Study of Chelation Therapy Should Not Be Abandoned

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ABSTRACT

Many physicians report that off-label use of EDTA chelation therapy for cardiovascular disease and other indications is effective and safe in their hands. Recruitment for a well-designed formal study, funded and managed by the National Institutes of Health, the Trial to Assess Chelation Therapy (TACT), was temporarily suspended pending a costly federal inquiry, because of the publication of a critique in the *Medscape Journal of Medicine*. The authors of the critique are participants in a long-standing campaign to suppress this therapy. Abandonment of this research could result in denial of a potentially life-saving therapy to many patients. Additionally, the use of political tactics to terminate freedom of inquiry has much broader implications for the future of medical innovation.

In May 2008, George D. Lundberg, M.D., editor of the *Medscape Journal of Medicine* and former editor of *JAMA*, facilitated the publishing of an "original article" entitled, "Why the NIH Trial to Assess Chelation Therapy (TACT) Should Be Abandoned," authored by Kimball C. Atwood IV, M.D.; Elizabeth Woeckner, A.B., M.A.; Robert S. Baratz, M.D., D.D.S., Ph.D.; and Wallace I. Sampson, M.D.[1] The 51-page article asserts that the authors have "investigated the method and the trial" and concluded that the trial is "unethical, dangerous, pointless, and wasteful." They claim that 30 deaths have occurred (over 50 years) from chelation therapy, and therefore the product is too dangerous for use in a clinical trial. Later in the article, they claim that nine documented deaths have occurred in 15 years.

The development and implementation of a well-designed and well-managed trial of EDTA chelation therapy, funded and managed through the National Heart Lung and Blood Institute (NHLBI) of the National Institute of Health (NIH) and National Center for Complementary and Alternative Medicine (NCCAM), is seen by many in the medical community as an important public health research activity that is well underway and that should be completed. But "a tiny but shrill minority of physicians," to use these authors' own phrase, appears to stand against scientific inquiry. Readers may be unaware that several of the authors of the Atwood paper have made a cottage industry of their opposition to chelation therapy and to complementary and alternative medicine.

Bias

To use their own words, Atwood et al. are "biased to the point of fanaticism." They frequently attack physicians who provide chelation therapy, generating lawsuits and medical board actions, and serving as paid witnesses. Atwood et al. devoted a great deal of ink in their article to argue that Nash, Chappel, and other TACT investigators are somehow less qualified to participate in research because they have been part of the development of the professional and research infrastructure for chelation therapy. At the same time, Sampson, Atwood, and Baratz are members of a web of organizations and activities whose sole purpose is to stand against the use of chelation therapy and alternative medicine. Over 30 years, these organizations have become known as the "quackbusters." Of note is that approximately 20 percent of their footnotes refer back to their own websites, and not to scientific references.

Medscape is a business activity of the WebMD Professional Health Network. *Medscape Journal of Medicine* is the new name for *MedGenMed*. On its website it is purported to be the "original open-access peer-reviewed general medical journal, exclusively electronic and available on Medscape, the premier online publication for medicine and healthcare." At a time when some journals charge $30 per article to access archived materials, the *Medscape Journal of Medicine* is providing an important public service by offering research and medical information online without charge. With that public service comes a responsibility to preserve the integrity of the peer-review process and promote the publication of fair and balanced articles from authors whose intentions are to publish accurate information that is prepared without prejudice and bias, and who honestly represent their credentials. Many respected journals invite an editorial by an expert with a differing opinion when determining to publish a paper with an obvious bias. Why did Medscape not reach out to the TACT principal investigator and provide the opportunity for a simultaneous response to the dozens of allegations put forward in the anti-chelation article by Atwood et al.? Physicians and patients deserve a balanced presentation on chelation therapy.

An internet search revealed a relationship between the *Medscape Journal of Medicine* and the National Council Against Health Fraud, whose history is detailed below. A key colleague of the authors, Stephen Barrett, the webmaster and a board member of the National Council Against Health Fraud (NCAHF), has posted online at www.quackwatch.com that he was a "Member, Editorial Board, MedScape/MedGenMed, 5/99-2/05" and that he is a panelist or occasional peer-reviewer for the journal *Medscape General Medicine.* This close ties between Medscape and the NCAHF, which are not mentioned in the "disclosures" section of the article by Atwood, et al., raise many questions in this reader's mind about the veracity of the peer-review process of the journal, and its true intentions in publishing a 51-page article that contains no original science.

How Should Experts Be Qualified?

Medscape readers deserve to know more about the TACT researchers, and the individuals who have called for an end to the TACT Trial. Of the tens of thousands of clinical trials currently funded by the NIH, why would these critics focus on this particular

research project? Who are they to make a determination about the fitness of the clinicians participating in the study, and what qualifies the Medscape authors, who are not now and never have been government officials involved in managing research, to investigate and make determinations about the NIH TACT Trial?

At first blush, the individuals who coauthored this paper present what appear to be illustrious credentials: editors of journals, professors at prestigious medical schools, presidents of nonprofit organizations. Upon closer inspection, however, many of the credentials appear to be at best overstated. An individualized analysis follows; first, however, it is important to provide an established standard for qualifying experts.

On what standard should critics be qualified to judge whether or not the NIH should suspend a clinical trial of any kind? At least two of the authors have participated in the tort system as experts and expert witnesses, and a third as a consultant; therefore, the criteria for expert witnesses from the American Medical Association (AMA) and the Federation of State Medical Boards (FSMB) seems a logical standard from which to establish their expertise.

In its framework on qualifications a physician should have in order to be considered an expert witness in court cases, the AMA states that expert witnesses should be:

1) licensed physicians or osteopaths,
2) trained and experienced in the same discipline or school of practice as the defendant or in the disease process or procedure performed in the case;
3) certified by a board recognized by the American Board of Medical Specialties or the American Osteopathic Association, or by a board with equivalent standards; and
4) active in the practice of the same discipline or school of practice as the defendant within five years of the date of the alleged occurrence or omission giving rise to the claim, or in teaching at an accredited medical school, or in university-based research pertaining to the medical care and type of treatment at issue.[2]

The FSMB,[3] the professional trade association for state medical boards, provides a state-by-state breakdown of criteria required for individuals to be approved as expert witnesses. In California for instance, "to qualify as an expert, the witness must have the professional knowledge, learning and skill of the subject under inquiry sufficient to qualify him to speak with authority on the subject, and must be familiar with the standards required of physicians under similar circumstances." California is among four states that specifically clarify that a physician providing false or misleading testimony will be subject to disciplinary actions. (South Carolina, North Carolina, and Mississippi are the remaining three.)

In Arizona, to qualify as an expert in a medical liability cause of action an expert must be "licensed in the same profession as the defendant, maintain board certification in the same specialty as the defendant if applicable, and devote a majority of his or her professional time to the active clinical practice or instruction of students in the same health profession as the defendant for the year immediately preceding the occurrence giving rise to the lawsuit."

In Florida the standard is, "Expert testimony must be provided by a licensed health care provider who practices in the same or similar specialty as the defendant. If the defendant is a specialist, the expert must have practiced in the same or similar specialty as the defendant for the past three years in active clinical practice, teaching, or in a clinical research program. If the health care provider is a general practitioner, the expert must have practiced in the same or a similar specialty for the past five years in an active clinical practice, teaching, or a clinical research program."

In comparing the qualifications of TACT researchers and their critics, as outlined by both the AMA and the FSMB, one would look for board certification in cardiology, direct experience providing chelation therapy, or documented experience as a research ethicist in academic research.

Qualifications of the TACT Principal Investigator

Principal investigator Gervasio A. Lamas, M.D., brings to the TACT Trial respected credentials and extensive academic and clinical research experience. Lamas serves as the Director of Cardiovascular Research and Academic Affairs at Mount Sinai Medical Center in Miami Beach, Florida, and as Associate Professor of Medicine at the University of Miami. He is board certified in internal medicine and cardiology. In the 1980s, he was an instructor and then an assistant professor of medicine at Harvard Medical School. Lamas completed three fellowships: clinical fellow in medicine, Harvard Medical School, 1979-1981; research/clinical fellow in medicine, Brigham and Women's Hospital, Boston, 1981-1983; and research fellow in medicine, Harvard Medical School, 1981-1984.

From his curriculum vitae (G.A Lamas, personal communication, 2008), prior to the TACT Trial, there are references to 16 funded clinical trials. In nine of these, Lamas was principal investigator, and in six others he had a leadership role. These studies show an extensive and varied expertise in developing and managing government-funded multi-center clinical trials. These studies included: Survival and Ventricular Enlargement (SAVE), 1987-1992; Clinical Evaluation of the Medtronic 4068 Lead System, 1992-1993; Cholesterol and Recurrent Events (CARE), 1990 to 1993; Healing and Early Afterload Reducing Therapy (HEART), 1993-1995. Pacemaker Selection in the Elderly (PASE), 1993-1996; Rate Responsive Dual Chamber Study, 1994-1998; Mode Selection Trial in Sinus Node Dysfunction (MOST), 1995-2002; the Advanced Elements of Pacing Trial (ADEPT); and the Occluded Artery Trial (OAT).

Lamas has published 100 original research papers in peer-reviewed journals as well as 142 abstracts. His research papers are published in respected journals such as the *New England Journal of Medicine*, *Annals of Internal Medicine*, *American Journal of Cardiology, American Heart Journal*, *Annals of Thoracic Surgery*, and *Circulation.* He additionally has published 52 reviews and 15 books and chapters.

By all measures, Lamas is highly qualified to develop and conduct multi-center clinical research programs looking at any cardiovascular intervention. He has an extensive and documented academic portfolio from two well-respected institutions, Harvard and the University of Miami.

Other Investigators

Atwood et al. go as far as to assert that *all* of the 100 clinicians involved in the TACT study are "unfit," and highlight a number of individuals, digging up and repeating decades-old information. The practice of medicine is regulated by state medical boards, and a review of license status is a more appropriate evaluation of worthiness for participation in TACT. I reviewed this information

from sites such as state licensure board sites. The details are beyond the scope of this article, but I satisfied myself that the clinicians whom Atwood et al. attack were in good standing as of Sep 22, 2008.

Qualifications of TACT Critics

None of the authors of the Medscape article are board-certified cardiologists. None claim to have any direct experience providing chelation therapy. None cite experience as academic research ethicists. Although Woeckner works with a small nonprofit organization with an interest in ethics, she does not hold a medical degree. In fact, the actual research credentials of all of the authors are quite slim, especially when it involves clinical research. Only one author has acted as a principal investigator in an NIH-sponsored grant—in studies related to dentistry and conducted before 1992.

Although three authors list academic titles of assistant clinical professor and clinical professor, the titles do not signify expertise in research. These are honorary titles granted to physicians who are on staff in a hospital where medical students and residents are training or who volunteer to allow medical residents to visit their private medical offices. This is the case for Atwood, Sampson, and Baratz. The actual title for Baratz, as provided by Stanford University, is adjunct clinical professor emeritus. I found no evidence that any of these authors actually teach or have ever taught academic courses at the universities with which they are affiliated.

Kimball C. Atwood, IV, M.D., is board certified in internal medicine and anesthesiology. A search of the NIH CRISP database indicates that he has never served as a principal investigator on an NIH-funded grant. Further, a search on PubMed of the peer-reviewed literature found only three non-Medscape publications, all of which were letters (condemning various complementary therapies), not peer-reviewed research articles. Atwood is on staff at Newton-Wellesley Hospital, which is a part of Partners HealthCare, a nonprofit medical network founded in 1994 by Brigham and Women's Hospital and Massachusetts General Hospital. This association may be prestigious; however, its reputation is marred by a Senate investigation that discovered that three doctors failed to report the millions they earned from drug companies.[4] Atwood states that he is the associate editor of the *Scientific Review of Alternative Medicine*, a journal that claims to be a peer-reviewed publication. A visit to the journal's website, www.sram.org, finds the "current" issue dated "Fall/Winter 2004/2005." No list of staff or advisors is provided. Given that from 1999 to 2004, the journal published twice a year (except 2001, when it published four times), and there has been no publication in more than three years, one wonders whether the journal is now defunct.

Second author Elizabeth Woeckner, A.B., M.A., lists her title as president, CIRCARE (Citizens for Responsible Care and Research) based in Columbia, Md. On its website, www.circacare.org, the organization, which was incorporated in 1996, puts itself forward as "the oldest nonprofit research protection advocacy organization in the United States." The address provided on the website, 10990 Shadow Lane, Columbia, Md., is a residential address and appears to be the home address of CIRCARE cofounder Adil Shamoo, Ph.D., according to a search of Googlemaps. A search on the Foundation Center's 990 Finder database found no filings by CIRCARE.

From Woeckner's academic webpage, updated in February 2008, one learns that she obtained her bachelors degree in classical languages from Bryn Mawr College in 1997, and in 2001 she was working on a Ph.D. in classics from Princeton University. She writes:

> I am a social and cultural historian of the early Roman Empire. My interest in Roman social relations extends to law, sexuality, and literary patronage. My graduate coursework includes training in epigraphy, numismatics, and Roman art. When pressed, I admit to an enormous fondness for Silver Latin literature. My dissertation identifies patterns of friendship between women and combines ancient history and sociology to extend our understanding of gender and social relations in private and civic contexts. In future I hope to focus on the relationship between diet and mental illness in the Greco-Roman world.[5]

Woeckner discloses in the article[1] that she "has received compensation for consulting in civil litigation and professional disciplinary actions." In a letter that Woeckner co-published with Shamoo,[6] Woeckner states that she "is employed on an *ad hoc* basis in civil litigation to provide research support in the area of regulatory affairs." In this article, the organization is listed as Citizens for Responsible Care and Research. A search in the New York Department of State Entity Information database found that this organization was formed Aug 21, 1996, with no registered agent and the Shadow Lane address in Maryland. Also registered in New York at the same address on the same day is another nonprofit corporation, the Citizens for Responsible Care in Psychiatry & Research, Inc. A Google search found that Shamoo has given public testimony at government meetings as a representative of this second organization. He is also quoted in the *New York Times* as founder of this second organization, which he stated to be a "patient advocacy organization."[7] It is unclear how or why Woeckner and CIRCARE have joined the network of the quackbusters in their quest to have chelation research terminated.

The third author, Robert S. Baratz, M.D., D.D.S., Ph.D., states that he is medical director of the South Shore Health Center, Inc., in Braintree, Mass.; assistant clinical professor of medicine, Boston University School of Medicine; and president, National Council Against Health Fraud, Inc. He also disclosed that, he has been "retained by state licensing boards, the Office of the US Attorney, and plaintiff counsel as an expert in disciplinary proceedings and litigation with regard to chelation therapy and associated matters. He is compensated only for his time and has no commercial interest in the outcome of the proceedings or litigation."

South Shore Health Center, Inc. (not to be confused with the South Shore Medical Center) advertises on the website SouthofBoston.com as a doctor's office that provides primary care, urgent care, occupational health, women's health, adolescent medicine, physical therapy, and weight management. South Shore Medical Aesthetics, a business entity for which Baratz is also medical director, is at the same location. Among the services it offers are laser hair removal, chemical peels, Botox, waxing, vitamin C firming facials, gentlemen's facials, and an eye treatment that "combines benefits of shiatsu massage and Vitamin C," and is said to decrease "tension, puffiness and lines." A current web special offer "10% off your first Botox or Restalyn treatment and 15% off your first visit for a facial, peel, microdermabrasion or waxing."

In cross examination in a legal case in Wisconsin, Baratz stated that he is "board certified in oral medicine which is a specialized area of dentistry that straddles the border between medicine and

dentistry." The board is not recognized by the American Board of Medical Specialties, nor is it recognized by the American Dental Association. When asked, "You're not board certified in any branch of medicine, correct?", his response was, "Not currently.... I have not passed the ABIM exam on a couple of occasions."[8] During testimony the following day, Baratz informed the court that the NCAHF is party to 40 lawsuits, "all involving a similar question of law that had to do with the propriety of advertising directed against the citizens of the State of California under the business and professional code of the State of California."[9]

As to Baratz's research credentials, a PubMed search found 12 articles in the peer-reviewed literature. The first six were published in the 1970s and were all animal studies focused on dental/oral issues. From 1980 to 1986, he published four articles, all related to dentistry; three were animal studies. From 1987 to 1990 there were three review articles regarding dentistry. After 1990, Baratz appears to have no articles indexed in PubMed. A Boolean search for Baratz AND chelation found no articles.

A search of the CRISP database at NIH found that Baratz acted as a principal investigator on a number of grants. These included a 1972 project entitled **"**Developmental Cytology of Teeth in Maine Bony Fish"; a 1983 project entitled "Microvascular Changes in Oral Mucosa in Diabetic Men"; and a 1991 entitled "Allergies to Materials Used in Dentistry."

Although apparently no longer conducting and publishing research, Baratz is frequently quoted in the news media. As president of NCAHF, Baratz filed a complaint with the Ohio Medical Board about congressional candidate Victoria Wulsin, M.D. D.P.H., because of her involvement with research done by the Heimlich Institute in Africa that used infection with malaria to treat HIV/AIDS.[10] Wulsin's role had been to do a literature search. The complaint was dismissed. Because of remarks he made to a television station about the Save a Life Foundation (SALF), which teaches the Heimlich maneuver to schoolchildren, SALF sued Baratz.[11] Baratz criticized the University of Pennsylvania School of Medicine for offering a master's degree in complementary and alternative medicine (CAM) and for making an agreement with the Tai Sophia Institute, an acupuncture school, for research and education. He called CAM "another name for snake oil."[12]

Fourth author Wallace L. Sampson, M.D., though listed in Medscape as a senior attending physician at Santa Clara Valley Medical Center, has not been on the medical staff there since 1998, and retired his medical license in 2005.The journal of which he purports to be editor in chief, *Scientific Review of Alternative Medicine*, appears, as noted above, to be defunct. A PubMed search found 11 articles by Sampson. Seven were letters, three of which concerned dying at home. There was one review article published in 1993, a 1972 case report, and a clinical research paper. A search on the CRISP database found no references to Sampson's serving as a principal investigator. Sampson's work as a physician indicates work in hematology/oncology, not cardiology.

According to the framework put forward by both the AMA and the FSMB, one might conclude that these individuals are not the appropriate experts to "investigate" an NIH study. Further they have misrepresented their qualifications and failed to disclose to readers their well-established bias against chelation therapy.

The double standard employed by Atwood et al. is notable. They search minutely for any possible flaw in TACT investigators, while their own records reveal failed board examinations, lack of relevant qualifications, overstatement of credentials, conflicts of interest, and a history of bringing unfounded lawsuits and board complaints. Their concern about rare deaths (less than one per year) attributed to chelation therapy seems hypocritical when Baratz's South Shore Aesthetics continues to sell Botox injections after Public Citizen announced that at least 16 deaths had been reported to the FDA.[13] Even if true, the number of deaths from EDTA might be considered proof of its safety considering the very large number of deaths that occur from proper use of drugs for FDA-approved purposes.

A History of the Quackbusters

Each of the four authors above, except Woenecker, have an official and published relationship with one or more of the organizations and their websites known loosely in the medical community as "quackbuster" groups and sites. Woenecker provides a link to the NCAHF from her academic website.

The NCAHF homepage at www.ncahf.org states: "NCAHF is a private nonprofit, voluntary health agency that focuses upon health misinformation, fraud, and quackery as public health problems. Our positions are based upon the principles of science that underlie consumer protection law. We advocate: (a) adequate disclosure in labeling and other warranties to enable consumers to make truly informed choices; (b) premarketing proof of safety and effectiveness for products and services claimed to prevent, alleviate, or cure any health problem; and (c) accountability for those who violate the law."

Using the term "health agency" may imply that this is a government agency or government-sponsored agency, but it is not. It is a nonprofit corporation, an organization of self-appointed individuals. Their opinions should carry no more weight than those of any other individual.

According to its official history, NCAHF evolved from the constituents of three organizations that formed independently out of concerns about quackery in their communities. These were the Lehigh Valley Committee Against Health Fraud, Inc. (LVCAHF, now called Quackwatch), Southern California Council Against Health Fraud (SCCAHF), and a group without a formal name in northern California. Stephen Barrett, M.D., and others incorporated LVCAHF in 1970 in Allentown, Pa. A plan to create a university-based health-fraud group, presented as a "consumer health studies center," was rejected by Loma Linda University. William Jarvis, Ph.D., together with others, incorporated the Southern California Council Against Health Fraud in 1976, and began operations as part of Jarvis's community dentistry activities. In 1978, this group merged with one created by Wallace Sampson and his colleague, Thomas Jukes, Ph.D., from the University of California at Berkeley to form the California Council Against Health Fraud. In 1984, after it was determined that a majority of CCAHF members resided outside of California, the decision was made to change the name and scope of the Council to national. From 1998 through 2000, NCAHF conducted some of its business as the National Council for Reliable Health Information (NCRHI).

NCAHF and its members have created a network of websites and affiliate organizations with the specific purpose of attacking dietary

supplements, chelation therapy, and alternative therapies. Throughout their history, no matter the amount or quality of the research, NCAHF, its members and affiliate organizations, and proferred publications have never accepted the validity of therapies and interventions commonly known as CAM. The NCAHF homepage links to 22 allied sites criticizing various forms of CAM.

At the hub of these 22 organizations is Stephen Barrett, the key to the link between NCAHF and Medscape, whose official resume is posted at www.quackwatch.com. The role of the network of quackbusters in impeding research into and use of CAM since the 1970s is essential to understanding the attack on TACT.

In a deposition taken on Feb 28, 1995,[14] Barrett made many important disclosures. The first is that quackbuster activities coincided with the AMA's attack on chiropractic, which resulted in an antitrust lawsuit. When asked about the Quackery Committee of the Lehigh Medical Society, of which he said he was chairman, he said it was not, nor ever really had been active. "The original purpose was simply to look into areas of concern that had to do with unscientific practice. Chiropractic was an early concern."

During the deposition, Barrett admitted that he had failed his board certification examination in psychiatry and decided not to take it a second time. He also admitted that he was not board certified in any area of the practice of medicine, and that he has done no clinical research.

Barrett appears to have a long history of litigation, reportedly bringing charges of defamation of character 40 times. After years of legal maneuvering, the latest case, *Barrett v. Ted Koren and Koren Publishing*, was thrown out by Judge Brian Johnson, in Barrett's home community of Lehigh, Pa. Judge Johnson issued a directed verdict ruling that there was insufficient evidence to support Barrett's claim.[15]

Why Chelation Needs To Be Studied

Examples of efforts to thwart medical progress and innovation are legion: hand washing, surgical antisepsis, and the role of *Helicobacter pylori* in peptic ulcer disease are just a few examples. Worthwhile innovations eventually may gain acceptance by clinicians who see their value. But with chelation therapy, there is an additional hurdle. The conclusion by many practicing physicians that evidence supports the efficacy of chelation therapy is moot because of the settlement agreement between the American College for Advancement in Medicine (ACAM) and the Federal Trade Commission (FTC).

"A consent agreement is for settlement purposes only and does not constitute an admission of a law violation. When the Commission issues a consent order on a final basis, it carries the force of law with respect to future actions," notes the agreement, under which ACAM is prohibited "from representing that EDTA chelation therapy is an effective treatment for atherosclerosis without possessing and relying upon competent and reliable scientific evidence to substantiate the representations."[16]

No less an authority than the former director of the National Heart, Lung, and Blood Institute (NHLBI) thought that study was warranted. In a Mar 10, 1999, Congressional hearing, Claude Lenfant stated:

> Chelation is a chemical term named from the Greek word chele, meaning "claw" or "claw-like". In chelation therapy, an organic chemical bonds with metals in the bloodstream and digs them out of the system. This therapy is standard treatment for heavy metal poisoning, such as lead poisoning, and the management of iron overload following repeated blood transfusions. During the 1960s, it was observed that a patient who was receiving chelation therapy for lead poisoning coincidentally experienced relief of angina symptoms. Since then many patients have sought and received chelation therapy for atherosclerosis…. The NHLBI is ready and willing to work with qualified researchers to resolve this important public health issue.[17]

Lenfant's remarks are far more relevant than commonly recognized. The effect of chelation in this patient may not have been simply serendipitous. A 2007 report from the Normative Aging Study linked elevated bone lead levels with increased heart disease in aging men. "Study participants were followed for 40 years, and those with the highest lead deposited in their bones suffered more heart attacks and heart pains than those with lower overall lead in their bodies."[18] Remember the children of the 1960s exposed to lead are the middle-aged adults of today, and may have retained lead in their bones.

Protecting the Off-label Use of Drugs

Were it not for chelation doctors in general and Dr. H. Ray Evers in particular, physicians in the United States might have lost the ability to recommend the off-label use of drugs in the 1970s. And as Evers stated, "One does not have true freedom until one is free to choose how he wishes to be treated medically."[19]

While Atwood et al. sought to taint Evers's name, every physician who has ever prescribed a drug off-label in the last 30 years, and patients who benefited, owe him a debt of gratitude. Too often physicians who become targets of a government agency, whether guilty or not, will settle a case because they are afraid of the seemingly insurmountable power of the government and its endless supply of Justice Department lawyers. As a former Congressional staffer, I heard this repeatedly from organizations and individuals. Legal bills in such matters can run in the tens and hundreds of thousands of dollars. Evers, known as a "Southern gentleman" who practiced medicine and volunteered as a Presbyterian Sunday school teacher,[20] became the target of the Food and Drug Administration (FDA) for his active use of chelation therapy off-label, but refused to kowtow to a government agency on a witch-hunt.

The FDA alleged that Evers had violated the Federal Food, Drug, and Cosmetic Act (the Act) under misbranding provision by promoting and administering a chelating drug, calcium disodium edetate (calcium EDTA), an FDA-approved drug for an indication not approved by the agency. Evers argued that as a licensed physician he has a right to prescribe any lawful drug for any purpose, whether or not the FDA has approved that purpose. The district court agreed with Evers, and held that no misbranding could result from a doctor's prescription of a lawful drug to his own patients. The court relied for this holding on the intent of the statute, which seeks to avoid interference with "the practice of medicine"; on supposed limitations on the powers of Congress; and on the patient's constitutional right to privacy in the context of medical care.[21]

How Important Is Off-label Prescribing?

Off-label prescribing, also known as unapproved use, is essential to the practice of medicine in the United States, and has been the avenue often used to achieve medical advances. In 2000, a Tennessee

appellate court observed in *Richardson v. Miller*: "Because the pace of medical discovery runs ahead of the FDA's regulatory machinery, the off-label use of some drugs is frequently considered to be 'state-of-the-art' treatment. In some circumstances, an off-label use of a particular drug or device may even define the standard of care." Although there are no accurate data, estimates of off-label prescribing run as high as 60 percent of all drug prescriptions written in the United States in a given year, including a large proportion of chemotherapy and pediatric prescribing.[22]

The *Wall Street Journal* reported in February 2008 that an estimated 31 percent of psychiatric-drug prescriptions, including antidepressants, antianxiety drugs, and antipsychotic medications, are off-label, while an estimated 42 percent of asthma medicines were used off-label.[23] Off-label usage is so widespread that the General Accounting Office has reported that doctors prescribe more than 50 percent of cancer drugs for treatment in cases that have not been approved by the FDA. [24]

"Licensed physicians, thank God, have been prescribing aspirin without FDA approval for years," said Dr. Stephen Weisman, director of clinical and medical affairs for the German drug giant Bayer AG. "Researchers at Oxford University in England estimate that 10,000 American lives could be saved each year through aspirin therapy." [24]

Had the courts not ruled in favor of Evers, the U.S. Supreme Court might not have concluded in *Buckman Co. v. Plaintiffs' Legal Comm*: "'[O]ff-label' usage of medical devices…is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine…. Doctors can legally prescribe a drug for such 'off-label' uses, but drug companies aren't allowed to advertise these unapproved uses."[25]

Recognizing the importance of sharing scientific data, the restriction on drug companies to share with physicians the off-label uses of their products may soon be lifted by the FDA, with the development of tightly controlled guidelines that restrict marketing but allow sharing of scientific articles on off-label use of approved products.

The law is clear that physicians are within their legal rights to prescribe drugs off-label, including EDTA chelation therapy. The path has often been rocky for many health professionals, often because the quackbusters have spent 30 years on the attack. Attorney Allan Dumoff is among a number of experts who have observed the hostility of medical and health licensing boards: "Based on differences of professional opinion, physicians and other health care practitioners have been subject to lengthy investigations that are financially draining and emotionally painful, sometimes leading to sanctions or even loss of licensure."[26]

Other Harm Done by Quackbusters

At the same time that quackbusters attack physicians for offering therapy without adequate evidence, and without warning of the risk of side effects, they attack these same physicians for developing professional organizations through which they might improve their professional skills, and for their attempts to develop scientific rigor and conduct research in line with federal regulations. The American Association for Medical Preventics (AAMP), which became the American College for Advancement in Medicine (ACAM), was created as a professional medical organization for physicians interested in chelation therapy and other integrative medicine approaches to wellness.

In attacking the use of EDTA chelation for cardiovascular disease, quackbusters probably also hinder its use for heavy metal intoxication. Although greatly diminished by the Clean Air Act and the removal of lead from gasoline, lead poisoning still exists. In fact, E-Medicine of WebMD makes the following statement about lead toxicity in the United States:

> Of the heavy metals, toxicity by chronic lead exposure is the most commonly encountered. The National Health and Nutrition Examination Survey (NHANES III) conducted from 1988-1990 found that 0.4% of persons aged 1 year and older had blood levels of lead of 25 mcg/dL or higher. The data also noted that, among those aged 1-5 years, an estimated 1.7 million children had blood levels greater than 10 mcg/dL. The syndrome of childhood plumbism caused by the ingestion of lead is believed to affect more than 2 million American preschool-aged children. Lead toxicity has a significantly higher prevalence among the African American population and in lower socioeconomic areas.[27]

According to the 1997 National Health and Nutrition Examination Survey (NHANES), 16.4 percent of children living in cities with more than a million people, or in homes built before 1946 have elevated lead levels. Generally, adults develop lead poisoning as the result of an occupational exposure or from exposure through a hobby. Mortality is rare today. However, death during the 1960s from lead encephalopathy was not rare in urban centers.[27]

Safeguards in the TACT Protocol

Despite their professed concerns about safety, at no point in their 51-page diatribe do Atwood et al. provide any substantial report of patient harm in the NIH TACT study. Had Atwood and his colleagues truly been concerned about lack of safeguards, they simply could have asked Lamas for further information. They would have learned, as I did, the following:

> During protocol development we worked closely with NIH scientists to estimate patient risk. Our reading of the chelation literature, and our discussions with chelation practitioners suggested to us that with disodium EDTA, the principal serious risks were infusion times less than 3 hours, weekly doses higher than 3 grams, not adjusting dose based on renal function, and too-frequent infusions. For these reasons, we put into effect multiple computerized and human safeguards that, after over 40,000 infusions of study infusion (EDTA or placebo), have reduced fast infusions to a tiny number, and warn the site and the coordinating centers when there are significant changes in renal function. Moreover, with the same computerized workflow, renal function is calculated 11 times during the infusion regimen, and EDTA dose adjusted accordingly. Nonetheless, in recognition of the imprecision of the estimates of serious side effects from chelation therapy, our consent form specifies that renal failure, heart rhythm disturbances, heart failure, and death, could result from study participation (G.A. Lamas, personal communication, 2008).

Atwood et al. would also have learned from Lamas that while many clinical sites, including several university and cardiology practices, had extensive experience in research, about 60 percent of the TACT sites are CAM practitioners without prior research

experience. This means that each site and site coordinator has to be given extensive training in the TACT protocol, in ethical treatment of human subjects, in the computerized methodology for recording data, and in Good Clinical Practices for research. Sites are visited for monitoring regularly, by trained monitors. Lamas states that the study receives high-quality data from all sites.

Lamas confirmed that, as required for all large-scale NIH trials, the TACT Trial is supervised by an independent Data and Safety Monitoring Board (DSMB). DSMBs are constituted by NIH and report to NIH, not to the study leadership. These DSMBs meet regularly, review unblinded data with NIH scientists and study statisticians, and advise NIH whether it is safe and ethical to continue the trial. The TACT DSMB has a cardiologist, a statistician, a bioethicist, a CAM practitioner, a pharmacologist, an expert on quality of life, and NIH scientists. No investigator is a DSMB member. At the last DSMB meeting on Apr 29, 2008, investigators were advised to continue enrolling, infusing, and following patients (G.A.Lamas, personal communication, 2008).

Effects of the Atwood Article

The publication of the Atwood article in Medscape has resulted in a mandated inquiry by the U.S. Office of Human Research Protections, the federal agency required by law to investigate all allegations of human subject violations in research. What is resulting is a long, labor-intensive, and costly investigation at taxpayer expense, as well as the temporary and voluntary suspension of recruitment in the study while these issues are sorted out. Months if not years of investigation will follow, even though Atwood et al. make no actual claim of patient harm in their paper.

Conclusions

An important clinical trial has been hindered by publication of an agenda-driven 51-page article in MedScape, despite the lack of expert qualifications and known bias of the authors, and the fact that most authors derive income from legal compensation for testifying against medical professionals who use chelation or other alternative or complementary therapies in their practices.

Investigation of off-label uses of FDA-approved drugs is essential for progress in medicine.

The assertions of self-appointed "quackbusters" should not be accepted at face value, even if published in a prestigious venue.

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Disclosure: My name is mentioned in passing in the article by Atwood et al. I have followed the chelation therapy controversy since 1994.

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