Clinical Research in the Lay Press: Irresponsible Journalism Raises a Huge Dose of Doubt

Elias J. Anaissie,[1] Brahm H. Segal,[55] John R. Graybill,[3] Carola Arndt,[49] John R. Perfect,[25] Michael Kleinberg,[12] Peter Pappas,[52] Danny Benjamin,[99] Robert Rubin,[27,28] Judith A. Aberg,[53] Elisabeth E. Adderson,[14,15,16] Felice C. Adler-Shohet,[95] Hamdi Akan,[87,88] Murat Akova,[100] Nikolaos G. Almyroudis,[55] Barbara D. Alexander,[26] David Andes,[44] Antonio Arrieta,[96] John W. Baddley,[52] Michelle A. Barron,[43] Howard Belzberg,[94] Helen W. Boucher,[30] Thomas G. Boyce,[49] Arturo Casadevall,[54] P. H. Chandrasekar,[64] John D. Cleary,[56,57] Catherine Cordonnier,[80] Oliver A. Cornely,[83] Manuel Cuenca-Estrella,[101] Jennifer S. Daly,[32] Nicholas Daoura,[7] David W. Denning,[67,68] Ben dePauw,[89] Louis de Repentigny,[76] Maria Cecilia Dignani,[84] William E. Dismukes,[52] J. Peter Donnelly,[71,72] Gerald R. Donowitz,[41] Bertrand Dupont,[79] George Drusano,[98] Michael Ellis,[102] Ana Espinel-Ingroff,[47] Jay A. Fishman,[31] Rhonda Fleming,[8] Graeme Forrest,[12] Mahmoud Ghannoum,[63] Mitchell Goldman,[41] Monica Grazziutti,[1] John N. Greene,[36] Richard N. Greenberg,[58] Paul O. Gubbins,[2] Susan Hadley,[29,30] Raoul Herbrecht,[81] John W. Hiemenz,[21] William Hope,[13] Durane R. Hospenthal,[93] Shahid Husain,[17] James I. Ito,[34] Robert M. Jacobson,[49] Melissa Johnson,[91] Michael R. Keating,[39] Daniel H. Kett,[37,38] Katherine Knapp,[14] Dimitrios P. Kontoyiannis,[6] Vladimir C. Krcmery,[103] Robert Larsen,[33] Michel Laverdiere,[75] Per Ljungman,[73,74] O. Lortholary,[79] Johan Maertens,[69] Debbie Marriott,[104] Gloria Mattiuzzi,[5] Michael R. McGinnis,[9,10,11] Michele Morris,[38] Marcio Nucci,[82] Frank C. Odds,[66] George A. Pankey,[20] Thomas Patterson,[3] Mike Pfaller,[35] Raymond R. Razonable,[50] Annette C. Reboli,[65] Michael G. Rinaldi,[4] Glenn D. Roberts,[48] Juan Luis Rodriguez Tudela,[101] Coleman Rotstein,[77,78] Markus Ruhnke,[105] Mindy Schuster,[19] Shmuel Shoham,[59] Irene G. Sia,[51] Nita Siebel,[61,62] Fernanda Silviera,[17] Nina Singh,[17] Jack Sobel,[64] Joseph S. Solomkin,[90] Tania C. Sorrell,[97] William J. Steinbach,[22,23,24] Zelalem Temesgen,[50] AnnaMaria Tortorano,[85] Shahe Vartivarian,[7] Paul VerWeij,[70] Claudio Viscoli,[81] Maria Anna Viviani,[85] Randall C. Walker,[50] Joseph L. Wheat,[42] Joseph Wiley,[92] Peter Williamson,[106] John R. Wingard,[40] Victor L. Yu,[17] and Theoklis Zaoutis[18]

In an era in which science and medicine make front-page news in the lay press, it is critical that the complex workings of clinical investigation be portrayed accurately to the public. The appetite for news of medical "breakthroughs" seems insatiable at times. In this setting, sensational articles about medicine, physicians, and pharmaceutical companies can easily find an attentive audience that may be unable to distinguish truth from sensationalism. To provide a case study for how inaccurate and dangerous the mainstream press can be if articles are not carefully written, as well as to correct inaccuracies and defend honesty in research, we offer our counterpoint to a recent article [1] that questions the various systems of checks and balances that govern the conduct of clinical trials and implicitly accuses one of our infectious diseases colleagues of unethical conduct in 2 clinical trials.

In "A Times Investigation: Drug Trials with a Dose of Doubt" [1], an article written by reporter David Willman and published in the *Los Angeles Times*, Dr. Thomas Walsh, the Chief of the Immunocompromised Host Section, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health (NIH), was implicitly accused of unethical conduct in 2 randomized, controlled trials of empirical antifungal therapy for persistent neutropenic fever. Walsh was the lead author of both of these multicenter trials, both of which were published in the New England Journal of Medicine [2, 3]. The first study compared conventional deoxycholate amphotericin B (D-AmB) with liposomal amphotericin B (L-AmB), and the second compared L-AmB with caspofungin. Specifically, Walsh, the principal investigator, was implicitly accused of deliberately underdosing the standard therapy drug to favor the investigational agent of the pharmaceutical sponsor.

We use the term "implicitly accused," because Willman is careful to not make explicit accusations of wrongdoing. However, when all of the misleading statements, nonsequiturs, loaded and pejorative descriptions, and selected quotations are strung together, Willman creates the image of a respected NIH scientist and pharmaceutical companies colluding to rig trials to win US Food and Drug Administration (FDA) approval for the favored drug (table 1). Willman implies that the biased trial design jeopardized patient safety because patients with life-threatening infections were treated with inadequate doses of antifungals. Implicit in these accusations is the contention that

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Author affiliations are listed at the end of the text.

Reprints or correspondence: Dr. Elias J. Anaissie, Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, 4301 W. Markham, Slot 816, Little Rock, AR 72205 (anaissieeliasj@uams.edu).

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experienced physicians at multiple levels of oversight—including physicians at the NIH and FDA, site investigators and members of institutional review boards at dozens of health care centers, and the members of the New England Journal of Medicine editorial boards—either actively colluded in this conspiracy or had such poor knowledge about empirical antifungal therapy that they did not realize that a conspiracy had occurred. Although the title "Drug Trials with a Dose of Doubt" is an attention grabber that sells newspapers, an accurate representation of the facts will show that these trials were conducted with sterling integrity.

JUST GETTING STARTED

Willman opens his "investigation" with the implicit accusation that Walsh had extraordinary influence over the FDA's approval of caspofungin. Caspofungin was initially approved as therapy for invasive aspergillosis in patients with refractory infection or intolerance to standard therapy. Willman correctly notes that the database involved a limited number of patients. However, this drug, representing a new class, was free of serious toxicity and had encouraging results in treating this life-threatening infection [5]. The FDA weighed the limited but supportive database, the acute, unmet need for effective therapeutics against aspergillosis, and the recommendations of its 12 independent advisory board members, and arrived at the very reasonable decision to approve caspofungin. Yet, Willman gives the false impression that Walsh had a singular influence over the FDA's decision. "Merck summoned to the microphone one of its announced consultants, a man whose government job was nearby, at the NIH. Dr. Thomas J. Walsh assured the committee that Merck's data describing the patients was 'extremely robust and very, very rigorous.' … The advisory committee voted unanimously to endorse the drug … Sixteen days later, the FDA approved it" [1].

On the basis of Willman's remarks, an intelligent lay person may question whether the FDA actually looked at the data or whether Walsh's remarks at the microphone were all the assurances that the FDA needed. The absurdity of this scenario is stunning, and yet Willman supports this allegation with a series of non sequiturs. Because Walsh and the FDA physicians are federal employees, Willman implies that Walsh must be in a unique position to influence FDA decisions and to single-handedly attain FDA approval of major drugs. The NIH and the FDA are entirely separate federal administrations with distinct missions and oversight. What is the evidence for Walsh's purported excessive influence over the FDA? None exists. Unfortunately, Willman was just getting started.

CONSPIRACY BETWEEN WALSH AND THE PHARMACEUTICAL INDUSTRY TO RIG THE DRUG-APPROVAL PROCESS?

At the heart of the Willman "exposé" is the contention (although it is never explicitly stated) that the 2 clinical trials were rigged to increase the likelihood of FDA approval of the investigational drugs. Willman's evidence consists of selective quotations from letters to the editor that raised concerns about the dose of standard drug used in the trials. Willman's use of these selective quotations is antithetical to the rigorous, unbiased science that he claims to defend. Letters to the editor serve as a forum for debating points in published material and are typically critical. Some letters make cogent arguments. Others do not. More importantly, letters to the editor are typically authored by one or a few physicians, do not reflect broad consensus, and, unlike the article that they critique, are not subject to rigorous peer review. The web of deceit that is implicitly alleged in this conspiracy theory is intricate but centers on 2 issues: selective enrollment of patients and picking dosages of antifungals to bias outcome.

PICKING PATIENTS

The first layer of purported deceit implicitly alleged by Willman's article [1] involved the selection of the type of trial that would have the highest likelihood of securing FDA approval. Willman states that, "for makers of new antifungal drugs, less burdensome clinical study standards could make it easier to get the products approved … for instance some companies wanted to enroll cancer patients with suspected but unproven fungal infections," thereby implying that studies of empirical therapy are not scientifically valid and are only designed for cherry-picked patients. We disagree. The rationale for empirical therapy is to treat a potential occult invasive fungal infection before it becomes clinically overt. This concept is based on the central tenet that early treatment of invasive fungal infections improves outcome and that lower doses, when used early, may benefit patients—particularly those patients with infections that are difficult to diagnose (such as invasive fungal infections). Before the development of empirical therapy, unsuspected infections with *Candida* species, *Aspergillus* species, and other fungi were frequently diagnosed at autopsy [6, 7]. Empirical antifungal therapy, as conducted in the 2 trials at issue, has been studied in >3000 patients and has been endorsed in authoritative guidelines from infectious diseases and hematology professional societies in North America and Europe [8, 9]. At the time that the 2 trials in question were designed, empirical antifungal therapy was a bedrock principle and standard-of-care for patients at risk for suspected fungal infections and was, therefore, a legitimate subject of clinical investigation. The recent availability of safe antifungal agents and improved diagnostic tools has opened a scientific debate about the current role of empirical therapy, with some investigators advocating different approaches [10]. These and other differences of opinion represent the scientific debate that is part and parcel of any scientific field.

Table 1. Statements made in the Willman article [1] and our rebuttal.

Willman's statements	Rebuttal
"U.S. law generally prohibits a federal employee from representing an outside party before a government agency."	As the principal investigator and chair of the data review committee of both trials in question, it was appropriate for Walsh to present the data to a US Food and Drug Administration advisory committee.
"…controversy has flared over whether results from two of the studies were misleading and whether some of the participating patients received adequate treatment."	The criticisms made in peer-reviewed journals related to the studies in question [2, 3] reflect honest debate about trial design. The criticisms cited by Willman were made by a distinct minority of clinical scientists. To our knowledge, the only published article that has implied unethical conduct in these studies is Willman's.
"In separate letters to a leading medical journal, other researchers criticized two of those studies. They questioned whether the studies artificially boosted the new products by comparing them to drugs that were given at doses that were too low."	Willman blurs the distinction between honest disagreement and debate in peer-reviewed journals and accusations of misconduct. A letter to the editor reflects only the views of the authors of the letter. In contrast, the conduct of a major multicenter randomized trial requires consensus among site investigators, institutional review boards, and regulatory agencies as to what constitutes standard of care.
"More patients died who took the 'comparator' drugs than those who got the new products."	This statement is misleading. In the D-AmB versus L-AmB (AmBisome; Fujisawa/Astellas) trial, overall survival was similar. In the caspofungin versus L-AmB trial, there was a trend toward superior survival among caspofungin recipients. As we discuss exhaustively in the text of our article, the dosage of L-AmB (3 mg/kg per day) was the same in both trials and was the FDA-approved dosage for this indication. The favorable results in the caspofungin arm do not denote that the study was rigged to favor this drug.
"No published study has established that a higher dose of an antifungal drug is more effective in treating suspected infection, and some studies have suggested that lower dosing may provide similar benefits. But the possibility that patients did not receive adequate doses, combined with Walsh's advisory role with the drug companies, adds a new dimension to the furor over NIH scientists' ties to industry."	Willman's first point concedes that there is no evidence that patients in the control arms of either study in question received an inadequate dosage of drug. As the principal investigator of the trials in question [2, 3], Walsh's relationships with the pharmaceutical industry were legitimate. It seems to us that Willman may be more interested in creating "a new dimension to the furor" than in reporting on one.
"Eight doctors, including seven who participated in one or the other major study with Walsh and who are not employed by the NIH, also contacted the newspaper and said they stood behind the validity of the research. The study designs, they said, 'were both scientifically and medically sound, reflect the state of the art in the field, and have advanced supportive care, improving the management of patients worldwide and saving lives.' Other researchers have said that doses of comparator drugs that are inadequate may endanger patients or make a new drug look more effective than it is."	These 8 researchers, along with over 100 other investigators who are authors of this article, stand by the integrity of these studies [2, 3]. Moreover, we take this stand in support of the integrity of these studies and of Dr. Walsh publicly. Willman makes his implicit accusations of misconduct in the studies in question behind the invisible facade of unnamed "other researchers." These "other researchers" are unwilling to state their views in the open and are thus accountable to no one.
"Patients with early fungal infections who were given AmBisome 'may have received suboptimal doses of that drug at a time when frontloading of therapy is critical to gain control of the infection,' Marty and a colleague wrote. 'You have a bad infection and you don't get enough drug, you may be dead,' Marty said. He noted that the medical-practice guidelines—cowritten by Walsh—suggested a dose of 5 milligrams per kilogram of body weight for aspergillus. For those patients, Marty said, 'you're not doing a good job with 3 milligrams.'	Willman confuses the distinction between empirical antifungal therapy and early treatment of an established fungal infection. Dr. Marty's last point has been proven incorrect. A recent high-quality, randomized study showed that L-AmB administered at 3 mg/kg per day was equally as effective as but less toxic than a dosage of 10 mg/kg per day as initial therapy for invasive mold infections [4]. This study, once and for all, ends any controversy regarding dosing of L-AmB for invasive mold infections. The implications of this study were pointed out to Willman by outside experts interviewed by Willman prior to publication. Willman dismisses this critical study in his article by mentioning its existence in the context of a statement by Dr. Walsh offered in his own defense. In fact, this study of proven invasive mold infections [4] unequivocally disproves the central tenet that L-AmB was underdosed in the 2 empirical antifungal trials in question [2, 3].
"Furberg, the former NIH clinical research specialist, said the two major antifungal studies fell short because they left unanswered which drug or dose was best against suspected infections. 'When you set up studies with controversial comparisons, you risk misleading everybody—regulatory agencies, physicians and patients,' said Furberg, now a professor at Wake Forest University."	Willman quotes Dr. Furberg, a cardiovascular diseases investigator with no published research in infectious diseases. We question Dr. Furberg's expertise in the nuances of antifungal dosing and strongly disagree with his remarks. The results from both trials in question have led to definitive conclusions regarding the questions that they aimed to address and have changed standards of care. The statements by Furberg are a fitting ending for Willman's article, which is filled with implications and cherry-picked quotations that are based on nothing.

NOTE. D-AmB, deoxycholate amphotericin B; L-AmB, liposomal amphotericin B.

AND PICKING DOSES

The second and more serious of Willman's implicit accusations is that Walsh deliberately chose to administer lower, less-effective dosages of comparator drugs in the 2 trials. In trial 1, D-AmB (0.6 mg/kg per day) was compared with L-AmB (3 mg/kg per day). In trial 2, L-AmB (3 mg/kg per day) was compared with caspofungin (70 mg administered once, followed by a regimen of 50 mg per day). Willman [1] implicitly alleges that D-AmB (the control drug) was underdosed in trial 1. He further suggests that, in trial 2, it was L-AmB (now the control drug), that was underdosed to favor caspofungin. That the dose of L-AmB was the same in both trials makes these allegations self-contradictory and logically untenable.

In fact, the dosages of all drugs used in both trials were appropriate on the basis of substantial published data. Consensus supporting the 0.6 mg/kg per day D-AmB dosage in trial 1 [2] and the 3 mg/kg per day L-AmB dosage in trial 2 [3] is based on the following data. First, D-AmB was administered at a dosage of 0.5–0.6 mg/kg per day in prior studies of empirical therapy that established the safety of this approach and suggested a protective benefit [6, 11].

Second, no evidence of superior outcomes associated with higher dosages of D-AmB or L-AmB has ever been published. In a randomized, controlled trial of empirical therapy that compared D-AmB 1 mg/kg per day versus L-AmB 1 mg/kg per day versus L-AmB 3 mg/kg per day, D-AmB recipients had a response rate comparable to that of patients treated with L-AmB, but they experienced greater nephrotoxicity (23%) than did patients receiving L-AmB 1 mg/kg per day (0%) or L-AmB 3 mg/kg per day (3%) ($P = .01$) [12]. These results were similar to those for trial 1 (D-AmB vs. L-AmB) [2], which showed comparable efficacy but higher nephrotoxicity in the D-AmB 0.6 mg/kg per day group than in the L-AmB 3 mg/kg per day group. In another study of empirical antifungal therapy, L-AmB administered at a dosage of 3 mg/kg per day and 5 mg/kg per day had similar efficacy and toxicity [13]. Finally, a recent trial of primary therapy for invasive aspergillosis (the AmBiLoad study [4]) showed that L-AmB (3 mg/kg per day, which is the same dosage that was administered in the empirical trials) was equally effective but less toxic than a 10 mg/kg per day regimen of L-AmB. Yet, Willman [1] creates the misleading impression that patients enrolled in these empirical trials may have died of breakthrough aspergillosis because of inadequate dosing of D-AmB or L-AmB. The results discussed above, particularly the findings of the AmBiLoad study, dispel the false notion that administering higher dosages of drug is equated with improved efficacy, and they unequivocally give further validation of the dosages used in the Walsh trials in question [2, 3].

Third, there is evidence of increasing dose-dependent toxicity with D-AmB. Even a superficial review of the literature would find multiple reports of high rates of dose-limiting nephrotoxicity associated with D-AmB use [4, 12, 14–18]. D-AmB–related nephrotoxicity has been shown to be an independent risk factor for mortality [14]. Yet, Willman [1] chose to ignore these well-documented, substantial patient safety concerns in his discussion of the D-AmB versus L-AmB empirical trial.

PATIENT SAFETY WAS OF PRIMARY IMPORTANCE

The majority of patients who receive empirical antifungal therapy do not have an occult fungal infection. Therefore, this approach necessarily entails treating many individuals to benefit a minority of patients. It is, therefore, of key importance that the regimen be safe. Willman's contention that patients were put at risk by unethical trial design flies in the face of his article's [1] total disregard of the inherent toxicities in AmB-based antifungal therapy mentioned above [4, 12, 14–16, 18]. Furthermore, the dosages of D-AmB and L-AmB in trial 1 [2] were agreed upon by all 32 investigators and by senior members and statisticians of the Mycoses Study Group and were approved by participating health care center institutional review boards, the National Institute of Allergy and Infectious Disease protocol review committee, and the FDA. Patient safety measures were stringent and relied on baseline evaluation to exclude invasive fungal infection, included monitoring for breakthrough invasive fungal infection during therapy, allowed for dosage modification (with dosage to be increased if invasive fungal infection was suspected and decreased in response to toxicity), and included prospective data review by an independent data safety monitoring board. D-AmB recipients had significantly more frequent dose reductions because of toxicity than did L-AmB recipients. This finding totally discredits the theory of deliberate underdosing of D-AmB. Further, the difference in the number of deaths associated with each therapy, emphasized in Willman's article [1], was, in fact, not statistically significant in this cohort of 687 patients [2].

Willman [1] further suggests a disregard for patient safety by claiming that the L-AmB dosage in the L-AmB versus caspofungin trial [3] could not be increased until a patient had received 5 days of the original dosage of investigational or comparator drugs and continued to deteriorate. The implication is that the patient's life and health were endangered by remaining on ineffective treatment until the 5-day limit. However, Willman acknowledges that "A patient also could be removed from the study and treated differently" and that "the five-day provision … was intended to standardize the conditions for increasing the dosages" and "was approved by all investigators, their institutional review boards, and the FDA" [1]. That is, the study design encouraged investigators to act as doctors and to err on the side of patient safety, even if doing so meant removing a patient from the trial, because patient safety was at the heart of the investigators' concerns.

The implied accusation that the L-AmB

dosage was suboptimal in trial 2 [3] (but not in trial 1, which used the same dosage [2]) is inconsistent with overwhelming evidence indicating that the 3 mg/kg per day L-AmB dosage is justified for empirical therapy. The implicit accusation also demonstrates a lack of knowledge of regulatory oversight. On the basis of the results of trial 1 [2], L-AmB was approved by the FDA as empirical therapy for neutropenic fever at a dosage of 3 mg/kg per day. The FDA requires the use of standard-therapy control subjects when investigating new agents, such as caspofungin. Therefore, the use of L-AmB at 3 mg/kg per day in trial 2 was logical, evidence-based, and required for regulatory approval.

MULTICENTER TRIALS REQUIRE BROAD CONSENSUS AND OVERSIGHT, NOT A SINGLE VOICE

Although Walsh was an active participant in discussions to determine dosage selection (and rightfully so), a consensus by a large group of expert investigators who had to approve the study design and numerous layers of regulatory approval were essential to implement the study. Indeed, a major element in the success of the American system of drug approval has been the system of checks and balances. These same concepts—plus skilled oversight by investigators, regulatory agencies, and institutional review boards—are an integral part of our approach to clinical research, providing expert council for all aspects of the drug development process. As imperfect as it might be, this model remains the gold standard for drug development.

HAVE ALL SYSTEMS OF INDEPENDENT OVERSIGHT BEEN CORRUPTED?

Willman [1] alleges, in effect, that dozens of investigators worldwide and regulatory entities conspired actively with Walsh to harm patients (including causing patient deaths) or were unaware that a conspiracy was plotted. If this is true, then the entire system of oversight of medical research in the United States and abroad is tainted or defective.

In addition, although he does not explicitly say so, Willman [1], in effect, implicitly attacks the NIH (for collaborating with the pharmaceutical industry and for incompetent oversight); the competence and/or integrity of dozens of investigators, senior Mycoses Study Group members, and FDA officers (for allowing patient enrollment in unethical trials with substandard care); the institutional review boards at numerous academic institutions (for uncritically reviewing the study protocols); the editorial board at the New England Journal of Medicine (for accepting publications of unethical research); and the FDA and its 12-member advisory board (for approving drugs on the basis of tainted trials). Indeed, all of these systems of independent oversight needed to have failed for the proposed conspiracy between Walsh and the pharmaceutical industry to be successful.

We also emphasize Willman's citation of Walsh's superiors: "There is no rational motivation for an investigator or sponsoring company to design a trial with a control arm that is not standard of care" [1]. We go one step further. We believe it is impossible to conduct a study involving dozens of health care centers worldwide if the control arm does not adhere to a general consensus of what is considered to be standard of care.

CAN PRINCIPAL INVESTIGATORS PROVIDE ADVICE TO BOTH THE PHARMACEUTICAL INDUSTRY AND THE FDA?

Willman [1] further attacks Walsh on the inappropriateness of his advice to regulatory agencies. In doing so, Willman disregards the major responsibility of principal investigators and the data review committee chair (in collaboration with other investigators) for study development, execution, and analysis, as well as for presenting results to the relevant agencies. It is entirely appropriate for a principal investigator and data review committee chair to provide advice to both the pharmaceutical industry and the FDA, particularly when he happens to be, like Walsh, an accomplished investigator with almost 600 peer-reviewed scientific publications and service on numerous scientific advisory boards. Being a federal employee does not disqualify Walsh from providing such advice; he is as qualified to do so as any other academic investigator with similar expertise. There is, indeed, a very small pool of highly qualified individuals who can deliver such necessary expertise to both the pharmaceutical industry and the FDA. Such expertise is critical to the vital scientific collaboration between the pharmaceutical industry and the scientific community, especially in this time of decreased federal funding. In fact, all drugs are brought to market through collaboration between the pharmaceutical industry, independent researchers (including some whose research is federally funded), and the FDA. The 2-decade–long collaborative federal and pharmaceutical industry support of the Mycoses Study Group is but one example of positive interaction that had led to major developments in antifungal therapy.

A HUGE DOSE OF DOUBT ABOUT THE *LOS ANGELES TIMES*

Newspapers owe their readership a modicum of objectivity. This does not equate with simply presenting both sides of an argument. It must also give some sense of the weight of the evidence supporting opposing positions, to give some context to readers and to enable them to reach considered judgments. Newspaper editors owe it to their readership to perform a thorough review of any proposed article for the validity of the evidence presented and the reliability of the article's sources. The *Los Angeles Times* has failed its readership on all counts. The destructive nature of Willman's implicit allegations and

the strong rebuttals made by several investigators and by Walsh's superiors several months before the publication of Willman's article [1] should have prompted Willman's editors to scrutinize carefully the quality of his "evidence." Their failure to do so calls into question the credibility of the *Los Angeles Times* as a serious newspaper. Accordingly, the editors bear responsibility, together with Willman, for this publication. One might ask at what point reporters and editors cross the line of ethical reporting. If anything, this sad chapter should give the public a huge dose of doubt about this newspaper.

The core of Willman's implied accusations against Walsh—that dosages of antifungals were manipulated to bias the 2 empirical trials in favor of the investigational agents—has been discredited in the preceding discussion. But another disturbing fact is the lack of objectivity displayed during the conduct of the "investigations" that led to the inaccurate article [1]. Willman began his "investigations" of Walsh in mid-2005 with several accusations (Thomas Walsh, personal correspondence). Eight of us rebutted Willman's accusations in a detailed, point-by-point response in November 2005. This response did not satisfy Willman, but prompted him to write another letter in February 2006, which contained even more queries. An extensive response was provided to Willman and his editors in June 2006 that further detailed the gross misrepresentations of his implied allegations. This, too, was willfully ignored, and Willman's article [1] was published in July 2006. Our criticisms of Willman's flawed assertions are acknowledged in passing in his article, by statements such as "much controversy still surrounds the optimal timing, dosage and duration of therapy for patients with suspected infections"; "no published study has established that a higher dose of an antifungal drug is more effective in treating suspected infection and that some studies have suggested that lower dosing may provide similar benefits"; "drug dosages were not chosen by Walsh individually but with assent of other researchers"; and, "study designs were reviewed and approved by the FDA and institutional review boards of participating centers" [1]. One would think that these statements, in and of themselves, would exonerate Walsh of culpability with respect to the core accusations. However, undaunted by the above-mentioned facts, Willman relies on far less authoritative sources, such as "some investigators" (unnamed) and selective quotations from the correspondence sections of medical journals, to support the implicit allegations of conspiracy.

POTENTIAL IMPLICATIONS OF WILLMAN'S ARTICLE

Sensational attacks on a respected academic and government employee (and, implicitly, on the entire drug-approval process) and fear-mongering addressed to the lay reader (implying that individuals should enroll in clinical trials at their own risk) may be attention-grabbing ways to sell more newspapers; for this purpose, Walsh served as a convenient scapegoat. As colleagues of Dr. Walsh, we are deeply concerned that his reputation is being unfairly maligned. To his patients and colleagues, Dr. Walsh is a compassionate physician whose dedication to the care of immunocompromised children and adults is central to his professional life. To his colleagues worldwide, Dr. Walsh is an outstanding investigator who has substantively advanced the field of antifungal therapy. This is the real story of Dr. Walsh.

The greatest danger of articles such as Willman's [1] is that members of the lay public do not read medical journals. By contrast, the *Los Angeles Times* is widely read, is disseminated online, and is perceived as an authoritative news source. Accordingly, there is good reason to fear that the public will conclude, on the basis of Willman's article [1], that the entire process of drug development in the United States and abroad is corrupt and that they should refrain from participating in clinical trials. We question whether Willman and the *Los Angeles Times* considered the possibility that future patients might suffer as a result of Willman's irresponsible report.

As clinical researchers who require the trust of the public, we expect and welcome scrutiny by the lay press. But we also have the responsibility to vigorously defend our colleagues when their professional integrity has been unfairly maligned and to restore public confidence in clinical research and its systems of independent oversight when they have been unfairly attacked.

AUTHOR AFFILIATIONS

[1]Myeloma Institute for Research and Therapy and [2]Department of Pharmacy Practice, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock; Departments of [3]Medicine and [4]Pathology, University of Texas Health Science Center at San Antonio, San Antonio, Departments of [5]Leukemia and [6]Medicine, University of Texas MD Anderson Cancer Center, and [7]Metropolitan Infectious Diseases, Houston, [8]Division of Infectious Diseases, Texas Tech University Health Sciences Center, El Paso, Departments of [9]Pathology, [10]Dermatology, and [11]Microbiology and Immunology, University of Texas, Galveston, and [93]Infectious Disease Service, Brooke Army Medical Center, Fort Sam Houston, Texas; [12]Marlene and Stewart Greenebaum Cancer Center, University of Maryland, and [92]Department of Pediatrics, Division of Pediatrics Hematology-Oncology, The Children's Hospital at Sinai, Baltimore, and [13]Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; [14]Department of Infectious Diseases, St. Jude Children's Research Hospital, and Departments of [15]Molecular Sciences and [16]Pediatrics, University of Tennessee Health Sciences Center, Memphis; [17]Department of Medicine, Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, and [18]Department of Pediatrics and Epidemiology, Pediatric Infectious Disease, The Children's Hospital

of Philadelphia Center for Clinical Epidemiology and Biostatistics and [19]Department of Medicine, Division of Infectious Disease, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; [20]Infectious Disease Research, Ochsner Clinic Foundation, New Orleans, and [21]Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, Shreveport, Louisiana; Departments of [22]Pediatrics, [23] Molecular Genetics, [24]Microbiology, and [25]Medicine, [91]Division of Infectious Diseases, and [26]Clinical Mycology Laboratory, Duke University Medical Center, and [99]Duke Clinical Research Institute, Duke University, Durham, North Carolina; [27]Department of Medicine, Harvard Medical School, [28]Division of Infectious Disease, Brigham and Women's Hospital, Divisions of [29]Geographic Medicine and [30]Infectious Diseases, Tufts University School of Medicine, Tufts New England Medical Center, and [31]Division of Infectious Diseases, Massachusetts General Hospital, Boston, and [32]Division of Infectious Diseases and Immunology, University of Massachusetts Medical School, Worchester, Massachusetts; [33]Department of Medicine, University of Southern California Keck School of Medicine, [94]Critical Care Services, Los Angeles County and University of Southern California Medical Center, and [96]Pediatric Infectious Diseases, Children's Hospital of Orange County, Los Angeles, [95]Infectious Diseases, Miller Children's Hospital, Long Beach, and [34]Department of Infectious Disease, City of Hope National Medical Center, Duarte, California; [35]Department of Pathology, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City; [36]Department of Infectious Diseases, H. Lee Moffitt Cancer Center, University of Florida College of Medicine, Tampa, [37]Medical Intensive Care Unite, Jackson Memorial Hospital, and [38]Department of Medicine, University of Miami Miller School of Medicine, Miami, [39]Department of Medicine, Division of Infectious Diseases, Mayo Clinic College of Medicine, Jacksonville, and [40]Department of Medicine, Division of Hematology/Oncology, University of Florida College of Medicine, Gainsville, Florida; [41]Department of Medicine, Immunocompromised Infectious Disease Service, Indiana University School of Medicine, and [42]MiraVista Diagnostics/MiraBella Technologies, Indianapolis, Indiana; [43]Department of Medicine, Division of Infectious Disease, University of Colorado at Denver, Denver; Departments of [44]Medicine and [45]Microbiology, University of Wisconsin, Madison; [46]Department of Medicine, University of Virginia Health System, Charlottesville, and [47]Department of Medicine, Virginia Commonwealth University Medical Center, Richmond; [48]Division of Clinical Microbiology, [49]Department of Pediatrics, and [50]Department of Medicine, Division of Infectious Diseases, Mayo Clinic, Rochester, and [51]Department of Medicine, Division of Infectious Diseases, Mayo Clinic College of Medicine, Buffalo, Minnesota; [52]Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham; [53]New York University School of Medicine and [54]Department of Microbiology and Immunology, Albert Einstein College of Medicine, New York, [55]Division of Infectious Diseases, Roswell Park Cancer Center, Buffalo, and [98]Division of Clinical Pharmacology, Albany Medical College, Albany, New York; [56]Department of Pharmacy Practice, Schools of Pharmacy and Medicine, and [57]Mycotic Research Center, Department of Medicine, Division of Infectious Disease, University of Mississippi Medical Center, Jackson; [58]Department of Internal Medicine, Division of Infectious Diseases, University of Kentucky School of Medicine, Lexington; [59]Washington Hospital Center and [60]Department of Medicine, Georgetown University School of Medicine, [61]Department of Pediatrics, George Washington University School of Medicine and Public Health, and [62]Department of Hematology/Oncology, Children's National Medical Center, Washington, DC; [63]Department of Dermatology, School of Medicine, Case Western Reserve University, Cleveland, and [90]Department of Surgery, Division of Trauma and Critical Care, University of Cincinnati, Cincinnati, Ohio; [64]Division of Infectious Diseases, Wayne State University, Detroit, Michigan; [65]Department of Medicine, Infectious Diseases Division, Robert Wood Johnson Medical School, Cooper University Hospital, Camden, New Jersey; [106]Department of Medicine, University of Illinois at Chicago, Chicago; [66]Department of Mycology, University of Aberdeen, and Departments of [67]Medicine and [68]Medical Mycology, Education Research Centre, Wythenshawe Hospital, Manchester, United Kingdom; [69]Department of Clinical Haematology, Catholic University of Leuven, Belgium; Departments of [70]Medical Microbiology and [89]Hematology, University Hospital Nijmegen, [71]Department of Haematology, Radboud University Nijmegen Medical Centre, and [72]Nijmegen University Centre for Infectious Diseases, Nijmegen, The Netherlands; [73]Department of Medicine, Karolinska Institutet, and [74]Hematology Center, Karolinska University Hospital, Stockholm, Sweden; [75]Department of Microbiology–Infectious Diseases, Hospital Maisonneuve-Rosemont, and [76]Department of Microbiology and Immunology, Sainte-Justine Hospital, University of Montreal, Montreal, Quebec, and [77]Division of Infectious Diseases, McMaster University, and [78]Infectious Disease Service, Hamilton Health Service, Hamilton, Ontario, Canada; [79]Service des Maladies Infectieuses et Tropicales, Hôpital Necker, Paris, [80]Hematology Department, CHU Henri Mondor, Creteil, and [81]Department of Hematology and Oncology, Hopital de Hautepierre, Strasbourg, France; [82]University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; [83]Department of Internal Medicine, University of Cologne, Cologne, and [105]Charité Universitatsmedizin, Campus Charité Mitte, Medizinische Klinik und Poliklinik II, Berlin, Germany; [84]Department of Infectious Diseases, Foundation for the Fight Against Leukemia, Buenos Aires, Argentina; [85]Department of Public

Health, Microbiology, and Virology, Università degli Studi di Milano, Milan, and [86]University of Genova, Division of Infectious Disease, San Martino University Hospital, Genoa, Italy; [87]Department of Hematology and [88]Bone Marrow Transplant Unit, University of Ankara, [100]Department of Medicine, Hacettepe University School of Medicine, Ankara, Turkey; [97]Department of Infectious Diseases, Centre for Infectious Diseases and Microbiology, University of Sydney, Westmead Hospital, Westmead, and [104]Department of Clinical Microbiology and Infectious Diseases, St. Vincent's Hospital, Darlinghurst, Australia; [101]Department of Mycology, Spanish National Center for Microbiology, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain; [102]Department of Medicine, United Arab Emirates Medical School, Al-Ain; and [103]Decane School of Health, Slovakia.

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R.F. has received research support from Cubicin and GlaxoSmthKline, is a consultant for Pfizer, Elan Pharmaceuticals, Abbott, and GlaxoSmthKline, and is a member of the speaker's bureau for Merck, Pfizer, and GlaxoSmthKline. G.F. has received research support from Astellas, Cubist, and Pfizer and is a member of the speaker's bureau for Astellas, Cubist, Pfizer, and Schering Plough. M. Ghannoum has received grant support from Astellas, Enzon, Indevus, Pfizer, Merck, Helix BioAlliance, Novartis, Anacor, Nex Med, Maruho, and Great Lakes Pharmaceuticals, is a consultant for Stiefel, Pfizer, Schering Plough, Novartis , and Enzon, and is a member of the speaker's bureau for Astellas, Merck, Pfizer, Schering Plough, and Enzon. M. Goldman has received research support from Pfizer and Glaxo, is a consultant for Gilead Sciences, Schering Plough, and Merck, and is a member of the speaker's bureau for Merck. J.N.G. has received research support from Pfizer and Schering Plough. 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J.W.H. has received research support from Astellas, Curagen, and Schering Plough, is a consultant for Astellas, Pfizer, Three Rivers, and Schering Plough, and is a member of the speaker's bureau for Astellas, Merck, and Pfizer. W.H. is associated with Astellas. D.R.H. has received grant support from Merck, Pfizer, and Schering Plough and is a member of the speaker's bureau for Merck and Pfizer. J.I.I. is a consultant for Enzon, Pfizer, and Schering Plough and is a member of the speaker's bureau for Astellas, Enzon, Pfizer, and Schering Plough. R.M.J. has received grant support from Merck, VaxGen, BioPort, and Chiron (Novartis). D.H.K. has received grant support from Pfizer, Wyeth, Merck, Astellas, and Hopira, is a consultant for Pfizer, Enzon, Cubist, Wyeth, Astellas, Lilly, Sanofi Aventis, and GlaxoSmithKline, and is a member of the speaker's bureau for Pfizer, Cubist, Wyeth, Merck, Astellas, Lilly, Sanofi Aventis, and Glaxo. 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