receives more than 60% of its commercial sponsorship from Knoll, had the courage to debate whether to write to Knoll to allow publication of the paper. Obviously, the members could not debate its merits as it was unpublished, and the senior author of the manuscript by Dong et al, Dr Greenspan, did not attend the meeting, partly because the gag clause in the contract forbade him from discussing it. The motion to write the letter was narrowly defeated. At stake was the crucial ethical issue of suppression of a manuscript coauthored by one of its most distinguished members. An outsider is left with the sad impression that the ability of the association to influence these events by speaking with moral authority was weakened by its heavy dependence on money from Knoll.

Having said this, I would point out that other specialty societies supported by Knoll have failed to address the issue at all. And the American Thyroid Association, at the same meeting, voted to write to pharmaceutical companies to indicate that clauses restricting publication be removed from contracts; to write to their members advising them to avoid such clauses; and to write to the FDA requesting appropriate guidelines for bioequivalence studies. The association has also taken steps to make itself more independent of corporate sponsorship: an essential prerequisite for maintaining the public trust.

But the fact is that though all of us believe we are personally uninfluenced by money or gifts, that is not how others see it. If academic societies wish to retain any credibility, they should consider making sure that no individual sponsor can contribute, for example, more than 5% of the total, and, for example, rely more on charging their members realistic dues. Meanwhile, if academics wish to be credible as objective authorities, they should be cautious when they accept speaker's fees and travel advances from individual companies, lest they be accused of conflict.

Institutions and researchers worry that research money will go to more compliant places in a race for the ethical bottom. The answer to this is for prestigious societies such as the Association of American Medical Colleges and the Association of American Universities, which work by moral persuasion, to set up standards for such contracts. I strongly recommend that they do this, and soon.

For Journals.—This has been an awkward time for *JAMA*. We put in a lot of work on the paper, only to see it suddenly withdrawn at the last moment. But when the news broke, we were constrained from discussing it because of the rules against discussing unpublished papers. We were then shocked when the reanalysis of "our" paper appeared in print.[10] A journal's job is to select the best, publish it, and then let the criticism come in, but certainly not to publish results hijacked from those who did the work. I believe that editors of the journal publishing the paper by Mayor et al should examine their policies carefully.

Is This Common?

The Synthroid case, where publication was delayed about 7 years, seems an extreme case. However, in this issue of THE JOURNAL, we publish a paper from Blumenthal et al[18] on withholding of research results by researchers. These authors found that almost 20% of 2100 life science faculty reported delay of over 6 months in the publication of their research results. Of 410 respondents to their survey who reported such delay, in 28% it was "to slow dissemination of undesired results." It is not clear whether such an unacceptable delay came from the scientists themselves or from industry sponsors. Blumenthal et al conclude that withholding is not widespread. Perhaps. But if "undesired results" are withheld by only about 5% of all researchers, the fears induced by the increased part industry is playing in the funding of research are not dispelled. And before we decide the danger is past, workers at Carnegie-Mellon University reported

that in their sample of university-industry research centers, 35% of the signed agreements allowed the sponsor to delete information from publication, 53% allowed publication to be delayed, and 30% allowed both.[19]

The ethical dilemma in which researchers may put themselves is also not trivial. In 1995, Dr Nancy Olivieri published an optimistic article on the effects of an oral iron-chelation agent.[20,21] As her trials proceeded, however, she became disturbed by increasing evidence of the agent's lack of effectiveness. She found an increase in hepatic iron in those on the oral therapy, despite good compliance over 2 years, and she was concerned about possible danger to patients. She had signed a confidentiality agreement with her sponsors, the makers of the drug. She decided she had to break confidentiality by reporting her results at a meeting.[22,23] The manufacturers disagreed with her interpretation of the results and tried unsuccessfully to block her presentation. Because she now feels that she risks litigation for having made her presentation, she would not, on the advice of her attorney, speak with me.

Rosenberg,[24] sounding the alarm, makes the point that secrecy in research is increasing and gives 4 examples from his personal experience. He writes: "The goals of medical research are clear: to prevent human suffering and premature death from disease. . . . Deliberately withholding useful information . . . is a violation of this principle." As I have pointed out before,[25] a major problem in medicine is failure to publish the results of studies that show no advantage to the intervention under study, so that treatments tend to be based on biases in favor of the new. I take Chalmers' position[26] that it is unethical not to publish such negative results. The Olivieri case, hinging as it does on the interpretation of data about the safety of a therapy, shows that this is not just a theoretical position.

Rosenberg[24] concludes, as do I, that scientists should never sign any agreements that give their sponsors veto power over publication.

Marshall[27] has recently described the battle in genome research between those who wish to lock up results by delaying publication and those, including sponsors both governmental and commercial, who see a wider societal good in putting gene sequences promptly into the public domain. Marshall notes that, for example, withholding DNA sequence data on pathogens could cost human lives, but is "commonplace." It is too early to see who will win, but unless the scientific community gives its strong support and approval to sponsors who forbid secrecy, we will all suffer the consequences.

Conclusion

We are proud to publish the article by Dong and her colleagues. We believe it is good work, not merely because it passed peer review by more than the usual number of experts, but because it has also passed careful and prolonged scrutiny by the university in response to widely disseminated allegations of scientific defects and ethical violations. We are also confident in the work because of the university's finding that none of the allegations had the slightest merit and because they came from those who had most to gain if the work was discredited. Now that the thyroid storm has passed, clinicians and third-party payers finally have the information they need to best serve their patients.

Coda

There is nothing new about commercial sponsorship of research, a fact brought home to me when I was privileged to attend the June 1996 meeting of the International Committee of Medical Journal Editors (the Vancouver Group) in the Council Room in the Trent Building of the University of Nottingham in England. As we editors discussed the implications of the suppression of the paper by Dong et al, we did so under the portrait of the man who would become Baron Trent (1850-1931) and who had given the land and the money for the Trent Building to be built in 1928. Lord Trent, who founded the chain of retail chemists (pharmacies) that have made his name a household word in the United Kingdom, started off life as Jesse Boot. I wondered whether Boot would have been prouder of the research his company had sponsored or of the skill with which his company had protected the interests of its shareholders.

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I have greatly benefited from the constructive comments of a score of colleagues, 12 of whom criticized an earlier draft of the manuscript.

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In Reply.—As Dr Maki and colleagues point out, experimental and metabolic studies offer strong evidence supporting a beneficial short-term effect of high-fiber diets on glucose metabolism. In patients with NIDDM, this effect appears to be greater for purified viscous soluble fiber than for less viscous fibers.[1] However, among healthy subjects, short-term supplementation of nonviscous fibers seems to have a greater beneficial effect on glucose tolerance than do viscous fibers.[2]

In our study population, the main source of dietary fiber is cereals, and more than 75% of this fiber is insoluble. However, the main sources of insoluble fibers are also the important sources of soluble fiber; thus the intakes of these components are highly correlated (r=0.89). When we compared the lowest and highest quintiles of energy-adjusted intakes, insoluble fiber was inversely associated with risk of diabetes (RR, 0.76; 95% CI, 0.61-0.95) after controlling for other important factors—whereas soluble fiber intake was not related to risk (RR, 1.07; 95% CI, 0.86-1.33). Thus, the apparent benefit of dietary fiber in our study was not primarily due to soluble components.

As Dr Nadler and colleagues state,[3] there is a growing body of experimental and clinical evidence suggesting that magnesium can play an important role in glucose metabolism and insulin resistance. Our epidemiologic data also provide evidence that adequate magnesium intake may be important in the prevention of NIDDM.[1,4,5] Thus, we agree about the need for further research on the potential benefits of magnesium supplementation, not only in diabetic patients, but also in populations at high risk for NIDDM.

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Virginia Apgar and the Apgar Score: Kudos and a Correction

To the Editor.—The captivating collage by Mr Skolnick on Dr Virginia Apgar[1] included the history of the Apgar Memorial String Quartet, the beguiling personality of Dr Virginia Apgar, and that incredible 1957 nocturnal caper at the Harkness Pavillion when she and Carleen Hutchins "liberated" the curly maple shelf of a telephone booth that they transposed to the back of Apgar's viola.

It is an unfortunate gaffe, however, that the article claims that the Apgar score "is often highly predictive of the child's later psychocognitive development" to those who would retire or defend the Apgar score. This issue has been debated ad nauseum with the usual conclusion that the Apgar score is still the best clinical tool for the evaluation of the newly born infant and that it was never intended to predict later outcome.[2]

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1. Skolnick AA. Apgar quartet plays perinatologist's instruments. *JAMA*. 1996;276: 1939-1940. Correction: *JAMA*. 1997;277:1819.
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CORRECTIONS

Incorrect Statement.—In the Medical News & Perspectives article entitled "Apgar Quartet Plays Perinatologist's Instruments," published in the December 25, 1996, issue of THE JOURNAL (1996;276: 1939-1940), an incorrect statement appears. The concluding phrase in the last sentence of the second paragraph in the first column on page 1940 should be deleted. That sentence should read: "Although it's almost absurdly simple and requires no sophisticated equipment, the Apgar score continues to provide a quantitative measure for evaluating obstetrical outcomes, procedures, and research."

Incorrect Statement.—In the Editorial entitled "Thyroid Storm," published in the April 16, 1997, issue of THE JOURNAL (1997;277: 1238-1243), an incorrect statement appeared. On page 1240, in the seventh full paragraph, Louis Sullivan, MD, was incorrectly identified as a board member of Knoll Pharmaceutical Company.