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Why the NIH Trial to Assess Chelation Therapy (TACT) Should Be Abandoned

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Abstract

The National Institutes of Health (NIH) Trial to Assess Chelation Therapy (TACT) was begun in 2003 and is expected to be completed in 2009. It is a trial of office-based, intravenous disodium ethylene-diamine-tetra-acetic acid (Na_2EDTA) as a treatment for coronary artery disease (CAD). A few case series in the 1950s and early 1960s had found Na_2EDTA to be ineffective for CAD or peripheral vascular disease (PVD). Nevertheless, a few hundred physicians, almost all of whom advocate other dubious treatments, continued to peddle chelation as an office treatment. They claim that chelation dramatically improves symptoms and prolongs life in 80% to 90% of patients. In response, academics performed 4 controlled trials during the 1990s. None favored chelation, but chelationists repudiated those findings.

We have investigated the method and the trial. We present our findings in 4 parts: history, origin and nature of the TACT, state of the evidence, and risks. We present evidence that chelationists and their organization, the American College for Advancement in Medicine, used political connections to pressure the NIH to fund the TACT. The TACT protocols justified the trial by misrepresenting case series and by ignoring evidence of risks. The trial employs nearly 100 unfit co-investigators. It conflates disodium EDTA and another, somewhat safer drug. It lacks precautions necessary to minimize risks. The consent form reflects those shortcomings and fails to disclose apparent proprietary interests. The trial's outcome will be unreliable and almost certainly equivocal, thus defeating its stated purpose.

We conclude that the TACT is unethical, dangerous, pointless, and wasteful. It should be abandoned.

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Executive Summary

The National Institutes of Health (NIH) is sponsoring a $30 million, 5-year, phase 3 Trial to Assess Chelation Therapy (TACT) for coronary artery disease (CAD). It was begun in 2003, but after 3 years only half of the planned 2000 subjects had been recruited. The trial involves the intravenous (IV) administration of the chelating agent disodium ethylene-diamine-tetra-acetic acid (EDTA), for which there was a brief enthusiasm among academics during the 1950s. That enthusiasm ended abruptly in 1963 with the publication of a disconfirming case series. Nevertheless, a tiny but strident group of physicians has continued to administer IV "chelation therapy" in their offices, claiming that it dramatically improves symptoms and prolongs life in 80% to 90% of patients with CAD or peripheral vascular disease (PVD). Chelationists also prescribe high doses of both IV and oral vitamin and mineral "supplements," asserting that these are necessary additions to the regimen. Unless otherwise stated, in this article "chelation" refers to IV infusions of disodium EDTA given with such supplements.

In response to chelationists' claims, between 1990 and 2001 academics conducted a series of randomized controlled trials (RCTs), studying a total of nearly 300 subjects. They found no evidence that chelation is superior to placebo for the treatment of CAD or PVD. Chelationists repudiated each of these studies.

We investigated the social and the scientific histories of chelation therapy beginning in the 1950s. We examined TACT protocols and consent forms, which, in response to Freedom of Information Act (FOIA) requests, the NIH provided to us with curious redactions. We examined the existing RCTs and the numerous case series cited by the TACT protocols. We examined evidence for risks, including information that is not in the standard medical literature. We examined various hypotheses that advocates have offered to explain how chelation "works."

We present our findings in 4 parts. First, we provide a brief history of the use of disodium EDTA as a treatment for CAD. Next, we describe the origin and nature of the TACT. Next, we discuss the evidence for chelation as a treatment for CAD and for atherosclerosis in general, and place it in the context of other proposed treatments that have been ineffective after an initial period of enthusiasm. Finally, we discuss the risks. For each topic, we contrast our findings with relevant statements in the TACT literature, to the extent that such statements exist.

We found the following:

- Most who persisted in advocating chelation after the 1960s have been outspoken advocates of other lucrative but implausible treatments, most notably *Laetrile*. In 1973 they created the American Academy of Medical Preventics "to promote the use of EDTA chelation therapy for cardiovascular disease." Later they changed the organization's name to the American College for Advancement in Medicine (ACAM). During the 1970s and 1980s, the editor of *Chest* and *Archives of Internal Medicine* called such advocates "pseudoscientific zealots"; the TACT protocols now describe them as "prominent experts." Several are assigned to trial committees, and nearly 100 have been employed as TACT co-investigators.
- In about 1980, ACAM members began publishing, mainly in a journal of their own creation, case reports of chelation for atherosclerosis. Those reports and an unpublished report by a convicted felon are the main sources cited by TACT investigators in support of effectiveness. We examined those reports and found them not credible. One of the most prolific pro-chelation authors, cited at least 5 times in the TACT protocols, admitted under oath in 1997 to having falsified his data.
- Since the mid-1970s, court documents and newspapers have reported at least 30 deaths associated with IV disodium EDTA, most of it administered by ACAM members. Nevertheless, not one death is mentioned in TACT literature, and the ACAM has long maintained that "millions of infusions have been administered over the last 30+ years, without any deaths being noted, when used in accordance with established guidelines." There is ample evidence of chelation morbidity, ranging from annoying side effects to life-threatening complications. An ACAM "Fellow" who belittles such risks has identified himself as a member of the TACT Data and Safety Monitoring Board.
- In about 1990, the ACAM and one of its offspring, the Great Lakes Association of Clinical Medicine (GLACM), created "institutional review boards" (IRBs). According to the GLACM's Web site: "With an increase in the number of physicians who are under review from state

medical boards for practicing alternative medicine, the IRB may offer protection." The GLACM IRB approved, among other representative studies, Henry Heimlich's "Induced Malaria Therapy" for HIV-positive subjects, conducted in China. In early 2000, with the GLACM IRB under investigation by the US Food and Drug Administration (FDA), both IRBs folded.

- We present evidence that in late 1999 the ACAM, through its ally -- a powerful US congressman -- had begun to pressure the NIH to sponsor a chelation study. A proposal was overwhelmingly rejected by the Scientific Review Committee of the National Heart, Lung, and Blood Institute (NHLBI) in 2000, but a year later the NHLBI and the National Center for Complementary and Alternative Medicine (NCCAM) jointly issued a Request for Applications (RFA) for a chelation trial "expected [to] investigate the EDTA Chelation treatment protocol recommended by ACAM." The winning application -- the 2001 TACT protocol -- was approved a year later by an NCCAM "Special Emphasis Panel" that included an ACAM officer among its 6 members. He had been the chairman of the GLACM IRB mentioned above. The protocol that the Panel reviewed had named him as a participant in the trial. The protocol also conferred explicit benefits on the ACAM.

- Early chelation investigators had chosen the disodium salt of EDTA, reasoning that if it could remove calcium from atherosclerotic plaques, it might shrink them. That notion was soon demonstrated to be invalid. It has largely been replaced by a "toxic heavy metals" antioxidant hypothesis, which is based on the potential for metal ions to produce free radical damage. Chelationists now cite "removing heavy metals" as the basis for their claim that chelation is effective for approximately 70 conditions, ranging from schizophrenia and autism to cancer. This provides them with numerous reasons to ignore any trial that finds chelation ineffective for CAD.

- It is the "heavy metals" hypothesis that the TACT protocols present as plausible. Calcium-sodium EDTA, the form that is used for lead poisoning, would be consistent with that and less dangerous than disodium EDTA. Nevertheless, disodium EDTA is still the preference of the ACAM, which clings to the "decalcification" hypothesis even as it espouses the newer one. That is the stated reason that the TACT will expose subjects to the disodium salt, which carries the risk for acute, life-threatening hypocalcemia.

- Biochemical literature, either not cited or misrepresented in the TACT protocols, has demonstrated that the heavy metals hypothesis is implausible. Antithetically, it also demonstrates that the chelation mixture used in the TACT has pro-oxidant effects in vitro.

- The RCTs mentioned above, together with the early case reports and the biochemical considerations, constitute compelling evidence -- more compelling than the evidence against several other obsolete treatments -- that chelation with disodium EDTA is an ineffective treatment for CAD or for atherosclerosis in general. Chelationists have rejected such findings.

- The TACT was thus begun in the absence of prior, supporting laboratory, animal, or human phase 1 or 2 studies, contrary to the usual requirements for a phase 3 trial, including those of the NIH itself. The NIH and the TACT principal investigator (PI) argued that there was a substantial demand for chelation, creating a "public health imperative" to perform a large trial now. The PI also argued that although several RCTs had been negative, "thousands" of positive case reports were at least as compelling. He asserted that the results of the TACT, supportive or not, would settle the matter and lead to rational practice. However, all evidence argues against those rationales: The demand is tiny; the case reports are not credible; chelationists have not changed their practices in response to previous controlled trials or other credible information; the results of the TACT are unlikely be either reliable or definitive.

- In our opinion, TACT literature -- including 2 versions of the protocol, the consent form, information posted on the NCCAM Web site, and 2 editorials co-authored by the PI -- has misrepresented chelation, its risks, and the facts of the study. It has exaggerated the value of supportive case series, not only by ignoring evidence of bias and incompetence, but by misrepresenting citations and reporting erroneous data. It has minimized the dangers, both by understatements and by omissions of specific, published complications. It has not acknowledged the deaths mentioned above. It has repeatedly conflated disodium EDTA and a different drug, calcium-sodium EDTA. It has ignored accumulating evidence that antioxidant supplements similar to those used in the TACT are ineffective and possibly dangerous.

- The TACT includes nearly 100 "chelation site" co-investigators who, in our opinion, are unsuitable to care for human subjects or to report trial data. Most espouse implausible health claims while denigrating proven methods; several have been disciplined, for substandard practices, by state medical boards; several have been involved in insurance fraud; at least 3 are convicted felons. Several were members of the ACAM or GLACM IRBs mentioned above. Few appear to have real expertise, required by TACT literature, in treating patients with CAD or in conducting clinical trials. Most continue to promote chelation while the TACT is in progress, contrary to good science, to human studies ethics, and to US Federal Code. The TACT consent form gives no hint of these points.

- The TACT is to have multiple primary and secondary endpoints, including subjective "quality-of-life" outcomes. There are about 160 distinct study sites. Thus, by chance alone the trial will likely yield equivocal results, although prior evidence overwhelmingly points to chelation being ineffective for CAD. The most likely outcome of the TACT is that nothing, in the tiny subculture of chelation with IV disodium EDTA, will change.

- We believe that the TACT violates numerous requirements of the Declaration of Helsinki. However, almost any journal to which the TACT investigators might submit a report must honor Helsinki, by virtue of its commitment to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors. It seems that it will not be possible to publish a report of the TACT without overlooking Helsinki and the Uniform Requirements.

For those reasons and more, we conclude that the TACT is pointless, dangerous, unethical, and wasteful. It should be abandoned.

Introduction

The NCCAM and the NHLBI have funded a $30 million, phase 3 clinical trial of intravenous IV EDTA chelation therapy for coronary artery disease: the 5-year TACT.[1-6] Begun in 2003, there are expected to be approximately 2000 subjects -- each more than 50 years old and having had a myocardial infarction (MI) -- at "approximately 100 (now 160) research sites across the country...[that] will represent a mix of clinical settings--university or teaching hospitals, clinical practices or cardiology research centers, or chelation practices.[3]"

According to the protocol submitted in 2001, "TACT has been designed and will be conducted in collaboration with the American College for Advancement in Medicine (ACAM), the world's largest and most respected organization of physicians who employ chelation therapy.[4]" The protocol named several ACAM members, whom it called "prominent experts in chelation therapy," to the TACT Liaison Committee to the ACAM.[4] ACAM members are also on other TACT committees, and nearly 100 have been named co-investigators.[7] The ACAM currently has about 1000 members, of whom fewer than 800 are in the United States.[8] By comparison, there are about 800,000 licensed MDs and DOs in the United States. Not long ago, a distinguished medical editor, who himself had investigated chelation in its early years, characterized such "experts in chelation therapy" as "pseudoscientific zealots.[9-11]"

The primary substance used in the trial is the IV chelating agent disodium EDTA (edetate disodium; edathamil disodium; Na_2EDTA [*Endrate*]). A potent chelator of cations, especially calcium, it is FDA-approved only for rapid, emergency treatments of hypercalcemia or digitalis toxicity,[12] and for those indications it has long been obsolete.[9] Na_2EDTA is specifically contraindicated for "generalized arteriosclerosis." Its labeling includes a

"black box" warning: "The use of this drug in any particular patient is recommended only when the severity of the clinical condition justifies the aggressive measures associated with this type of therapy.[12]" Several deaths have been associated with unapproved uses of the drug by ACAM members.[13-20]

Prior to the TACT, 4 RCTs and several substudies of chelation for either CAD or PVD, involving 285 subjects, had been reported.[21-28] None found chelation superior to placebo. Nevertheless Dr. Gervasio Lamas, the PI of the TACT, argued that the trials had been underpowered to "exclude a small or moderate benefit of EDTA chelation," and that "case reports and case series encompass thousands of patients with successful outcomes...we believe a state of clinical equipoise exists and support a definitive trial [that] would...put to rest the lingering questions of efficacy....[29]" He asserted that "evidence [from such a trial], when widely disseminated, leads to changes in clinical practice, ultimately benefitting patients.[29]"

Both Dr. Lamas and the NIH have also asserted a "widespread use of chelation therapy,[2]" implying substantial demand among the "34% [of Americans who] reported using at least one alternative therapy in the last year.[4]" The late NCCAM Director Stephen Straus asserted that "The public health imperative to undertake a definitive study of chelation therapy is clear.[2]" Chelation, however, is received by considerably less than 0.01% of Americans each year. Even if the fraction were higher, it would not justify curtailing usual protections for human subjects. We shall discuss each of these points.

Contrary to the repeated suggestions of the NCCAM, the TACT protocol and consent form, and the ACAM, Na_2EDTA is not approved for treating heavy metal poisoning.[1-3, 5,6,30] That approval -- which applies only to lead, not to heavy metals in general -- belongs to a different EDTA salt, calcium-disodium EDTA (CaEDTA *Versenate*), which does not carry the warning of acute hypocalcemia.[31] The rationale for Na_2EDTA is that in the 1950s, when investigators proposed IV chelation as a treatment for atherosclerosis, they reasoned that if it could remove calcium from plaques, it ought to shrink them.[32]

Decalcification is no longer the favored purported mechanism.[33-35] The authors of the TACT protocols dismiss it, preferring a more sophisticated but still implausible antioxidant hypothesis that is based on chelation of heavy metals.[4,5] Nevertheless, the ACAM literature continues to assert the decalcification theory, and its "standardized protocol" continues to require Na_2EDTA.[33,36] That appears to be the only reason that the TACT is exposing subjects to the more dangerous disodium salt.[1,4,5]

The trial also exposes subjects to "high dose antioxidant vitamin and mineral supplements" that are part of the typical chelation regimen given by ACAM members.[4,5] Among these are IV vitamin C at 7 g per infusion and oral vitamins E, A, and beta-carotene. The TACT will not compare chelation with standard therapies for CAD; all subjects are expected to receive standard medical treatments. The trial is a "2 x 2" design in which the chelation and placebo arms are each further randomized to receive either high or low doses of supplements.

The Timeline in the 2001 TACT protocol called for subject recruitment to take 36 months.[4] The TACT began to recruit subjects in the fall of 2003.[2] By the fall of 2006, only 1000 subjects -- half of the planned sample -- had been recruited.[37] According to ClinicalTrials.gov, the "expected completion" of the trial has been postponed to July 2009.[38]

Through FOIA requests, we obtained "redacted" copies of the original (2001) and 2003 TACT protocols,[4,5] the roster of the committee that approved the grant application,[39] and the June 2003 consent form.[6] Because the trial had already begun and because our initial FOIA requests were frustrated by delays and incomplete responses, we did not seek further revisions of the protocol or consent form, or other documents that are not available on the NCCAM Web site. It is possible that such revisions or other documents have addressed some of the problems reported here; it is also possible that the PIs have discussed some of these problems at meetings of trial committees or IRBs. We can only vouch for what we know, and we reserve the right to change our opinions if we become aware of new information that warrants such a change.

Nevertheless, "an experiment is ethical or not at its inception; it does not become ethical *post hoc*....[40]" Most of the problems we report were present when the trial began. Among them:

- Substantial evidence that IV Na_2EDTA is neither a safe nor effective treatment for CAD or atherosclerosis;
- Evidence that the TACT was motivated by political pressure rather than by scientific or medical considerations[41,42];
- The listing of a key ACAM officer on the NIH Special Emphasis Panel that reviewed the grant application.[39,43]
- The enlistment of numerous "chelation site" co-investigators who, in our opinion, are unfit to be responsible for human subjects or to report data[7, 9-11];
- The absence of mention, in the protocols or the consent form, of several known risks for both Na_2EDTA and of the supplements used in the TACT regimen;
- Citations in the RFA and the TACT protocols of several articles co-authored by a chelationist who had admitted, under oath in 1997, to having falsified his data[44]; and
- The PI's inaccurate review of chelation case series.[4,5,29]

Dr. Lamas' favorable portrayal of the case series would have been necessary to convince IRBs that human subjects would be exposed to a substance likely to be effective enough to justify its dangers.[45,46] Because he granted that chelation has risks, he had to provide sufficient evidence of a therapeutic effect. All credible RCTs, however, had found no evidence of effectiveness; thus Dr. Lamas argued that "case reports and case series encompass thousands of patients with successful outcomes,[29]" implying that the case series nullified the disconfirming RCTs.

The TACT protocols' representations of the case series, however, are replete with errors. The protocols also ignore additional information, readily available from other sources, necessary for a thorough interpretation of those series. A comprehensive review of the case series -- which we provide in Part III of this article -- does not support chelation as an effective treatment for atherosclerotic disease. Rather, it agrees with the RCTs that chelation is ineffective, and indicates that it is more dangerous than the TACT protocols acknowledge. In our opinion it also suggests that the authors of most of the "positive" case series, including all of the large ones and all of those reported after the 1960s, have been biased to the point of fanaticism.

Scientific and ethical problems with the TACT have continued since its inception. Examples are the repeated conflations of Na_2EDTA and CaEDTA, the appointment of a conspicuous advocate of chelation to the TACT Data and Safety Monitoring Board,[47] and the recent addition of several Canadian co-investigators who, we maintain, are also unfit for the task.[7,48] The PI has also continued to misrepresent chelation literature.[49]

I. A Brief History of EDTA Chelation for Cardiovascular Disease

Beginning in 1956, a few small, uncontrolled case series reported that IV Na_2EDTA seemed to have striking, beneficial effects on CAD, PVD, and cerebrovascular disease.[32, 50-53] By 1963 it became clear that those reports, which were based primarily on subjective outcomes, had been wrong. When followed for more than a few months, subjects with CAD had rates of death and MI similar to those expected for untreated patients at that time.[54] Two small series of subjects with intermittent claudication had also shown no evidence of improvement.[54,55] Several autopsies from various series had revealed no evidence of decalcification of plaques or reduction of plaque size. Within a couple of years, case series of IV Na_2EDTA for cardiovascular disease no longer appeared in the academic medical literature.

Nevertheless, a tiny group of advocates continued to practice "chelation therapy," usually in the office. Then as now, it consisted of an initial series of IV infusions of disodium EDTA, magnesium, vitamins, and minerals, followed by monthly "maintenance" infusions. At first, chelationists called the treatment a "chemical Roto-Rooter" or a "chemical endarterectomy," but eventually promoted it as a near-panacea for conditions as disparate as multiple sclerosis, schizophrenia, autism, cancer, peptic ulcer, back pain, and chronic obstructive pulmonary disease.[34,56,57] According to a recent article reprinted on the Web site of the ACAM, the most conspicuous organization of chelationists, "heart patients undergoing chelation typically receive 30 to 40 weekly treatments, then are scheduled for lifelong monthly sessions to keep the arteries free of plaque.[58]" The article quoted the price of a single chelation treatment -- the ingredients of which cost a few dollars[59] -- to be $120-$125. In addition, according to the Trial Chelation Consultant for the TACT,[4] there are "nutritional supplements in the range of $20 to $200 per month [and] diagnostic study costs and professional fees...ranging from a few hundred to several thousand dollars.[57]"

The article on the ACAM Web site reported that TACT co-investigator and "prominent expert[4]" Allan Magaziner "said his center [was] treating 400 to 500 heart patients with chelation.[58]" L. Terry Chappell, another "prominent expert" and co-investigator, told a government hearing in 1999 that he had treated "at least 2500 to 3000 patients with chelation therapy" over a period of about 18 years, but that this represented "only 20-25% of [his] medical practice.[41]" Former ACAM president and convicted extortionist Ted Rozema,[60] also a TACT co-investigator, testified at the same hearing that in 16 years he had treated "over 2000 patients [with] over 80,000 infusions of EDTA.[41]" The 2001 TACT protocol states that Trial Chelation Consultant, prominent expert, and TACT co-investigator Dr. Martin Dayton, who was convicted of conspiracy and mail fraud in 1986,[61] "has clinical experience with over 75,000 chelation infusions.[4]" The late H. Ray Evers, a convicted felon revered by chelationists as a "pioneer of chelation therapy," reportedly claimed to treat, during the 1970s, 1000 patients per year at $3000 each.[62,63] According to a former practitioner, "chelation is a big cash cow.[59]"

The Rise of Activism-Based Medicine: *Laetrile* Spawns Chelation

In their early days many chelation advocates also favored, and some still favor, the lucrative quack cancer treatment *Laetrile*. Most chelationists still offer other dubious treatments, such as IV hydrogen peroxide, "detoxification," hair analysis, "antineoplastons," "live cell therapy," coffee enemas, "ozone therapy," magnets, homeopathy, and more, while denigrating the methods of modern medicine and public health, including surgery, pharmaceuticals, immunizations, fluoride, and controlled clinical trials.[7,64] By the mid-1970s, their activities had drawn the attention of the FDA, Medicare, state medical boards, professional ethics committees, and criminal prosecutors.[18, 65-67] In an effort to protect themselves, advocates established organizations, symposia, "certification boards," journals, political connections, lobbies, and -- a few years later -- political action committees, IRBs, and "Achievement Awards" (at times bestowed upon, presumably, unsuspecting recipients[68]).

Among such early organizations were the National Health Federation, which had been around since the 1950s and included, among its officers and board members, Drs. H. Ray Evers, Garry Gordon, Michael Gerber, James Privitera, W. Douglas Brodie, and Bruce Halstead -- all chelationists[69]; and the Committee for Freedom of Choice in Cancer Therapy (later renamed the Committee for Freedom of Choice in Medicine), founded by John Bircher and Stanford lab technician Robert Bradford who, in addition to smuggling millions of dollars worth of *Laetrile*, hawked filmstrips entitled *Chelation Therapy and the Killer Diseases*.[63,70,71] Halstead was the Committee's vice president. Each of these organizations was primarily concerned with protecting its members' freedom to peddle *Laetrile*.[69-73]

In 1973 chelationists established the American Academy of Medical Preventics (AAMP) "to help educate physicians and to promote the use of EDTA chelation therapy for cardiovascular disease.[34]" Among the founders, officers, and key members were the 6 physician members of the *Laetrile* organizations named above. Four of the 6 -- Evers, Halstead, Brodie, and Privitera -- were subsequently convicted of felonies.[62,67,69,74,75] The first AAMP president was Harold W. Harper, another *Laetrile* advocate.[75] When *Laetrile* sales were mostly forced underground by the US Supreme Court's decision in the Rutherford case of 1979[76] (the AAMP had filed an amicus curiae brief in opposition to the eventual decision[77]), chelation emerged as heir-apparent to the title of "most successful medical fraud in history.[78]"

In its early years the AAMP mounted one of the first "direct-to-consumer" drug advertising campaigns in the form of "An Open Letter to Those Persons Interested in Chelation Therapy.[79]" The letter suggested that chelation was better, safer, and cheaper than the mainstream alternatives:

> All too often, the remarkable benefits available from low fat dietary regimes, in conjunction with megavitamin, chelation, and hyperbaric oxygen therapy are not offered to patients who may be facing needless vascular surgery, such as bypass heart surgery, or even amputation of an extremity (because of impending gangrene), or a future of continual pain and disability and eventual premature death, when frequently these alternative approaches could have provided as good, if not better results at less cost, and without surgery.[79]

The letter recommended a "filmstrip presentation with sound, suitable for showing to all community groups," which "is self explanatory and does not require a physician's attendance.[79]" The filmstrip appears to have been Bradford's *Chelation Therapy and the Killer Diseases*: The reader could buy it for $50 from the "Committee for Freedom of Choice.[79]" The letter exhorted readers to "become involved in one or both of the lay organizations that are attempting to increase the general public awareness regarding these new therapies": the Association for Chelation Therapy and the National Educational Society for Natural Healing.

The AAMP also hired a law firm to advocate for chelation.[80] Within a few years, AAMP members had founded the American Board of Chelation Therapy (ABCT), GLACM, and the American Preventive Medical Association (APMA).[34] In 1986, the AAMP changed its name:

> The members of the American Academy of Medical Preventics (AAMP), recognizing that their training, experience, and clinical practice would form the basis for emergence of new medical paradigm, [*sic*] changed the name of their organization to the American College for Advancement in Medicine (ACAM).[34]

The ACAM now refers to itself as "the voice of Complementary, Alternative and Integrative Medicine.[81]" In 1988, the ACAM created the *Journal of Advancement in Medicine*, which has since published most of the pro-chelation articles.[82] In 2000, the journal's name was changed to *Clinical Practice of Alternative Medicine*.[83] The AAMP offspring have also changed their names: the ABCT to the American Board of Clinical Metal Toxicology (ABCMT), the GLACM first to the Great Lakes College of Clinical Medicine (GLCCM) and recently to the International College of Integrative Medicine (ICIM), and the APMA to the American Association for Health Freedom (AAHF).[84-86]

The ACAM "Industry Directory" currently lists American Biologics as one of its "Legacy Partners.[87]" American Biologics has marketed numerous quack products, including *Laetrile*.[70] It is owned by convicted *Laetrile* smuggler Robert Bradford, who founded it in the early 1970s.[70,71]

Reports of uncontrolled series of IV Na_2EDTA for cardiovascular and other diseases began to reappear in about 1980. Unlike the original reports, these were written exclusively by advocates, all members of the AAMP/ACAM, and published, with 1 or 2 exceptions, in little-known, nonrefereed journals. Several articles reported sample sizes in the hundreds or thousands. Each series reported dramatic improvements in 80% to 90% of subjects.[34,57,88,89]

Complications, if mentioned, were described as minor. Rates of death from any cause, if mentioned, were implausibly low. For example, in a report of 2870 subjects, most of whom were said to have CAD (844 subjects), PVD (1130 subjects), or cerebrovascular disease (504 subjects), followed in Brazil for a 2-year period in the early 1980s, the authors reported 7 deaths; 2 were in the CAD group.[90,91] In a subsequent report, the same authors wrote that when chelation had been "administered according to the ACAM protocol," there hadn't been "a single reported incident of renal failure or death since 1960.[92]" As discussed in Part III of this article, the claim was false and the authors had reason to know it.[18,93,94] One of those authors, James Carter, is now a TACT co-investigator.[7]

Two reports were "meta-analyses" of the others, reporting more than 20,000 subjects and creating, for their statistical analyses, imaginary control groups "defined to have no improvement in cardiovascular capability.[95,96]" The first author of those reports is "prominent expert" L. Terry Chappell, also now a TACT co-investigator.[4,7]

One of the most prolific chelation authors is Edward McDonagh, DO, the author or co-author of more than 30 exclusively pro-chelation articles.[89] According to a reporter:

> In December 1996, the [Missouri medical] board brought suit against McDonagh, alleging 13 counts of negligence and malpractice.
>
> [The] state investigation of McDonagh's records revealed a pattern: Since the late '70s, he'd diagnosed patients without obtaining their medical records or recording the results of their physical exams. Other mistakes were charted on the racked bodies of former patients. In the 1980s, he misdiagnosed a case of gangrene, which festered until the patient fell into a coma and had to have his leg amputated above the knee.
>
> The only consistent thing about his files was that each record had serious inconsistencies, argued David Meyers, a KU cardiologist who analyzed McDonagh's records for the board's initial case against the doctor. Meyers testified that McDonagh hadn't used orthodox methods to treat anything. In some cases, McDonagh's prescriptions and diagnoses ran contrary to existing medical knowledge.
>
> On the witness stand, McDonagh argued that he had kept slipshod records, recording only positives about his experiments, to avoid possible liability lawsuits.[44]

That admission resulted in the following exchange between the board's attorney and Dr. McDonagh:

> Attorney Bradford: "Do you think it weakens the validity of your conclusions as represented by your papers that you can't show your underlying data?"
>
> Dr. McDonagh: "I think it might.[44]"

Despite such testimony, the administrative hearing commission found in favor of McDonagh. The opinion was upheld by a circuit court, but in 2003 it was "reversed and remanded" by the Missouri Supreme Court.[97]

A few years before that testimony, Dr. McDonagh had "failed to pass the Special Purpose Examination after the Board found probable cause to question his competency to practice medicine," and thus in 1995 the Missouri Board revoked his license to practice medicine.[98] He continued to practice, however, because the "Board action [was] stayed by court order on 1/17/95 while appeal was pending.[98]" In 1997 the Board reinstated his license "in accordance with a Settlement Agreement.[98]" McDonagh was the subject of a series in the *Kansas City Star* investigating his peddling of chelation to trusting, scientifically naive Amish and Mennonite patients.[99]

As it became clearer that the decalcification theory was no longer taken seriously by medical scientists, chelationists sought new explanations for the putative effects of Na_2EDTA, though never relinquishing the old one.[80,100] Several were proposed, among them platelet function inhibition, anticoagulation, lowering of serum lipids, and calcium channel blockade. The most popular one, which persists, was based on the removal of toxic heavy metals. Through the removal of iron, mercury, aluminum, lead, and other metals that, according to advocates, are toxic even at the miniscule levels found in most people, the panacea effects of chelation are explained.

Thus, proponents claim:

- Chelation reverses autism by removing mercury introduced by childhood immunizations and dental amalgams.[101,102]
- It reverses Alzheimer's disease by removing aluminum, copper, and zinc from the brain.[35,103]
- It reduces high blood pressure, which "has been shown to be associated with increased total body burden of lead.[104]"
- It prevents cancer because "the metals interact with the DNA, RNA, enzymes, mitochondria, and cellular components to contribute to the causation of diseases. The immune system appears to be effected [*sic*] to allow cancers already in the body to manifest into a diseased state.[104]"
- It reverses atherosclerosis by reducing "free radical" production dependent upon iron.[105]
- And more.

All in all, according to Elmer Cranton, a past president of the ACAM, one of the "prominent experts" named to the TACT Liaison Committee to the ACAM,[4] and author of *Bypassing Bypass Surgery: Chelation Therapy: A Non-Surgical Treatment for Reversing Arteriosclerosis, Improving Blocked Circulation, and Slowing the Aging Process*[106]:

> The use of EDTA to restore the balance and distribution of essential metallic elements, while at the same time removing toxic heavy metals and catalytic free iron, has been shown to slow or arrest progression of diseases of aging. Other benefits of chelation occur from uncoupling of disulfide and metallic cross-linkages between molecules, by normalization of calcium metabolism, by reactivation of enzymes poisoned by lead and other toxic metals, and by restoration of normal prostacyclin production along blood vessel walls. Lasting benefits follow a series of intravenous EDTA infusions, plus nutritional supplementation and lifestyle improvements.

> This well-documented, safe, and effective therapy deserves widespread recognition and acceptance.[105]

Removing toxic heavy metals has the additional appeal of parroting an approved use of the similarly named, but different drug: CaEDTA.[31] Chelationists and the TACT literature frequently conflate the 2 drugs, as in this statement posted on the NCCAM Web site: "When used as approved by the FDA...for treatment of heavy metal poisoning, chelation with EDTA has a low occurrence of side effects.[3]" Chelation advocacy organizations cloak their agenda in euphemism: The ICIM urges Web-surfing practitioners to "Check out our friends at ABCMT for more information about certification in Heavy Metal Toxicology[85]"; in 1998 the ACAM's phone number was 1-800-LEADOUT.[34]

Such explanatory sleight of hand has fooled not only patients, but regulators. After the recent hypocalcemic death of a 5-year-old autistic boy in the office of an ACAM member, the chief of the US Centers for Disease Control and Prevention (CDC) Lead Poisoning Prevention Branch mistakenly "determined 'without a doubt' that it was medical error, and not the therapy itself, that led to the death of [the] 5-year-old boy," because "'only Calcium Disodium EDTA should be used...No medical professional would ever have intended to give the child Disodium EDTA.[107]'" Similarly, the Pennsylvania Board of Medicine subsequently charged that the practitioner had "...used disodium EDTA to chelate [the boy] for metal toxicity which should be treated with $CaNa_2EDTA$ instead.[108]"

After the hypocalcemic death of a 53-year-old woman in Oregon in 2003, to whom a naturopath had administered chelation therapy in order to "remove heavy metals," the CDC reported: "The Oregon State Naturopath Licensing Board is conducting an investigation to determine whether Na_2EDTA or CaEDTA was administered to this patient.[13]" The Oregon Board investigated and found that the naturopath "was medically negligent in performing a chelation procedure," but the order does not name the chelating drug.[109]

Curiously, the Oregon naturopathic formulary lists EDTA without a cation, adding, "Board approved certification required before therapeutic IV chelation is allowed.[110]" In 2003 such certification was likely to have come from the ACAM: The Oregon Naturopathic Board included, on its list of approved continuing education courses, an ACAM course entitled "Heavy Metal Detoxification.[111]" Thus, in our opinion it is virtually certain that Na_2EDTA was the drug that killed the woman, and "therapeutic IV chelation" is a state-sanctioned oxymoron in Oregon. Would the Board have found the naturopath, himself an ACAM member, at fault for administering the very drug that its approved certification course had urged him to administer?

In each case, regulators missed the point and revealed their naiveté about fraudulent medical practices: These "medical professionals" almost certainly intended to give disodium EDTA, although there was no indication for any chelating agent. Each practitioner was, ipso facto, "medically negligent in performing a chelation procedure,[109]" not merely in performing it in an especially reckless way. In our opinion, no competent, ethical, medical professional would have given EDTA in any form.

Chelationists have also used the toxic heavy metals hypothesis for another purpose. Health insurers typically do not cover chelation treatments because of lack of demonstrated efficacy, so most patients pay out of pocket.[112] In order to collect payment from insurers, some chelationists falsely report that patients have toxic levels of heavy metals.[113]

The ACAM's "certification" organization is the ABCMT (formerly the American Board of Chelation Therapy). It is not recognized by the American Board of Medical Specialties. At the time of its creation in 1982, it offered this "Definition of Chelation Therapy":

> A form of medical therapy designed to restore cellular homeostasis using various mechanisms including metal binding and restoring ionic balance. For optimal results Chelation Therapy should be complimented [*sic*] by utilizing other modalities such as nutrition and exercise.[114]

Chelationists have recently contrived to change both standards of care and third-party payments without having to resort to evidence. The ABCMT has implored all state medical boards to adopt its "Standard of Care for Increased Body Burden of Toxic Metals.[102]" This declares the ABCMT to be "the only professional organization with over twenty years of continual teaching, testing, monitoring results and seeing marked improvement in patients' symptoms with metal detoxification." It extols hair analysis and "provoked urine testing," and refers to "in office intravenous detoxification of documented toxic metals" without naming chelation per se. It "resolves" that "established detoxification techniques, which have been proven safe and effective over time, be employed to detoxify these patients.[102]"

In a "Cover Letter to all State Medical Boards" sent with the "Standard of Care" document in July 2004, Chairman Robert Nash wrote:

> ABCMT is now ready to certify competence and assist in your concerns about patient and public safety.
>
> Physicians who complete the toxic metals toxicology course and successfully pass the appropriate tests should be recognized as Physician Clinical Metal Toxicologists by each state's medical board.
>
> If you have not provided us with a more thorough, updated Standard of Care within 30 days, we will conclude that our Standard of Care has been accepted.[115]

Nash is a former ACAM board member and is now, according to the abstract of a recent article by him, "on the Data and Safety Management Board" [*sic*] of the TACT.[47] Assuming that Nash is a member of the Data and Safety Monitoring Board of the TACT, he appears to have conflicting interests.

Nash was an "expert witness" called by chelationist Robban Sica, a TACT co-investigator who filed a federal lawsuit in 2004 in an attempt to prevent the Connecticut Bureau of Health Care Systems from disciplining her for numerous instances of substandard care.[116-118] In ruling against Dr. Sica, the federal judge wrote:

> While most "mainstream" physicians would see Dr. Sica as treating, for example, cardiovascular disease with EDTA Chelation, Drs. Nash and Sica concede only that Dr. Sica was treating [heavy metal] toxicity....[119]

At least 1 state medical board appears to have been duped by the heavy metals ploy even prior to the "Standard of Care for Toxic Metals" project. In 2001 the Missouri Code of State Regulations added language about chelation. It begins with a promising statement:

> ...the board declares the use of ethylinediaminetetracetic acid (EDTA) chelation on a patient is of no medical or osteopathic value except for those uses approved by the Food and Drug Administration (FDA) by federal regulation.[120]

Notwithstanding that preamble:

> The board shall not seek disciplinary action against a licensee based solely upon a non-approved use of EDTA chelation if the licensee has the patient sign the Informed Consent for EDTA Chelation Therapy form, included herein....[120]

The consent form warns that chelation "may be harmful" and "has been authoritatively demonstrated to be ineffective in the treatment of vascular diseases," (emphasis in the original) but also includes these statements:

> My physician has explained to me and I fully understand:
>
> (a) that the use of ethylenediaminetetracetic [*sic*] acid (EDTA) has been approved by the federal Food and Drug Administration (FDA) only for the use of removing heavy metals from the body;
>
> (b) that the FDA has not approved the drug EDTA for treatment of diseases or conditions other than heavy metals poisoning;
>
> ...(i) that the Missouri State Board of Registration for the Healing Arts strongly recommends that Missouri citizens not undergo EDTA chelation therapy for the treatment of any human disease, illness, malady, or physical condition other than heavy metals poisoning;
>
> *Notwithstanding having read and understood the above, I hereby elect to undergo treatment with EDTA chelation therapy under the protocol recommended by the American College for the Advancement in Medicine (ACAM) [*sic*].*[120]

It seems odd that the Missouri Board would warn citizens to avoid chelation, which it deems dangerous and ineffective, but declines to discipline licensees who push it. The Board appears to have been unaware, when it wrote that rule, that the statements about heavy metals undermine the statements urging citizens to refuse chelation, and are also quite false: The EDTA salt recommended by the ACAM protocol,[33] Na_2EDTA, is not approved by the FDA for removing heavy metals.[12] Even the somewhat safer CaEDTA is approved for the removal of only 1 heavy metal (lead), not heavy metals.[31] Because there is nothing in the Missouri rule requiring a proper diagnosis of "heavy metals poisoning," chelationists can conform to the letter of the law by doing exactly what they've been doing for years: prescribing chelation ostensibly to remove heavy metals, no matter what may or may not ail the patient.

Several other state medical boards or practice acts have language addressing unapproved uses of EDTA or chelation.[121] They vary in the extent to which they tolerate or condemn the practice, but most appear to have been misled by the heavy metals gambit. Tennessee is a laudable exception.[122,123]

Statements that disodium EDTA removes toxic heavy metals suggest, at least in regard to CAD, that several unproven speculations are true: (1) that individuals are "poisoned" by trace amounts of ubiquitous environmental substances; (2) that these alleged poisonings cause atherosclerotic CAD; (3) that disodium EDTA safely and effectively removes these unnamed heavy metals; and (4) that it thereby reverses CAD.

Despite their organizational efforts during the 1970s and 1980s, chelationists continued to be inconvenienced by regulators and criticized by influential physicians. Alfred Soffer, the Editor-in-Chief of both *Chest* and *Archives of Internal Medicine*, had performed trials of Na_2EDTA during its early days and concluded that it was not useful for CAD or PVD.[55] In a series of editorials, he called chelationists "pseudoscientific zealots" whose practices were "an abuse of the physician's freedom of choice.[9-11]" Others referred to promotions of chelation as "the next generation of medical sleight of hand," "deceptive," and "pseudoscience"; to chelation itself as "fringe medicine," "scientific chicanery," "sham therapy," and a "medical fraud" with "all the classical hallmarks of quackery"; and to its practitioners as "super salesmen" and "modern quacks," who "rip...willing victims off for $3000 to $5000 for a few weeks of injections of EDTA.[63,78, 124-126]"

Chelation for atherosclerosis was condemned by the *Medical Letter*, the American Heart Association (AHA), the American College of Physicians, the American Academy of Family Physicians, the American Society for Clinical Pharmacology and Therapeutics, the American College of Cardiology, the American Medical Association, and the American Osteopathic Association.[127] In 1989, the FDA included chelation therapy on its list of "Top 10 Health Frauds.[128]" Within a few months, however, the FDA bowed to pressure from former AAMP President Ross Gordon to remove chelation from the list because of a pending "approved study" that was never completed.[34,129]

In response to such criticism, in the early 1990s the ACAM and the GLACM created their own IRBs.[34] The GLACM Web site explained the mission of its IRB:

> With an increase in the number of physicians who are under review from state medical boards for practicing alternative medicine, the IRB may offer protection. The IRB recommends that any GLACM members who want to organize procedures in their offices and get peer-reviewed, officially-sanctioned research contact Karen at Dr. Chappell's office (419) 358-4627, to get guidelines for preparing a proposal.[130]

The GLACM IRB approved numerous projects eventually subjected to criminal, civil, and FDA actions, among which were "Evaluation of the Effect of the Immunotherapeutic Technique Enzyme Potentiated Desensitization (EPD) for a Considerable Variety of Illness/Conditions/Diagnostic Conditions," "Extracorporal Hemo-Infusion Therapy," "The Effects of DMPS (Dimercapto-propane sulfonate) in a Total Mercury Detoxification Protocol," "Insulin Potentiation Therapy," and "Gene-Activated Therapy (GAT) for Treatment of Cancer.[131,132]"

At least 2 projects involved the deaths of experimental subjects: The "induced malaria therapy for HIV" study conducted in China by Henry Heimlich, and the "DMPS Mercury Detoxification" study conducted by IRB member Paula Bickle, who had obtained her "PhD" from a mail-order degree mill.[133-136]

Another study approved by the GLACM IRB was exposed as a fraud after "Stimulated Autologous Immune Serum" was sold to a woman for $15,000 with the promise of "an excellent chance [that she] would respond favorably to the serum treatment and that it could effect a cure of her [ovarian cancer].[137]" A laboratory analysis subsequently found the "serum" to consist of "water, lactic acid, a dye substance, and no protein material.[137]" GLACM IRB member George Kindness was the president of the company, Amscot Medical Labs, Inc., that had manufactured the serum. According to a 22-count criminal federal indictment in 2003, Kindness "falsely represented to FDA investigators that he had an M.D. in general medicine.[138,139]"

In 1999 the FDA inspected the GLACM IRB and found multiple violations of federal regulations.[140,141] IRB members had voted to approve their own projects. Some projects involving new drugs were approved without having Investigational New Drug Applications. Several informed consent

documents were found to lack "the basic elements"; the following examples are quoted from the inspector's report:

- There is no statement indicating that the study involves research.
- There is no description of the procedures to be followed.
- Procedures that are experimental are not identified.
- There is no description of any reasonably foreseeable risks or discomforts to the subject.
- Exculpatory language is used through which the subject is apparently made to waive their [*sic*] legal rights.
- There is no statement indicating that participation in the study is voluntary...
- There is no description of additional costs...
- [The] statement appears to suggest that this investigational therapy is superior to conventional therapies...
- [The] statement...appears to suggest that this investigational therapy is safe.
- There is no disclosure of appropriate alternative...treatment[s] that might be advantageous to the subject.[140]

Referring to "the IRB's written policies and procedures," the inspector wrote:

> It appears that this document was written not for the purpose of having a relevant, functional, and useful document for the IRB's operations but more for the purpose of fulfilling a regulatory requirement for written procedures.[140]

In 2000 the FDA banned the GLACM IRB from approving new studies or admitting new subjects to ongoing studies. The FDA letter to the IRB secretary, L. Terry Chappell, concluded: "Based on the deficiencies found during this inspection, we have no assurance that your IRB procedures are adequately protecting the rights and welfare of the human subjects of research.[141]"

The FDA did not inspect the closely related ACAM IRB, but we believe that if it had the findings it would have been similar. That IRB's "Sample Protocol for Chelation Therapy for Arteriosclerotic Disease," updated in 1993, stated that the study's purpose "is to accumulate evidence to demonstrate the effectiveness and safety of chelation therapy for arteriosclerotic disease.[142]" It asserted that "3500 abstracts attest to the efficacy and validity of EDTA chelation therapy," but made no mention of a recent controlled trial failing to demonstrate effectiveness.[21,22] It recommended "self-selection" of subjects to receive EDTA after they had been told that it works. It did not stipulate real control groups or blinding, but recommended that patients serve as their own historical controls. It described mainly subjective outcome measures.

The Sample Protocol's Consent Form stated:

> I understand that this project is conducted under the aegis of the Institutional Review Board ("IRB") of the American College for Advancement in Medicine ("ACAM"), for the purpose of establishing the effectiveness of treatment of arteriosclerotic diseases by intravenous ("IV") administration of EDTA with magnesium, according to protocol. The study will continue until this therapy is approved by the Food and Drug Administration.[142]

The Consent Form falsely suggested that the FDA had approved Na_2EDTA for the treatment of heavy metal toxicities, and stated that for atherosclerosis the drug was "considered 'experimental' by most physicians." It referred to "persantin" [*sic*] as "experimental and unproven," thus implying that for treating atherosclerosis, "most physicians" would rate chelation at least as favorably as they rated dipyridamole (*Persantine*). The Consent Form required the subjects -- not the "treating physicians" -- to decide whether to consider standard medical and surgical therapies: "If I desire further information about these types of drug therapy, I will ask my physician...There are various kinds of vascular surgical procedures, and if I am interested in these I will ask my physician...I understand that all these therapies have certain risks about which I should ask my physician if I am interested.[142]"

Those statements and the following paragraph in the Consent Form illustrate what the FDA Inspector presumably meant when he criticized the GLACM consent forms as "exculpatory":

> I understand that no compensation for participation in this study will be provided by Dr._____, his office, or the ACAM or the IRB, and I also understand that neither ACAM nor the IRB has a policy to medically treat or compensate for physical injuries incurred as a result of participating in biomedical or behavioral research. I understand and agree that ACAM is not a participant in the study and that the IRB merely serves as a reviewer and collator of the data produced under this study. I expressly agree, as a condition of my participation in this study, that ACAM and the IRB shall not in any manner be responsible for any physical injuries incurred as a result of my participation in the study and I waive, in advance, any claims against either and both of them [*sic*].[142]

In 2001 both the GLACM and the ACAM IRBs "ceased operations," citing FDA "requirements" and "restrictions.[143-145]" At least 8 former members of the GLACM and ACAM IRBs are now TACT co-investigators.[7] Two, Drs. Chappell and Ralph Miranda, are "prominent experts" named to the TACT Liaison Committee to the ACAM.[4] Dr. Chappell was also a member of the NIH Special Emphasis Panel that reviewed the original TACT proposal.[39,43] It is instructive to compare Dr. Chappell's opinion of the GLACM IRB[146] with that of the FDA.

Meanwhile, in response to the tiny but shrill minority of physicians promoting chelation (the ACAM had fewer than 400 members in 1986), a few academic investigators performed RCTs. Between 1991 and 2002, four adequately designed trials and several substudies, involving 285 subjects, were reported.[21-28] These compared Na_2EDTA with placebo for several objective measures of CAD or PVD. None showed an advantage for Na_2EDTA.

Other authors have challenged the hypothetical mechanisms by which Na_2EDTA was claimed to attenuate the process of atherosclerosis:

- The dosing of Na_2EDTA, although capable of toxicity in the short run, is far too small to effect a significant, lasting reduction of metallic free radicals or calcium.[147,148]

- EDTA is relatively ineffective in removing mercury, iron, and copper, as contrasted with lead, because the former metals are more tightly bound to tissues and proteins.[147,148]

- There is evidence of EDTA's paradoxical generation of reactive oxygen species in the presence of iron, and a possible augmentation of that effect by high ascorbate concentrations, such as those in the chelation solution advocated by the ACAM and used in the TACT.[147-150] Thus, "instead of protecting against and neutralizing metallic free radicals, EDTA in the presence of iron and ascorbate produces free radicals and potentially induces the changes that it is intended to prevent.[148]"

More recently, it has become clear that clinical trials of antioxidants, even of those that had shown promise for preventing and treating atherosclerosis in laboratory and animal studies, have been disappointing.[151] Thus well before the TACT began to recruit subjects, 2 experts in atherogenesis had called for a moratorium on clinical trials of antioxidants: "Instead, we should concentrate on developing the scientific base that will enable us to design an appropriate trial to test the oxidation hypothesis.[151]"

Controlled trials notwithstanding, chelationists refused to accept negative results, claiming that the authors had been dishonest because of "vested interest[s] in catheterization and surgery"; that the trials hadn't followed the "ACAM protocol" closely enough; that the results had actually been favorable to chelation; that one trial had been too long, another too short; and more.[57,94, 152-162] To counter the negative publicity of disconfirming RCTs in the 1990s, the ACAM posted "Consumer Information" on its Web site:

> Chelation therapy is a safe, effective and relatively inexpensive treatment to restore blood flow in victims of atherosclerosis without surgery.
>
> Every single study of the use of chelation therapy for atherosclerosis which has ever been published, without exception, has described an improvement in blood flow and symptoms. Adverse editorial comment to the contrary lacks evidence and stems primarily from physicians with a vested interest in catheterization and surgery.
>
> Chelation therapy promotes health by correcting the major underlying cause of arterial blockage. Damaging oxygen free radicals are increased by the presence of metallic elements and act as a chronic irritant to blood vessel walls and cell membranes. EDTA removes those metallic irritants, allowing leaky and damaged cell walls to heal. Plaques smooth over and shrink, allowing more blood to pass. Arterial walls become softer and more pliable, allowing easier expansion. Scientific studies have proven that blood flow increases after chelation therapy.[152]

In 1998 the Federal Trade Commission (FTC) ordered the ACAM to stop advertising chelation as effective against cardiovascular disease.[163] Nevertheless, the ACAM continued to publish similar statements. According to its Position Paper on EDTA Chelation Therapy, posted on its Web site as recently as June 2003 and still posted on the HealthWorld Web site, "hundreds of doctors nationwide have successfully treated hundreds of thousands of patients with EDTA chelation therapy," not only for coronary and other vascular diseases, but for "dementia, cancer, arthritis and numerous other diseases...; it is a safe and effective treatment for atherosclerotic vascular disease, as it consistently improves blood flow and relieves symptoms associated with the disease in greater than 80% of the patients treated." It is not merely complementary to standard treatment, but "an effective first step alternative to surgical treatment for atherosclerotic vascular disease in most cases.[164]"

Most chelationists include promotional language on their own Web sites. Of the nearly 100 "chelation practices" involved in the TACT, about 80 have Web sites. Of those, at least 70 promote chelation.[7]

In 1997 and 2000, "complementary medicine" researcher Edzard Ernst authored 2 critical reviews of Na_2EDTA for atherosclerosis, each concluding that the method "should now be considered obsolete.[165,166]" After the first review, chelationists L. Terry Chappell and John Wilson wrote an angry rebuttal to the editor of *Circulation*.[158] Dr. Ernst offered this response:

> Regardless of what Chappell and Wilson state, chelation therapy is not based on good science.
>
> A perhaps more important point relates to a repetitive pattern in the scientific investigation of "bogus" therapies. Proponents first manage to mobilize supporters to campaign in their favor. This brings financial gain. When skeptics ask about the evidence, the burden of proof is swiftly put on their shoulders, and the lack of evidence is made to look like a "conspiracy" of orthodoxy against the alternative. If scientists then decide to rigorously test the method, its proponents would celebrate this as a breakthrough for their method. Again, this amounts to financial gain. Subsequently, a study may prove that the method is ineffective. Proponents now claim that the research was flawed, did not adhere to their protocol, or was wrongly analyzed. The press coverage yet again brings financial gain. This pattern repeats itself with depressing regularity, e.g., when laetrile or Di Bella's cancer cure were promoted. I wonder whether chelation therapists are trying to play a similar game.[158]

That conjecture appeared in print in January 1999. Dr. Ernst was soon proven correct.

II. The Genesis of the TACT

In March 1999, ACAM presidents L. Terry Chappell and Ted Rozema shilled for chelation at a hearing of the House Committee on Government Reform, chaired by a powerful "health freedom" ally and veteran of the *Laetrile* wars, Rep. Dan Burton (R-IN).[41,167,168] NHLBI Director Claude Lenfant, whom Burton had summoned, was present. Burton criticized the NHLBI for "never funding any research into chelation therapy"; he criticized the National Library of Medicine for not listing the *Journal of Advancement in Medicine* on MEDLINE; he criticized the FTC for "launch[ing] an attack on the free flow of information from a non-profit professional medical association.[41]"

Burton scolded Director Lenfant for his institute's "bias" against chelation and other "alternative" methods and declared that he, Burton, would personally bring the purportedly large number of applications for chelation research "right to your office and lay them on your desk.[41]" Dr. Lenfant replied that there had been only 1 proposal to the NHLBI for a clinical study of chelation in the previous 30 years.

In February 2000, the NHLBI Advisory Council, chaired by Dr. Lenfant, rejected a new proposal for a study of chelation for CAD. The Council had apparently accepted, without question, the erroneous claim that "this therapy is currently being used by half a million people.[169]" Nevertheless, the Council judged chelation to have little scientific basis, deemed a trial to be too expensive ($24 million), and observed that:

> ...many patients who use alternative therapies may not be subject to a scientific argument of non-efficacy. It is unclear that any outcome would have an impact upon current clinical practice.[169]

Yet Rep. Burton seems to have been heard at the NIH. In the previous month, just as the FDA was completing its investigation of the GLACM IRB, the NHLBI had solicited "a market survey to assess the availability and technical ability of small business firms to act as the Coordinating Center in the conduct of a clinical trial to determine whether EDTA chelation therapy" is effective in patients with chronic stable angina.[170] Dr. Chappell, according to his curriculum vitae, provided a "consultation in Bethesda in March 2000" to the NIH.[43] In May 2000, the NCCAM's National Advisory Council for Complementary and Alternative Medicine approved the "concept" of funding a large trial of chelation, by a vote of 11 in favor, none opposed, and 2 abstentions.[171] One of the speakers during the Public Comment session of that meeting was Beth Clay, a staff member of Rep. Burton's House Committee on Government Reform.

In approaching the newly established NCCAM, Rep. Burton and the ACAM were surely aware that the Center's founding history and the charters of its advisory councils make it beholden to political and ideologic, rather than to scientific or medical interests.[172] After all, the American Association for Health Freedom, an ACAM offspring, takes credit for having been "instrumental in creating the National Center for Complementary and Alternative Medicine.[173]"

In the ACAM newsletter of May 2000, President Ted Rozema heralded the anticipated chelation study:

> On a national note: a very large research grant application has now been made to the National Heart Lung and Blood Institute at the NIH for a 2,200 patient, 100 site study called the Trial to Assess Chelation Therapy (TACT). This application must first be scored and then monies allocated for it. This is a time-consuming and politically charged issue. We have wonderful allies in the person of Representative Dan Burton (Republican - Indiana), along with his great staffer, Beth Clay. His Government Reform Committee has been overseeing chelation therapy to see it gets a fair shake in research even though there are other elements that do not want studies done. Any assistance you can give Congressman Burton will be assistance well spent to make the playing field equal. Our lobbyist, Bill Chatfield has really been diligent in his opening doors for us to actually get to those in power who are so well protected by their staff. This is not an easy task, but after 20+ years of respect in Washington, Bill is able to do this job with great skill and effectiveness.[42]

In the July 2000 issue of the *American Heart Journal*, Edzard Ernst offered his review of EDTA chelation therapy for CAD.[166] Noting that the literature consisted of numerous enthusiastic but uncontrolled case series countered by a few, exclusively negative controlled trials, Ernst again concluded: "The most striking finding is the almost total lack of convincing evidence for efficacy. Given the potential of chelation therapy to cause severe adverse effects, this treatment should now be considered obsolete.[166]"

In an accompanying editorial Drs. Gervasio Lamas and Alan Ackermann, soon to be named, respectively, the PI and the trial co-manager of the TACT, disagreed. Estimating that "more than 500,000 patients may" undergo chelation each year, they argued that:

> Ernst and others have over-interpreted meager clinical trial data in coming to this conclusion...the randomized trials have studied fewer than 200 patients in aggregate...the absence of evidence of efficacy does not constitute evidence of absence of efficacy...case reports and case series encompass thousands of patients with successful outcomes...a small or moderate benefit of EDTA chelation cannot be excluded...patients with coronary disease have not been systematically studied...biologically plausible mechanisms of benefit have not been thoroughly explored.
>
> ...we believe that a state of clinical equipoise exists and support a definitive trial to measure the effect of chelation therapy on clinical and physiologic endpoints.[29]

On April 30, 2001, the NCCAM and the NHLBI jointly issued a Request for Applications (RFA) for a $30 million, "multi-site, randomized, double-blinded, placebo-controlled trial investigating the efficacy and safety of EDTA (ethylene diamine tetra-acetic acid) chelation therapy in individuals suffering from Coronary Artery Disease.[1]" The ACAM's influence was explicit: "It is expected that the trial will investigate the EDTA Chelation treatment protocol recommended by ACAM." It was also implicit: "Common conventional medical treatments for CAD include percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) surgery, procedures that are invasive and costly.[1]" There was no mention of statins, aspirin, angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, nitrates, antihypertensives, smoking cessation, diet, exercise, or other common "conventional" medical treatments for CAD.

The RFA cited several articles by Edward McDonagh, the chelationist who had previously admitted in a court of law to having falsified his data.[44] The 2001 and 2003 TACT protocols contain at least 5 more references to studies by McDonagh, including one purporting to show that chelation is not nephrotoxic and another purporting to show that it does not cause bone loss.[174,175] The protocols misrepresent a large part of the rest of the chelation literature, as we discuss in Parts III and IV.

In August 2002, the NCCAM announced the TACT award, naming Dr. Lamas as PI.[2] Director Straus, citing "the widespread use of chelation therapy in lieu of established therapies [and] the lack of adequate prior research to verify its safety and effectiveness...," declared that "The public health imperative to undertake a definitive study of chelation therapy is clear.[2]"

According to the TACT press release, "Over 800,000 patient visits were made for chelation therapy in the United States in 1997.[2]" That number was an estimate provided by the ACAM.[3] It included all visits for chelation, not merely those for CAD. Courses of chelation typically include at least 30 infusions given over 10-30 weeks,[58] so even if the ACAM number had been correct it meant that at most 27,000 people -- 0.01% of the population -- underwent chelation in 1997. This is about 1/20 of Dr. Lamas' estimate in the *American Heart Journal*, and a tiny fraction of the "34% [of Americans who] reported using at least one alternative therapy in the last year," later cited by Dr. Lamas as a justification for the trial.[4]

It was ironic that Director Straus cited a "lack of adequate prior research." The usual order of in vivo investigations of a proposed treatment is as follows: (1) animal studies; (2) phase 1 human trials; (3) phase 2 trials; (4) phase 3 trials, with the understanding that each step is contingent upon the previous one having suggested at least safety and, in the case of phase 2 studies, efficacy. That sequence is compelling for both ethical and scientific reasons, and is stipulated in part or in its entirety by pertinent treatises, including the Helsinki Declaration, the US Code of Federal Regulations, and the NCCAM's own policies.[176-178]

With regard to how chelation for cardiovascular disease fits into this scheme, the only relevant literature comprises the controlled trials cited above. They correspond, roughly, to phase 2 trials, but none has "suggested effectiveness of the drug" or shown "efficacy," as Federal Code and NCCAM policy stipulate prior to a phase 3 trial.[177,178] The trials have also revealed more than trivial risks, as discussed in Part IV of this article. Paradoxically, the NCCAM itself, in a 2002 statement of its priorities for 2003, observed that "premature efficacy studies" were scientifically unwise, even if it overlooked ethics and safety:

> ...the research portfolio would be better served by an increased emphasis on studies of the mechanisms underlying CAM approaches, and by more thorough examination of the interventions themselves, as critical preparation for, and to better ensure the success of, more substantive phase II and III trials.

> Lack of adequately defined products or optimal dosage schedules risks that premature efficacy studies might fail, casting a pall over further research into otherwise promising modalities.[179]

The same document, published nearly a year before the first subjects were enrolled in the TACT, named "studies of the biology of EDTA chelation therapy in animal models" as a "FY 2003 Research Priority.[180]" By 2007, however, the NCCAM Web site had listed no such animal studies. Without commenting on that history, in 2006 Director Straus wrote in *Science*: "NCCAM now has a policy of requiring dose-range studies and other preclinical research before conducting clinical trials.[181]" His statement was in response to a critical article that had asserted, among other points, that the TACT is a wasteful project.[182]

The TACT press release made false statements about the drug to be investigated:

> EDTA, which effectively speeds removal of heavy metals and minerals such as lead, iron, copper, and calcium from the blood, is approved by the U.S. Food and Drug Administration (FDA) for use in treating lead poisoning and toxicity from other heavy metals.[2]

The NIH Special Emphasis Panel that approved the TACT protocol included L. Terry Chappell,[39] whom the protocol had named as a participant in the TACT.[4] This is curious in light of the NIH policy on "avoiding conflicts of interests during scientific review group meetings," which should have required Chappell to "be absent from the room during the review.[183]"

The TACT press release revealed that NHLBI Director Lenfant, who had stood his ground at the meeting of the NHLBI Advisory Council in 2000 despite having been browbeaten by Rep. Burton,[41,171] had finally capitulated to the pressure. In so doing, he seemed relieved that the NCCAM was taking primary responsibility for the TACT: "NCCAM's leadership in initiating and supporting this study is to be commended.[2]" At a recent meeting of the NCCAM Advisory Council, however, "Dr. Kirschstein explained that because heart disease is a key focus at NHLBI, the [TACT] grant will be transferred to NHLBI after the review by the data and safety monitoring board on February 23, 2007.[184]"

According to the August 2001 protocol, which is the application that the NHLBI and the NCCAM must have originally approved, the PIs and ACAM members had been jointly planning the TACT since well before the RFA was issued. Charles Hennekens, the trial co-principal investigator, "was the recipient of the 1997 Prevention Award from the ACAM.[4]" Drs. Lamas and Hennekens each had "a longstanding interest in rigorously testing the most plausible small to moderate benefits of chelation therapy in cardiovascular disease," and "accordingly, in early 1999, collaboration was initiated with a multidisciplinary team...that includes experts in alternative medicine, specifically chelation therapy....[4]"

The 2001 TACT protocol cites the ACAM protocol as its source for the TACT treatment regimen.[4] It cites the "ACAM's protocol and safety information," without rigorous justification, as its sources for "absolute contraindications" and for assurances of safety.[4] It cites the ACAM's formula for dose adjustments on the basis of creatinine clearance.[4] It requires every "Clinical Unit" to have at least 1 senior investigator or "chelation practitioner sub-investigator" who "must have formal training and certification by ACAM in chelation therapy, and must be approved for participation in TACT by the ACAM Liaison Committee.[4]" It assigns ACAM members not only to the ACAM Liaison Committee, but also to other key committees, including the Operations Committee and the Publications Committee.[4]

The protocol names, as Trial Chelation Consultant, Martin Dayton, MD, DO, "the former Director of the Scientific Research Committee of the ACAM.[4]" It names Dayton and other "prominent experts," including the aforementioned Chappell, Cranton, Magaziner, and Miranda, to the Liaison Committee to the ACAM.[4]

The 2001 protocol also names, as a "prominent expert," current ACAM president-elect Jeanne Drisko, Clinical Assistant Professor of Alternative Medicine at the University of Kansas Medical Center, Kansas City, Kansas, and Research Consultant at the Center for the Improvement of Human Functioning International in Wichita, Kansas.[185] Among the methods that the latter Center's Web site espouses are hair analysis; chelation; intravenous vitamin C; "orthomolecular medicine"; "colon health"; and, ironically, the toxic heavy metal colloidal silver, which it calls "completely nontoxic.[186]" The Center has a restaurant at which patients, whom it calls "co-learners," can eat lunch while listening to a lecture entitled "Improving AUTISM Outcomes with Mercury Chelation." It sells "supplements," books, audiotapes, videotapes, software, and "health accessories."

The Center charges "co-learners" $600 for an initial consultation and "$2000 or more" for initial laboratory tests.[187] Payments must be made in advance; the Center does not extend credit or accept third-party payments. Fees are usually not covered by insurance "because many of the services provided by The Center involve biochemical and nutritional concepts unfamiliar to insurance companies and standard medical people....[187]" A Sample Report page, which gives the results of a "Health Hunter/Beat The Odds Mega (Comprehensive) Panel," reveals what some of those unfamiliar concepts are: claims for "nutrients" and antioxidants that are exaggerated, misleading, or simply false, but that will likely entice co-learners to spend money at the Center's "Gift of Health" store.[188]

Dr. Drisko was a signatory of the Discovery Institute's pro-Intelligent Design "Dissent from Darwinism" petition.[189] She is also a TACT co-investigator.[7]

Another "prominent expert" on the TACT Liaison Committee is psychiatrist Michael Schachter, the ACAM president from 1989 to 1991. During the 1970s, Schachter had been investigated by the New York State Board of Professional Conduct for allegedly treating cancer patients with *Laetrile* and "a secret formula called MA-7.[190]" He recommended *Laetrile* (amygdalin) on his Web site as recently as February 2003, and continues to report "success stories" in which he has given it to cancer patients, "although some of these patients have since passed away.[191,192]" His current recommendations for cancer include coffee enemas, chelation, shark cartilage, bovine tracheal cartilage, and IV hydrogen peroxide.[193] In 2003 he recycled the original decalcification claim for chelation for CAD, but associated it with a new treatment:

> The amount of Calcified Plaque in your Coronary Arteries is directly related to your risk of having a heart attack. Cardiovascular decalcification can decrease your risk of having a heart attack. New research studies have shown that coronary artery plaque calcification is caused by an infection that can be treated.
>
> If you have Heart Disease, Coronary Artery Disease, Angina or have had Bypass or Stents you are probably a candidate for NanobacTX and this Study.
>
> Compared to surgery or other treatment, NanobacTX is extremely inexpensive at $290 for a one-month prescription. Patients are expected to pay for their medication as a part of participation in this program. At this time, you should assume that your insurance company would not cover NanobacTX.
>
> CALL our office today to see if you qualify to participate & receive NanobacTX.[194]

Dr. Schachter is also a TACT co-investigator.[7,38]

The NCCAM press release in 2002 announced that the TACT was to involve over 2300 subjects -- each more than 50 years old and having had an MI -- at "approximately 100 research sites across the country...[that] will represent a mix of clinical settings--university or teaching hospitals, clinical practices or cardiology research centers, or chelation practices.[2]" That number of subjects was higher than the 1600 stated in the original proposal.[4] More recently, the number appears to have been reduced to 2000,[49] possibly because of difficulty in recruiting subjects. The 2003 TACT protocol had predicted that 36 months would be adequate to recruit 2372 subjects.[5] After 36 months, however, only 1000 subjects had been recruited.[37] In 2007, twenty-one new sites in Canada, most appearing to be chelation practices, were added.[7,38,48195]

Each trial site must have a "senior investigator," and each senior investigator "must have substantial experience in the treatment and management of CAD and in the design, implementation and evaluation of clinical trials.[1,5]"

According to the TACT protocols there are 4 arms in the study, reflecting the practice of chelationists to give "high-dose antioxidant vitamin and mineral supplements" along with EDTA. There are 2 chelation arms whose subjects each receive 40 infusions of the chelation solution, with a low-dose oral vitamin and mineral regimen and either a high-dose oral vitamin and mineral regimen ( ) or placebo pills, and 2 nonchelation arms whose subjects each receive 40 placebo infusions of 563 mL normal saline and 1.2% dextrose, with the low-dose oral regimen and either the high-dose regimen or placebo. The ingredients of the chelation infusion include[5]:

- 500 mL sterile water;
- "Up to" 3 g Na^{++}EDTA (adjusted for creatinine clearance);
- 2 g MgCl;
- 100 mg procaine HCL;
- 2500 u heparin;
- 7 g ascorbate;
- 2 mEq KCL;
- 840 mg $NaHCO^{3}$;
- 250 mg pantothenic acid;
- 100 mg thiamine; and
- 100 mg pyridoxine.

High- and Low-Dose Oral "Vitamin and Mineral Supplement" Regimens in the TACT (From the 2001 TACT Protocol)[4]

High Dose	Low Dose
Vitamin A (fish liver oil) 1656.67 mg	Manganese 15 mg
Vitamin A beta-carotene 333.3 2500 mg [*sic*]	Chromium 50 micrograms (mcg)
Vitamin D3 200 mg	Zinc 25 mg
Vitamin E succinate 135 mg	Copper 2 mg
Vitamin C 200 mg	Vitamin B6 25 mg
Vitamin K1 0.01 mg	
Thiamine mononitrate granular 18.57 mg	
Niacinamide 25 mg	
Niacin 18.33 mg	
Biotin 0.05 mg	
Pyridoxine 18.33 mg	
Pantothenic acid 88.87 mg	
Cyanocobalamin 0.017 mg	
Folic acid 0.133 mg	
Calcium citrate 80 mg	
Calcium ascorbate 3 mg [*sic*]	
Iodine 0.025 mg	
Magnesium 80 mg	
Magnesium 3 mg [*sic*]	
Copper 0.33 mg	
Zinc 3.33 mg	
Potassium 6.5 mg	
Potassium aspartate 10 mg	
Manganese 3.33 mg	
Choline bitartrate 25 mg	

Citrus bioflavonoid 16.67 mg	
Chromium 0.033 mg	
Selenium 0.033 mg	
Molybdenum 0.025 mg	
Vanadyl sulfate 0.033 mg	
Boron 0.333 mg	
Coenzyme Q10 (ubiquinone) 50 mg	

The high-dose oral regimen (or placebo) is to be taken twice daily.[5]

Each subject is to receive 30 weekly infusions followed by 10 "maintenance" infusions given less frequently. Each infusion is to be administered "over 3 hours at a...rate of 166cc/hr.[5]" "Every effort will be made to conduct infusions with the smallest gauge catheter or a 25 gauge butterfly needle as this will limit the maximum infusion rate.[5]" "The entire regimen can take up to 27.5 months to complete.[4]" There is a requirement that each clinical site have "intravenous calcium gluconate available and be trained in recognizing and treating hypocalcemia.[5]" There are no requirements, in the protocols that were provided to us, for continuous electrocardiographic (ECG) monitoring, IV infusion pumps, the continuous presence of nurses or physicians, materials for administering advanced cardiac life support, or the presence of individuals trained in advanced cardiac life support protocols.

The 2001 protocol describes the ingredients of the low- and high-dose supplement regimens "defined by consensus with the ACAM Liaison Committee.[4]" The NIH "redacted" the ingredients of the oral supplement regimens from our copy of the 2003 protocol, stating instead, "p 38 withheld in entirety 'proprietary info' [*sic*].[5]" We question why such ingredients, none proprietary by itself and all given in the context of a taxpayer-sponsored trial, should be "proprietary." If the reason is that the mixtures might eventually be marketed for the treatment of CAD, then this should have been disclosed on the consent form, and the mixtures would have required Investigational New Drug exemptions.[196]

The experimental solutions must be mixed on-site. The 2003 TACT protocol describes a method to preserve blinding and reports that this "has been piloted successfully," presumably in a supervised, academic setting.[5] Nevertheless, the mixing procedure presents simple opportunities for distinguishing between the chelation and placebo solutions. For example, the site coordinator must inject 14 mL of concentrated ascorbate or sham solution into a 500-mL IV bag. The plan calls for the 14-mL solutions to have similar viscosity and to appear similar in color, but a tiny drop applied to the tongue during transfer would instantly identify the ascorbate by its sour taste. Ascorbate goes exclusively with the Na_2EDTA solution.

The TACT RFA and the original TACT protocol included plans for a substudy of biochemical markers of oxidative stress.[1,4] The 2003 protocol lacks the substudy, without commenting on its absence. Perhaps the explanation is that it is not yet clear what markers are clinically useful for measuring oxidative stress, and what subjects are at particular risk. In 2002, more than a year before the first subjects were recruited for the TACT, 2 NHLBI-supported scientists made the point after noting that human trials of antioxidants for atherosclerosis had been disappointing:

> With the benefit of hindsight, the decision of the 1991 National Heart, Lung, and Blood Institute workshop to give a green light to trials, even trials that use safe, naturally occurring antioxidants, may have been premature. Not knowing how LDL is oxidized in vivo, we cannot be certain which antioxidants are likely to be most effective. We lack markers that would let us evaluate the efficacy of any given antioxidant intervention, and we lack criteria for rational selection of patients under high oxidative stress. Until we have such basic information, we should put a hold on further clinical trials. Instead, we should concentrate on developing the scientific base that will enable us to design an appropriate trial to test the oxidation hypothesis.[151]

That opinion is consistent with the NCCAM's own 2002 statement of "2003 Research Priorities," mentioned above: "...the research portfolio would be better served by an increased emphasis on studies of the mechanisms underlying CAM approaches....[179]" We observe that Na_2EDTA is not even a safe, naturally occurring antioxidant. This is another reason that if science had been the real issue, the NIH ought to have "put a hold" on the TACT.

Depending on when they have been recruited, subjects will apparently be followed for as little as 1.5 years or as long as 5 years.[5] The end of the follow-up period is stipulated as the "study close-out" date. Because the "expected completion" is now predicted to be July 2009, we wonder whether follow-up periods will be longer than 5 years for some subjects.[38]

The 2001 TACT protocol stipulated a 5-part, composite primary endpoint comprising all-cause mortality, MI, stroke, hospitalization for angina, and hospitalization for congestive heart failure. It included at least 14 secondary endpoints, including the individual components of the primary endpoint.[4] The 2003 protocol retains most of the composite primary endpoint, but replaces "hospitalization for congestive heart failure" with "coronary revascularization." It also calls for examining the individual components of the primary endpoint, but warns that "the trial will not have adequate statistical power to test any individual component of the primary endpoint.[5]" The 2003 protocol stipulates several subgroup comparisons and "economic analyses, cost-effectiveness analyses, and quality of life data collection and analyses.[5]"

After the announcement of the TACT, the ACAM issued a press release announcing that its "member physicians will be part of a nationwide effort to recruit a patient study population" for the trial.[197] ACAM President Ron Hoffman, another prominent expert TACT appointee, said that he "look[ed] forward to chelation taking its rightful place among officially acknowledged cardiac treatment strategies.[197]" As of September 2007, nearly 100 chelationists had been designated TACT co-investigators.[7] For unstated reasons, 20 that had previously been listed on ClinicalTrials.gov were now absent from the NCCAM roster.[7,117,198] Neither the 2001 nor the 2003 protocol describes a complete set of criteria that would qualify a potential site investigator to be included in the TACT.[4,5]

In our opinion, the activities and associations of chelation practice co-investigators should have disqualified almost all of them. Contrary to language in the 2001 TACT protocol, few if any "have substantial experience in the treatment and management of CAD and in the design, implementation, and evaluation of clinical trials.[4]" Rather, most have denigrated proven treatments for CAD and other serious diseases, instead offering "genuine practice builders,[199]" such as chelation, NanobacTX, *Laetrile*, antineoplastons, IV hydrogen peroxide, detoxification, "longevity medicine," "energy medicine," shark cartilage, "immune boosters," homeopathy, "magnetic healing," "antiyeast medicine," "Wilson's thyroid syndrome," "colon hydrotherapy," and more.[7] At least 18 have been subjected to state medical board actions, criminal convictions, or federal civil judgments[200,201] At least 3 are convicted felons.[60,61,202,203]

Few, if any, have been involved in legitimate clinical trials. Instead they have either reported or accepted the claims of dubious "case series" of chelation, discussed in Part III of this article. Most are members of organizations that have advocated "officially sanctioned research" as a ruse to shield "alternative medicine" practices from regulatory scrutiny.[130-132, 140-142, 204] More than 20 are officers in those organizations.[204] At least

7-- Ali, T. Born, Carter, Casdorph, Chappell, Miranda, and Rozema -- were members of either the GLACM IRB that the FDA cited for numerous violations of human studies protections, or of the closely related ACAM IRB.[7,55,140,144,145,204] Co-Investigator Richard Fleming, who may not even be a chelationist, is currently under federal indictment for allegedly sending fabricated data to the sponsor of a clinical trial.[7,205]

A TACT co-investigator in British Columbia, Galina Bogatch, appears to be licensed in Canada only as a naturopath.[206] Total Sensory Wellness Center in Waldorf, Maryland, is owned by a naturopath and appears to have no medical or osteopathic doctors among its practitioners.[207] The Web site of the Coyote Healing Center, a TACT chelation site in Tucson, Arizona, identifies David Rupley is its sole "doctor.[208]" Rupley is not licensed by the Arizona Medical Board; he is licensed by the Arizona Board of Homeopathic Medical Examiners, which appears to be a regulatory haven for dubious practitioners.[208-210] The FDA Bioresearch Monitoring Information System (BMIS) identifies the Investigator at "Coyote Healing Ctr" in Tucson as Lewis Mehl Medrona (*sic*; the correct spelling is "Mehl-Madrona"), and the Submission Date as April 13, 2005.[7,211] Mehl-Madrona's curriculum vitae, however, mentions neither the TACT nor the Coyote Healing Center, and reveals that he has lived in Saskatchewan, Canada, since 2005.[212] The NIH and pertinent IRBs ought to know that neither naturopaths nor homeopaths are competent "in the treatment and management of CAD," and they must know that Mehl-Madrona cannot act as the PI for a study site in Arizona if he lives in Canada.

The FDA BMIS posts records of trial sites and their corresponding investigators.[211] Such records, which are updated quarterly, demonstrate that a trial's sponsor has submitted required information about sites and investigators to the FDA.[213] As of September 3, 2007, the BMIS had no record of the Total Sensory Wellness Center -- listed on ClinicalTrials.gov as a TACT site since June 2004 -- or of 21 other US TACT sites.[7,211,214]

At least 3 TACT co-investigators are officers in the North Carolina Integrative Medical Society (NCIMS), which has positioned itself squarely in opposition to standards of medical care promulgated by the North Carolina Medical Board.[215] The Board has recently charged one of them, Rashid Buttar, with selling "unproven and wholly ineffective" treatments, including IV EDTA and hydrogen peroxide, to cancer patients:

> Dr. Buttar charged exorbitant fees for his ineffectual therapies. The total cost of the intravenous injections and other therapies for these cancer patients at times ranged in the thousands, sometimes tens of thousands, of dollars. Not only would Dr. Buttar order and have administered unproven and ineffectual therapies for Patients A, B and C in an attempt to drive up his billings, he would also order numerous tests and lab work for these patients that had no rational, medical relationship to the Patients' cancer diagnosis. Moreover, many tests and lab work that were ordered by Dr. Buttar were never adequately justified in the medical records of the patients, were never linked to the patients' diagnoses or clinical condition, and in some instances never interpreted.[216]

Dr. Buttar is President of the NCIMS and the current chairman of the ABCMT.[217,218] It is instructive to compare the North Carolina Medical Board's statement with a recent description of Dr. Buttar by Congressman Burton and Congresswoman Diane Watson [D-CA].[219]

As previously stated, about 70 of 80 identifiable TACT chelation practice Web sites promote chelation.[7] Some reproduce, verbatim, several of the statements that the FTC cited as false in its complaint against the ACAM in 1998.[163,220,221] One such site, the Wellness and Longevity Center of Louisiana, is owned by Sangeeta Shah, listed by the ACAM as a member of its Board of Directors, a member of the TACT Liaison Committee, and a member of the ACAM Marketing/Public Relations committee.[222]

Such postings introduce bias into the trial and are contrary to Federal Regulations that prohibit investigators from promoting investigational new drugs[223]; the postings may also constitute "misbranding" of Na_2EDTA, for which there is a precedent involving "chelation pioneer" H. Ray Evers.[18] The same co-investigators appear to be selling chelation infusions outside of the context of the TACT, which, if true, is also contrary to Federal Regulations.[224] Such practices call attention to language in the TACT RFA requiring that "all trial sites have routine...audits to monitor for...non-compliance with...regulatory requirements....[1]" We wonder whether TACT auditors have informed the FDA of these apparent violations of regulatory requirements.

In 2006, TACT chelationist Co-Investigator Rajiv Chandra advertised for subjects in a semiannual report of the Parrish Medical Center in Titusville, Florida:

> If you participate in this study, you will receive 28 months of treatment, and be asked to participate in up to 32 months of follow-up. You will not be charged for participating in this exciting study and will receive the study drug and vitamin and mineral supplements.[225]

Is Dr. Chandra giving the "study drug" to all of his TACT subjects, contrary to protocol, or is he merely making that promise as a recruitment ploy?

Almost all chelationist co-investigators are members of an organization or one of its offspring founded "to promote the use of EDTA chelation therapy for cardiovascular disease.[34]" The ACAM has repeatedly misrepresented the evidence for safety and effectiveness of chelation.[30,33,34,152,164,204] The future success of the ACAM and its related organizations is substantially dependent on the outcome of the TACT, which it expects to vindicate its claims.[41,100,102,197] Thus it is imprudent for the NIH to rely on ACAM members to answer subjects' "questions about the risks[6]"; to recognize, treat, and report adverse events; to maintain allocation concealment and blinding; or to provide the objective and thorough reporting of data necessary to minimize bias in a trial.

Many TACT sites have been approved by the Sterling IRB.[117,226,227] The Sterling IRB's 2003 Investigator/Site Questionnaire asked whether any sub-investigator or member of the research staff had been convicted of a crime, had been subjected to a medical license action, had received a warning letter from the FDA, and other questions pertinent to the protection of human subjects and to the ethical conduct of research. Several TACT co-investigators should have answered "yes" to those questions.[141,200,201,204] Did they? If so, how did the IRB determine that they were acceptable co-investigators?

The 2003 TACT protocol states:

> All surgical and medical therapies will be at the discretion of the responsible health care providers. Nonetheless, procedures will be implemented to comply with the TACT protocol and to ensure that participants are afforded the same quality of care that is given in other NIH funded trials.[5]

Despite that assurance, surgery and cardiologic procedures will remain entirely "at the discretion of the health care provider." Medical therapies, however, are to be monitored quarterly by the Data Coordinating Center, which will give a "quarterly 'Report Card'" to each site. If a site is not in compliance with established guidelines for post-MI patients, it will be queried to "determine [the] reasons...Sites with continued non-compliance [and] no valid reasons for such will be discussed in the Steering Committee. Possible actions range from enhanced educational efforts to suspension from future patient accrual. In all cases they will be obligated to continue infusing and following randomized patients.[5]"

Such language seems surprising for an NIH-sponsored protocol. It is reasonable to expect the NIH to involve only co-investigators who practice according to current ethical and clinical standards, as required by universally accepted human studies treatises. Chelationists, however, routinely eschew proven medical and surgical treatments for coronary disease, instead offering questionable "alternatives.[7, 228-230]" TACT Chelation Consultant Martin Dayton has written:

> Chelation is often used as a safer method to replace much costlier conventional surgical and related medical procedures.[57]
>
> Unlike surgical approaches, no strokes, deaths nor heart attacks have been reported to be due to intravenous chelation therapy, and fewer side effects are reported than with many pharmaceutical medical treatments.[57]

Dr. Dayton's practice Web site includes a consent form with this language:

> I am informed that I may benefit and/or be harmed by having, refusing, quitting or delaying either customary standard medical care and/or non customary non standard medical care.
>
> I hereby release my physician, Dr. Dayton, and facility in which I am being diagnosed and treated from liability from my CAM care[*sic*].[231]

The ICIM (formerly the GLCCM), whose president is "prominent expert" L. Terry Chappell and many of whose members are TACT investigators,[204] recently announced a:

> ...Congestive Heart Failure Task Force which offers all ICIM members the opportunity to participate in a patient-based outcome study to investigate and validate beneficial therapeutic nutritional alternatives to orthodox drug-based protocols. The task force is intended to be a collaborative effort among physicians who have experienced success replacing conventional treatment models and physicians who are seeking to treat patients they may have otherwise felt compelled to refer to orthodox practitioners...Several of the participating Task Force members have already treated difficult cases with cutting-edge therapies not yet in general use which will offer ICIM members advanced information. This promises to be a genuine practice-builder.[199]

Some chelationists object to standard therapies not only for clinical practice, but for trials in particular. "Prominent expert" Elmer Cranton offered this in his repudiation of the negative findings of the Canadian PATCH trial[27,28]:

> [Many subjects] were given potent anti-anginal drugs...There was...no true "placebo" group. The F.D.A. in the United States has never approved a new drug to treat angina without first requiring trials wherein all other anti-anginal medications had been discontinued.[161]

Thus, chelation site co-investigators have a choice: They may either uphold the current standards of care for patients with coronary disease, and thus be armed from the outset with what they consider to be an ironclad objection to the study, or they may withhold standard therapies, thus putting TACT subjects at undue risk.

The TACT consent form (version June 16, 2003) was provided to us, with some parts "redacted," under the FOIA.[6] It states, "(EDTA) is approved for use by the FDA as a treatment for lead poisoning but not for coronary artery disease." In fact, the FDA has not approved disodium EDTA, the preparation used in the TACT, for the treatment of lead poisoning.[12] That approval goes to calcium-sodium EDTA, which does not carry the risks for acute hypocalcemia or bone loss, although it does carry a significant risk for renal toxicity.[31] The FDA, moreover, has done more than merely not approve disodium EDTA for CAD: It has specifically contraindicated the drug for the treatment of "arteriosclerosis.[12]"

The consent form also fails to state that the standard protocol for treating lead poisoning with CaEDTA involves different dosing and timing, and careful monitoring in a hospital setting -- unlike the way chelationists administer Na_2EDTA. Those pieces of information, the reasons for them, and the implications with regard to the character of chelation practice co-investigators are things that IRBs and prospective subjects have a right to know. Instead, the form blandly states that "chelation therapy has been practiced in the community for many years" and is "thought to bind specific toxic elements circulating in your blood.[6]" It also states, "if you are assigned to the chelation group you will receive a standard intravenous mixture established by the American College for Advancement in Medicine.[6]" Such statements amount to tacit endorsements of the practice and the practitioners.

The consent form fails to state that chelation offered for CAD has long been considered fraudulent by the FDA, the FTC, medical scholars, and respected professional organizations.[9-11, 18, 63,65,78, 124-129] It fails to state that a plausible scientific rationale for the treatment is lacking.[147,148] It fails to state that no body of basic science or animal studies supports the treatment. It does not state that formal phase 1 studies -- the standard means by which the safety of a drug is investigated -- have not been done. It does not state that the only controlled clinical studies so far -- totaling 285 patients -- have found no evidence for efficacy.[21-28] It does not state that conducting a phase 3 study of a method with that background is highly irregular and is contrary to formal language in human studies treatises, in US Federal Code, and in the NCCAM's own literature.[176-180]

The consent form does not state that the preponderance of current opinion within the field of cardiovascular disease is that chelation is an ineffective treatment for CAD. The AHA, for example, has written: "According to qualified scientists who are familiar with research in heart disease, there's only a very small chance that chelation therapy will work.[232]" The AHA, furthermore, would support a human trial only if a preliminary study were to demonstrate that EDTA could safely and effectively "dissolve" atherosclerotic plaques.[232]

The consent form fails to cite several realistic risks. Among these are bone loss, of particular concern in a study group that includes postmenopausal women, and the paradoxical generation of oxygen-free radicals.[23,148]

The consent form fails to state that the ACAM is not the authoritative, ethical organization that its name implies, but has consistently made unsupported claims for chelation and has been cited for this by the FTC.[30,33,34,152,163,164] It fails to state that the ACAM, the GLACM, and many of their members, including several TACT co-investigators, have systematically endangered patients under the guise of human studies, and several have been cited for this by the FDA.[7, 130-132, 140-142, 204] It fails to state that many key ACAM members, including several TACT co-investigators, have been disciplined by medical boards, convicted of crimes, or indicted for either civil or criminal actions.[17,18,20,59-62, 200,201] It fails to state that there have been 20-30 deaths associated with Na_2EDTA infused by ACAM members.[13-20]

The form fails to state that every site investigator who has previously treated patients with disodium EDTA for atherosclerosis, outside of the context of a legitimate study, has not given it merely "off-label," but in direct contradiction to its label.[12] It fails to state that merely 20 years ago such a practice was reasonably described as "an abuse of the physician's freedom of choice,[11]" and subsequent unfavorable findings in

controlled trials have reinforced that description. It fails to state that most TACT chelation site co-investigators promote numerous other dubious practices and, contrary to human studies ethics, scientific integrity and federal law continue to promote chelation as safe and effective for CAD even as the study purported to make this determination is under way.[7]

The form fails to state that the "standard intravenous mixture established by the ACAM" is not based on rigorous, ACAM-sponsored research, but is merely a reiteration of language in the edetate (*Endrate*) package insert coupled with a fanciful batch of supplements.[12,33] The form lacks language explaining redacted "proprietary info" that would seem to describe the oral supplement mixtures used in the TACT.[6,233] The disclosure of proprietary interests is pertinent to informed consent.

The consent form fails to state that ACAM members typically discourage standard therapies for CAD. Instead, the form places the burden of such therapeutic decisions on the subjects themselves: "You should continue to use proven standard medicines for heart attack patients whether or not you participate in this study.[6]"

The realities of chelation "as practiced in the CAM community[5]" predict that even an entirely negative outcome would not dampen the enthusiasm of advocates. Most now claim that chelation's primary purpose is to remove toxic heavy metals, which secondarily "reverses or slow[s] diseases of aging," CAD being merely one among more than 70.[13,47,57, 101-105, 114,115,119] In the same year that Dr. Lamas assured *American Heart Journal* readers that a large trial of chelation for CAD would "lead to changes in clinical practice,[29]" his colleague Martin Dayton summarized the opinions of chelationists for an article about "detoxification therapies" in *InnerSelf Magazine*:

> Martin Dayton, M.D., of Florida, who is board-certified in family medicine, chelation therapy, and clinical nutrition, says that chelation therapy has multiple benefits, and long life is one of them: "Dramatic increases in life span are found with chelation. While there are no longevity studies per se, this conclusion is implied indirectly by studies which show a lessening of killer degenerative diseases. In fact, chelation favorably impacts all four major causes of death in the United States [heart disease, cancer, cerebrovascular disease, and lung disease]."

Once in the bloodstream, EDTA attaches itself to heavy metals such as lead, cadmium, and mercury and holds onto those toxic substances until they exit the body through the urine. Dr. Dayton explains why removal of these substances is vital to good health: "The toxic material prevents normal function and repair. For example, lead prevents normal enzymatic processes so that the body cannot function properly and repair itself. This leads to premature aging and the premature development of disease. Removal of toxic material through chelation keeps the body functioning optimally."

Dr. Dayton notes that an excess even of iron, which is necessary for life, accelerates free radical production and causes harm... "At this time, arterial clogging accelerates. Chelation removes this excess iron."

Since modern people are overwhelmed by pollutants, Dr. Dayton recommends chelation therapy for anyone over thirty. "Lead is found everywhere, in the air we breathe, the water we drink, the food supply. It is even found at the North Pole. Lead and other toxic pollutants are hard to avoid in today's world..."

"Unclogging carotid blockage is vitally important because the American College of Physicians states that patients with an obstruction of 70 percent of greater are at a high risk for stroke. They even recommend chelation therapy as a preferred treatment. I take that to heart and use chelation therapy on these individuals. People who have carotid artery disease improve as their arteries open up. I see this happen over and over again.[234]" (brackets in the original)

According to Dr. Dayton, who in 1986 had been convicted of mail fraud,[61] he and Dr. Lamas began planning a chelation trial well before the "TACT was designed and funded.[57]" This is consistent with Dr. Lamas' statement that his collaboration with chelationists began in "early 1999.[4]" It is surprising that more than a year later Dr. Lamas could have remained naive enough to predict that a negative CAD trial would significantly reduce chelation advocacy.

In researching the literature for his rebuttal to Ernst's 2000 editorial, moreover, Lamas ought to have discovered that "prominent experts in chelation therapy" had repudiated every negative trial of chelation for atherosclerosis, and he might have correctly predicted that they would continue to do so.[152-162] Even at that time, the Canadian PATCH trial was anticipating the TACT by involving ACAM members in an attempt to deflect their predictable objections.[27,235] After the PATCH published its negative findings in 2002, it became clear that the attempt had been futile.[161,235] Thus, another trial that finds no evidence that chelation is effective for CAD, particularly one in which all subjects are expected to receive standard therapies, is unlikely to be the first to persuade true believers to change their minds.

III. State of the Evidence

In the *American Heart Journal* in 2000, Dr. Gervasio Lamas argued that regardless of disconfirming RCTs, chelation for CAD ought to be studied in a large human trial: "...case reports and case series encompass thousands of patients with successful outcomes...; a small or moderate benefit of EDTA chelation cannot be excluded...; we believe that a state of clinical equipoise exists and support a definitive trial....[29]" In TACT protocols submitted in 2001 and 2003, he reiterated this assertion, citing "biologically plausible mechanisms," "ample suggestions of benefit" from "the very large number of published case reports," and the small sample sizes of controlled trials to date.[4,5] According to the 2003 protocol, "the totality of the evidence on chelation therapy includes basic research, clinical investigation, descriptive and observational epidemiologic studies and 3 small, randomized trials.[5]"

By 2003, the reports of the Canadian PATCH study of Chelation for Ischemic Heart Disease -- which, in a sample size of 84, had found no effect on "exercise time to ischemia, exercise capacity, quality of life measurements" or, in a substudy of 47 subjects, endothelial function -- had been published.[27,28] This brought to 275 the number of subjects acknowledged by Dr. Lamas to have been studied in adequately designed, controlled trials of IV Na_2EDTA for either CAD or PVD. In none of those trials was a treatment effect demonstrated.[21,22,25,27,28]

Another small RCT of chelation for CAD, not cited by Dr. Lamas, had found no difference between active and placebo groups of 8 subjects each.[26] Dr. Lamas himself has conducted a "pilot" RCT, "PACT," in which 30 of 40 subjects were to have received Na_2EDTA.[5] It should have been completed several years ago, but its results have not been made public. We suspect that it also did not support chelation, because otherwise it would have been a newsworthy event that the NCCAM and its ACAM collaborators could hardly have resisted publicizing.

Antioxidant vitamins, also part of the TACT regimen, have been extensively studied for the prevention or treatment of atherosclerosis and have failed to demonstrate a favorable effect.[151]

The relevant basic research, previously cited, suggests the opposite of what the TACT investigators have hypothesized: EDTA is more likely to act as a pro-oxidant, particularly in the presence of iron and vitamin C, than as an antioxidant.[147-149] More recent work has supported this finding.[236] Others have noted pro-oxidant effects of vitamin C and its tendency, when taken in large doses, to enhance iron absorption from the gut.[150, 237-240] The importance of potential pro-oxidant effects of vitamin C in vivo is uncertain.[241]

In scarce recent studies of EDTA in animal models of atherosclerosis, the results have been conflicting.[242,243] The 2001 TACT protocol does not cite animal studies; the 2003 protocol cites only one,[244] published in a journal devoted to chelation advocacy[82] and co-authored by Edward McDonagh, who had previously admitted under oath that he had "kept slipshod records, recording only positives about his experiments, to avoid possible liability lawsuits.[44]"

Thus Dr. Lamas' "totality of the evidence" in support of chelation for CAD appears limited to case series reporting "thousands of patients with successful outcomes.[29]" We therefore consider the case series in some detail. Next we discuss the RCTs that had been completed by the time the TACT began; there is no need to do so at length because the TACT protocols do not dispute their validity, only their "power." We do, however, comment on the import of those trials when contrasted with the case series. We also compare the existing evidence for chelation with evidence for other health claims that were long ago dismissed.

Very few case series of chelation for atherosclerosis, including none of the large ones, are credible. Only the early series (from the 1950s and 1960s) are worthy of consideration, but the TACT protocols misrepresent their findings by omitting pertinent information, reporting erroneous data, and citing "positive" data pools more than once. A naive reader could become aware of such errors and duplications only by consulting the primary sources. The TACT protocols also fail to observe that enthusiastic reports among the early series are best explained by nonspecific effects that were known, even at that time, to be common to uncontrolled trials of treatments for angina pectoris. The most plausible of the early reports concluded that there was no evidence for an effect of chelation on the course of CAD[54]; the 2003 TACT protocol summarizes that report as having suggested almost the opposite.[5]

The later "positive" series cited by the 2003 TACT protocol are even less credible than the early ones: The largest was unpublished, and its author denied well-documented complications and deaths. Each series reported outcomes that are unlikely in the extreme. All were written by a few fringe practitioners -- "pseudoscientific zealots," in the words of an expert who studied both chelation and the social phenomenon of chelationists[9-11] -- with significant financial interests in chelation, *Laetrile*, IV hydrogen peroxide, "ozone therapy," "electrodermal screening," and other dubious methods. Most were published in a journal created to make chelation and other dubious methods appear to have scientific backing. The journal is the mouthpiece of the ACAM, the major chelation advocacy organization.[82] Neither the TACT protocols nor Dr. Lamas' editorial in the *American Heart Journal* suggests such distinctions.[4,5,29] On the contrary, the TACT protocols call the pseudoscientific zealots "prominent experts.[4,5]"

On page 8 of the 2003 version of the TACT protocol is a table purporting to summarize the results of case series of chelation for CAD. We reproduce it here ( ), save the original reference numbers.

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First Author (Year)	Sample Size	Outcome Measures	Result
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Deycher (1992)	215	Symptoms	70% improvement
Hancke (1992)	42	Need for surgery	39 canceled surgery
Hancke (1993)[269]	470	Symptoms	Significant improvements

ECG = electrocardiogram
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Perusing , it can be seen that there is a temporal gap between the early studies, ending with Lamar (1966), and the later ones, beginning with Evers (1979). As suggested above, the early articles were part of the legitimate medical literature of the time, whereas the later ones were either unpublished or were published in non-refereed, advocacy journals. The early investigations abruptly ended when it became clear that chelation did not change the natural history of CAD, and that whatever subjective and ECG effects it seemed to have were transient and similar to those reported in early trials of other treatments later shown to be ineffective. Neither nor the text of the TACT protocols gives any suggestion of that history.

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is also misleading in a more direct sense: several of the cited case series are redundant; several are erroneously reported; and several did not address the relevant question. We therefore discuss the early series in some detail, contrasting them with their portrayals in .

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Clarke (1956)[245]: In 1955 Clarke and colleagues[245] reported the results of IV Na_2EDTA given to a single subject with "extensive nephrocalcinosis." The subject also had impaired hearing and a history of an ulcer with "3 attacks of intestinal bleeding." According to the authors, "50-65% of the metastatic calcium [was] dissolved out of the kidney"; there was a "striking improvement" in hearing; and "ulcer symptoms [were] completely relieved." The authors mentioned having treated 22 patients with "EDTA for various related diseases and the general results will be the subject of a future paper." They did not report those results in the 1955 article. Thus the entry in -- "Sample Size 22, some improvements" -- is erroneous.

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Clarke (1956)[32]: In 1956 Clarke and colleagues[32] reported the results of IV Na_2EDTA given to 20 subjects with angina pectoris. Their rationale was that the drug was a potent chelator of Ca++, and therefore might "disintegrate the organic atheromatous matrix and allay the symptoms of angina pectoris." The report was of an uncontrolled series lacking eligibility or inclusion criteria other than "angina pectoris," the definition of which was not stated. Diagnoses were not standardized, but appear to have been made by 1 or more of the following criteria: frequency of chest pain, exertion necessary to bring on chest pain (usually measured by the number of city blocks walked), number of nitroglycerin tablets used per day, ability to work, history of MI, and resting ECG. The "disease was confirmed independently by two or more physicians," but there was no mention of potential or actual diagnostic disagreements.

Most subjects were followed from 1 to 12 months; 5 were followed for up to 22 months. The study authors reported dramatic, subjective improvements in frequency of angina and in exercise tolerance for 19 subjects, and improved ECG findings in 6 subjects. shows the differences in self-reported horizontal walking distances before the onset of angina for the 8 subjects in which the study authors reported both pre- and posttreatment figures.

Horizontal Walking Distances Reported to Produce Angina, Before and After Chelation Treatments (Generated From Data in Clarke [1956])[32]

Case Number	Prechelation	Post chelation
1	Half block	> 1 mi
5	Half block	"Any required distance"
6	"Across a room"	10 blocks
8	< 100 ft	"Several miles"
14	1 block	12 blocks
18	50 yd	2 mi
19	1 block	> 8 blocks
20	200 ft	10 blocks

The only relevant data from a controlled trial, with which to compare these walking distances, comes from the Canadian PATCH study.[27] It did not report distances per se, but "time to ischemia," defined as "time to reach at least of 1 mm ST-segment depression" on a treadmill. Among 84 subjects with stable angina, after 27 weeks and 33 Na_2EDTA or placebo infusions, the mean time to ischemia increased from approximately 9.5

minutes to approximately 10.5 minutes. There was no difference between the active and placebo groups, and the PATCH study authors observed that the improvement was "consistent with a combination of placebo and training effects commonly seen in studies of angina patients.[27]"

In the Clarke study, 1 subject died; the authors "suspected that he died from a calcium embolus that had been freed from a large arterial plaque.[32]" At autopsy, "his aorta showed extensive atheromatosis....The coronary artery sections showed intense medial sclerosis with calcification....[32]" The autopsy report did not suggest "disintegration" or decalcification of atherosclerotic plaques.

As they had in their previous report, Clarke and colleagues also reported dramatic effects for conditions other than angina, including complete resolution of intermittent claudication, musculoskeletal pain, and ventricular ectopy. They reported, in 3 subjects who may or may not have been among those treated for angina, the following: healing of a necrotic neck ulcer containing "extensive deposits of metastatic calcium" that had been present in a man for 7 years after thyroidectomy and radiation therapy for cancer; continued dissolution of kidney stones, seemingly in the subject described in their previous report; and removal of calcium from the mitral valve of a woman with rheumatic heart disease, whose "immediate symptomatic relief resemble[d] a successful surgical commissurotomy."

The man with the neck ulcer "extruded through a sinus tract many small to large calcified plaques" for at least 10 months after chelation treatments had ended. The man with nephrocalcinosis "continued to pass large amounts of sand and stones in his urine" for at least a year after the last treatment.

Boyle (1957)[246]: Boyle and colleagues,[246] including Clarke, published 7 detailed case reports among a group of "20 patients with angina." These appear to be identical to the 20 subjects with angina reported in "Clarke (1956).[32]" Thus, is in error in reporting them twice. Boyle 1957, moreover, refers to "the numerous patients with angina treated by the Providence Hospital group in Detroit," suggesting that considerably more than 20 had been treated. This raises the possibility of selection bias.

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Clarke (1960)[50]: In 1960 Clarke and colleagues[50] published another uncontrolled series of Na_2EDTA treatments in 76 subjects with angina pectoris, 31 subjects with intermittent claudication, and 25 subjects with cerebrovascular disease. Unstated numbers of subjects in each of the latter groups appear to have also been included in the angina group.

The authors raised the possibility of a controlled trial, but dismissed it because "the double blind test for appraising new drugs has been found to be far from infallible...." They did not identify any subjects as having been involved in their previous series. Eligibility criteria were vague. The diagnostic criteria for angina pectoris appear to be similar to those in their previous report, but in the newer report there were no individual case descriptions. The diagnostic criteria for intermittent claudication seem to have included some combination of a history of rest pain or pain with walking, physical exam suggestive of circulatory insufficiency, and "greatly decreased oscillometric readings."

The authors reported that they had followed all subjects for 2 years. They rated 87% of subjects with angina "much improved," defined as "90% to 100% symptom relief," and 9.2% as "improved," defined as "75% symptom relief." Paradoxically, 13% died. There were no reports of autopsies, ECGs, or other objective outcomes. The TACT protocol's "Results" entry for the 1960 Clarke series -- "58 improved" -- does not follow from the report ( ).

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Of the 31 subjects with intermittent claudication, 23 were rated "90% to 100% relieved" and 4 were rated "75% relieved." Three died: 2 of myocardial infarction" and 1 of "C.V.A." Among the 25 subjects with cerebrovascular disease, "all who had cerebellar vertigo or dizziness had complete relief and the manifestations of senescence were significantly alleviated...; the paralysis caused by recent cerebrovascular accidents seemed to improve faster and more completely than usually expected and tinnitus, even of long standing, has been relieved." Six of these subjects died, 2 of "C.V.A." and 4 of "congestive heart failure." No other quantitative outcome data were reported.

As they had done previously, the authors also reported beneficial effects on other conditions: Several subjects, including 2 with "familial hypercholesterolemia," experienced dramatic reductions in serum cholesterol lasting up to 2 years after their final chelation treatments.

In an editorial, also published in 1960, Clarke referred to "an accumulated experience of several hundred patients...[with]...occlusive vascular disease...," including "a large [number unstated] series of patients with angina pectoris.[247]" The 1960 series, however, appears to be the final report from the Providence Hospital group of their own subjects treated with EDTA for atherosclerosis. This constitutes more evidence of selection bias.

Meltzer (1960)[51]: In 1960 Meltzer and colleagues[51] reported an uncontrolled series of Na_2EDTA treatments in 10 male subjects with "severe, persistent angina pectoris which had not been controlled with previous therapies." Six had previous MIs; 9 had abnormal ECGs "compatible with coronary artery disease"; 3 had "radiographic evidence of cardiomegaly"; and 3 had intermittent claudication. After 2-3 months the treatments were stopped because of an apparent lack of efficacy, but after 3 more months the subjects were noticeably better: "Nine out of ten men had a significant reduction in the number and severity of anginal attacks, five out of nine electrocardiograms showed improvement, and all three patients with cardiomegaly showed a reduction in heart size."

The study authors also reported x-ray evidence of reduction in calcification of an aortic valve in 1 subject, "rather dramatic improvement" of "long-standing extensive keratotic skin lesions" in another, and "definite decreases in severity of...symptoms" in 2 subjects with arthritis. The intermittent claudication in 3 subjects, however, did not improve.

Kitchell (1961)[248] and Boyle (1961)[249]: The 10 subjects reported by "Meltzer (1960)" appear identical to the 10 subjects attributed in to "Kitchell (1961)" and to "Boyle (1961)." These 10 are also among those reported in "Kitchell (1963),[54]" in which they and 28 new subjects were treated and observed for a substantially longer period. Thus, "Kitchell (1963)" is the only report from which conclusions about the original 10 can legitimately be drawn, as will be further discussed. has erred in listing the original series of 10 subjects 3 times, thus implying that there were 3 distinct series, and in failing to acknowledge the final report of that series.

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[illegible]			

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Olszewer (1988)*[90,91]	844	Symptoms	821 improved
McGillen (1988)	1	Angiography	No evidence of benefit
Wirebaugh [*sic*] (1990)	1	Angiography	No evidence of benefit
Deycher (1992)	215	Symptoms	70% improvement
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Hancke (1993)[269]	470	Symptoms	Significant improvements

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Meltzer (1961)[250]: This study of chelation treatments in 81 subjects did not report therapeutic outcomes at all; it reported, as suggested by its title, side effects and toxicity of Na_2EDTA. quotes the article as having reported that the treatment was "effective" at producing an outcome that was not stated. This appears to have been inferred from a phrase in the article's final paragraph: "...our plan of alternate day infusions has been therapeutically effective...." Two sentences later, however, Meltzer and colleagues made it clear that the intended meaning of "effective" in this context was not what the author of must have imagined: "We are currently studying the maximum effectiveness (calcium excretion) with varying periods."

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There is language in the article suggesting that Meltzer and Kitchell's group may also have been guilty of selection bias: "...infusions of disodium EDTA were given to 81 subjects in a study of the effectiveness of this therapy in coronary artery disease during a two-year period...; 62 patients have now been followed from 8 to 30 months." Yet these investigators eventually reported outcomes in only 38 subjects.

Kitchell (1963)[54]: In 1963 Kitchell and Meltzer's group issued a "reappraisal" report. They had found that after observing and treating their original 10 subjects for up to 2 more years, and having added and followed another 28 subjects for 18 months, the apparent early improvements had proved illusory. MIs and deaths occurred at rates that would have been expected without chelation treatments. Five of the original 10 were dead, all by MI. Among the survivors, initial symptomatic and ECG improvements had largely disappeared; only 2 of the original 10 were thought still "improved."

Among the 28 new subjects, 16 had considered themselves "improved" and 2 "markedly improved" after 6 months; those numbers could be the source of the "18 improved" entry in . After the full 18 months of the study, however, 7 of the 28 were dead (6 of MI, 1 in congestive heart failure); 2 were worse, 6 were deemed "no change"; and 13 "remained improved."

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Of the 13 subjects who died, 6 had autopsies: none showed evidence of decalcification or attenuation of coronary plaques.

The study authors concluded that chelation "does not significantly alter the natural history of coronary artery disease, nor does it offer any protection against repeated infarctions and death." They granted that it "may slightly influence the anginal syndrome," but cautioned that "similar percentages of improvement...have been reported after varied medical and surgical therapies.[54]"

Thus the 2003 TACT protocol has misrepresented the findings of Kitchell and colleagues by citing the original positive sample 3 times, by failing to acknowledge the subsequent unfavorable outcome of that sample, and by reporting erroneous results of the additional sample of 28 ( ). The table's entries for "Kitchell (1963)" are wrong in every category: Sample Size, Outcome Measures, and Result.

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The discussion in the text of the protocol is only slightly less misleading: "In 1963, Kitchell and co-workers reported on 28 patients...; within 3 months of therapy, about 60% of patients reported improvement based both on patients' impression and their documented exercise tolerance. Nonetheless, the benefit was not felt to be long-lasting.[5]" There is no mention of the original 10 subjects, the deaths, the MIs, the autopsies, or the study authors' conclusions, including their telling remark about "similar percentages of improvement." A reader of the 2003 TACT protocol would likely suppose that the outcomes of "Kitchell (1963)" were nearly the opposite of what Kitchell and colleagues reported.

Lamar (1964)[52]: In 1964 Lamar reported the results of Na_2EDTA treatments in a group of diabetics:

> Of 15 diabetic patients suffering from severe vascular complications, all were relieved of their various degrees of peripheral vascular insufficiency: 8 were restored to normal after suffering from strokes or advanced brain syndrome; 4 were improved of their cardiac failure and 3 patients with different degrees of diabetic retinopathy obtained dramatic subjective and objective benefits....Seven of these 15 diabetics have shown persistent improvement with reductions of their insulin needs after EDTA.[52]

There were no eligibility criteria other than "diabetic with severe occlusive vascular disease," which seems to have included PVD affecting the lower extremities in all subjects, and cerebrovascular disease as evidenced by stroke or "chronic brain syndrome" in 8 subjects. None of the subjects were reported to have had angina or CAD prior to treatment. The diagnostic criteria for PVD were not standardized or specified for each subject, but were reported to be "some degree of peripheral vascular insufficiency manifested by atrophic pedal changes, diminished pulses and oscillometric readings, vascular calcifications observed in x-ray films, and by intermittent claudication or rest pain of the lower extremities."[52]

Lamar provided detailed case reports of 8 subjects, mentioning evidence of PVD in only two. Three of the 8 died, but only after each had demonstrated, according to Lamar, dramatic clinical improvements. ("After one of these active, fun-filled days, she was found dead one morning....") Autopsies were performed in 2 subjects: In the first, "*Severe generalized arteriosclerosis* involved primarily *the abdominal aorta and its branches and as well as the coronary arteries*...[there was] *fresh myocardial necrosis of the anterior wall and interventricular septum*..."; in the second there was "...*unusually severe generalized arteriosclerosis*....Death had occurred *from recent thrombosis of the basilar artery. The walls of the cerebral artery system were markedly calcified* [italics in the original]." Lamar's curious interpretation of 3 dead subjects having improved suggests that there may have been other deaths, left unmentioned.

Lamar also reported a case of a nondiabetic 54-year-old man, "disabled for 5 years by hypertrophic osteoarthritis of the hands...and a painful calcific tenosynovitis of the left shoulder with a large calcified area visible on the x-ray film and easily felt by palpation." The man had requested chelation treatments

> ...after the satisfactory results observed in his own severe diabetic 76-year-old and senile mother...for whom EDTA totally relieved severe rest leg pains and intermittent claudication...[and who] became a more stable diabetic....Above all, the most appreciated benefit she enjoyed was disappearance of senile irritability and intolerance, and conversion to a pleasant and cheerful attitude.[52]

Lamar described the results of EDTA given to the son:

> After receiving 45 gm of EDTA in 3 weeks, he reported excruciating pain at the shoulder. Palpation gave the feeling of many crepitant, small, gravel-like pieces, apparently fragments of the calcified area previously felt as a solid hard mass. X-ray films confirmed this impression and a local injection of a steroid and local anesthetic combination resulted in immediate and lasting relief. At the completion of the series of 30 injections, there was no pain at all; no calcification was detectable in the x-ray film or by palpation; and full mobility was restored to the shoulder and to the hands and fingers. A year later, this very grateful patient was found still entirely normal on follow-up examination.[52]

Lamar, like the other authors, revealed that his report might have suffered from selection bias: "The cases described above belong to the group of the first 15 diabetics among some 40 patients affected with severe occlusive vascular disease....[52]"

Thus 's designation of "15 improved" for the Lamar report is in error, even discounting the absence of angina or CAD as the target of the intervention. Atherosclerosis per se is a reasonable basis for including an article in a literature search for evidence that chelation might be effective for CAD, but this article is not accurately represented by : At least 3 of the 15 subjects died, and among the rest the diagnostic criteria were mostly unstated and not rigorous enough to draw conclusions. The naive enthusiasm of the author and the evidence of selection bias further suggest that the stated results are doubtful, at best. Lamar's subsequent article, discussed next, offered no grounds for granting a benefit of that doubt.

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Lamar (1966)[53]: The table's entry for this report does not appear to support a role for Na_2EDTA in treating CAD or atherosclerosis, nor does it make arithmetic sense: "Sample size: 3. Result: 1 improved, 1 died." We summarize it only to further characterize the lack of rigor both in Lamar's work and in the table's entries. In 1966 Lamar reported:

> A carefully selected group of 50 patients with various forms of occlusive atherosclerosis, have been under study for the last six years [*sic*]....The consistently good results may be reasonably interpreted as due to the breakdown of the atherosclerotic plaques as EDTA

> chelated and removed metastatic calcium from the lesions, thus widening the contracted arterial lumen [etc.]....In a private practice it is not possible to carry on double-blind or cross-over control studies, so we must rely upon the experience and clinical judgment acquired in four decades of intensive medical practice and observation.[53]

Unfortunately, criteria for "careful selection" of patients are almost entirely absent from the report, and outcomes are described for only 4 subjects. One died; his autopsy, like the two in the previous report, showed that "the amount of severe atherosclerosis in most...areas of the body was quite extensive...." Of the other 3 subjects, one was described as having CAD: "...at age 70 years [he] had had severe congestive left ventricular failure for five years following a myocardial infarction." His ECG "show[ed] first-degree heart block, complete RBBB, old posterior wall infarction, left ventricular hypertrophy and strain...toxic effects of digitalis." He had:

> ...labored breathing, ascites, marked edema of the feet and legs, cardio-hepatomegaly....He had been intensely digitalized and was also receiving 2 to 3 intramuscular injections of mercurial diuretics per week and daily oral doses of thiazide diuretics....His diet was rigidly restricted in sodium. Nausea, anorexia and severe mental depression had developed.[53]

After he began chelation treatments, he was said to have improved markedly over a period of about 2 months: He lost 12 lb and his dyspnea, peripheral edema, hepatomegaly, ascites, and cardiomegaly were reported to have completely resolved. The ECG now showed "elimination of the complete RBBB, isoelectric S-T segments in all leads, improvement in myocardial depolarization, and disappearance of the signs of left ventricular strain and of digitalis toxicity." During that time, however, his digitoxin dose had been reduced from 0.25 mg daily to 0.1 mg daily, and his mercurial diuretics had been discontinued. Lamar did not provide information about serum electrolytes, nor did he comment on whether the man was hospitalized or was otherwise in bed.

This man's marked improvement is most simply explained by relief from digitoxin toxicity, effective diuresis, and gradual replenishment of whole-body potassium and sodium after the cessation of the mercurial diuretic. At most, Na_2EDTA treatments may have tweaked the process by transiently lowering serum calcium and increasing intravascular volume during and shortly after infusions -- thus possibly reducing the toxic effects of digitoxin[55] while increasing the glomerular filtration rate -- but there is no need to invoke other, specifically antiatherosclerotic effects.

In this article Lamar also reported an incidental, complete reversal of "prostatism" in a man who was being treated for PVD. According to Dr. Lamar, the softening and shrinking of the prostate were heralded, after 6 months of chelation treatments, by "the passing of large amounts of urinary 'sand'...." Within 2 months the man's prostate was normal.

By 1966 Lamar should have been aware of the 1963 Kitchell reappraisal report. He did not cite it, although he cited all of the Clarke articles and even "Kitchell (1961)." Such selective citations, together with further evidence of selective reporting and a barely qualified enthusiasm for chelation as a near-panacea for all manner of "calcinoses," render Lamar's 2 reports unworthy of being taken seriously. 's entry for the report, in any case, bears no relation to the report itself. The apparent reason for that will become clear.

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Soffer (1964)[55]: This report is notable for not being cited by the TACT protocols. Alfred Soffer, later to become the editor of both *Chest* and the *Archives of Internal Medicine*, gave 2 courses of 20 treatments of Na_2EDTA to each of 5 patients with "signs and symptoms of peripheral atherosclerosis":

> With one exception, intermittent claudication, standardized walking tolerance, oscillometric data, dependent rubor or blanching upon elevation of the extremity, and strength of pulses were relatively unaffected by therapy.[55]

Soffer also found the treatment ineffective in 3 patients with scleroderma heart disease and in 1 patient with aortic stenosis. Together with findings of no improvement in the only 3 subjects with intermittent claudication among Meltzer and Kitchell's original group of 10,[51] Soffer's small series raised a red flag.

Others had noticed, even by the 1950s, that several proposed treatments for angina pectoris had at first been reported to have dramatic effects, only to be found ineffective when subjected to more rigorous study -- usually in the form of controlled trials. In 1961 Beecher illustrated this by reviewing the history of bilateral ligation of the internal mammary arteries, a method that had enjoyed a brief popularity at about the same time as the early chelation reports.[251] Beecher contrasted the reports of "enthusiasts," who reported outcomes comparable to the early chelation series, with those of "skeptics" who were wary enough to perform controlled trials. In the case of internal mammary artery ligation, 2-3 negative controlled trials involving a total of about 40 subjects convinced experts in the field to dismiss prior positive case series involving thousands. The practice was promptly stopped.

Later, Benson and McCallie expanded the discussion. They reviewed the history of 5 ineffective treatments for angina pectoris -- 3 medical and 2 surgical -- ranging from the 1920s to the 1960s, and found a striking pattern:

> Data from enthusiasts' studies reveal that subjective improvement was seen in 82.4±9.7 per cent (mean ± S.D.). This small variance in 13 studies of 1187 patients, evaluating five different inactive treatments over the course of four decades, strongly attests to the constancy and predictability of the placebo effect in the relief of angina pectoris.[252]

The authors found that objective improvements, including increased exercise tolerance, reduced use of nitroglycerin, and improved ECGs, were also common to early studies by "enthusiasts," although not so common as subjective improvements. Finally, they demonstrated a consistent finding of treatments that were eventually studied in controlled trials: About 35% of subjects in each group, "active" or placebo, reported improvement.

We summarize the early "case series" cited by the 2003 TACT protocol as follows. They were small, uncontrolled, vaguely described series involving only 3 groups of investigators. Two of the groups (Clarke and colleagues and Lamar) were unrepentant enthusiasts who touted chelation for multiple conditions, and the third group (Kitchell and colleagues) was, at first, only slightly less enthusiastic. Many of the individual case reports are quite fanciful. There is evidence of selective reporting by all 3 groups. Only the Kitchell "reappraisal" report demonstrated the objective outcomes, attention to follow-up, and skepticism that can make an uncontrolled case series useful, but it was misrepresented by the TACT protocol. The other notable disconfirming report of the time, by Soffer, is not cited by the TACT protocols.

In a review of chelation for occlusive vascular disorders, published in the Federal Register in 1970, the National Academy of Sciences--National Research Council's "Panel on Cardiovascular Drugs" summarized only the Kitchell and Soffer reports. The Panel called "investigations by other authors," citing Clarke and Lamar, "little more than testimonials.[253]"

Even prior to the Kitchell "reappraisal," the previous reports' deaths by MI and autopsies showing extensive atherosclerosis had suggested the truth of the matter: The early chelation reports had demonstrated the same pattern of error that had occurred in reports of other ineffective treatments for angina pectoris.[243] Only Kitchell and colleagues eventually acknowledged that history, possibly because of what they had learned from having also been among the early enthusiasts for mammary artery ligation.[251,254] Their reappraisal and Soffer's 1964 report brought chelation back to reality: There was no credible evidence for an effect of IV Na_2EDTA on CAD or on atherosclerosis in general.

Later case series. The later case reports provide even less support for chelation. Not long after the 1963 reappraisal article,[54] reports of trials of Na_2EDTA as a treatment for atherosclerosis largely disappeared from the mainstream medical literature for nearly 3 decades. When they returned, they did so in the form of reasonably well-designed, controlled trials, all of which were negative.[21-28] The remaining positive case series cited by Dr. Lamas have thus emanated from a tiny group of practitioners who share an enthusiasm for chelation, *Laetrile*, IV hydrogen peroxide, and other fringe practices, and who fail to appreciate the pitfalls of uncontrolled case series performed by enthusiasts. Their reports are not credible, and not merely because they were uncontrolled.

What follows are summaries of the 3 largest case series listed in , which provide the bulk of Dr. Lamas' "thousands of patients with successful outcomes,[29]" and a summary of "Casdorph (1981)[255]" because it is discussed in the text of the 2003 TACT protocol. There are also brief discussions of 3 other pertinent references. The first is a "meta-analysis,[95]" the first author of which is L. Terry Chappell. That article, reporting 19 studies involving more than 22,000 subjects, is the source for much of the "evidence" cited by the second reference, a book written by the TACT Trial Chelation Consultant, which the 2001 TACT protocol cites in support of "published case series suggesting clinical benefits.[4,57]" The third reference is a case report of a single subject followed by academic investigators at the same time that he was being treated at a "chelation clinic.[24]" The discrepancies in reported outcomes between the 2 settings are revealing.

Summary of Case Series (From the 2003 TACT Protocol)[5]

First Author (Year)	Sample Size	Outcome Measures	Result
Clarke (1955)[245]	22	Symptoms	Some improvements
Clarke (1956)[32]	20	Symptoms	19 improved, 1 died
Boyle (1957)[246]	20	Symptoms, ECG	Significant improvements
Meltzer (1960)[51]	10	Symptoms, ECG	9 improved
Clarke (1960)[50]	76	Symptoms	58 improved
Kitchell (1961)[248]	10	Symptoms	9 improved
Boyle (1961)[249]	10	Symptoms, ECG	9 improved
Meltzer (1961)[250]	81	Not stated	"Effective"
Kitchell (1963)*[54]	28	Symptoms, ECG	18 improved, [*sic*]
Lamar (1964)[52]	15	Symptoms	15 improved
Lamar (1966)[53]	3	Symptoms	1 improved, 1 died

Evers (1979)[256]	3000	Symptoms	> 90% improved
Casdorph (1981)*[255]	18	Ejection fraction	17 improved
Robinson (1982)	248	Symptoms, ECG	Significant improvements
Olszewer (1988)*[90,91]	844	Symptoms	821 improved
McGillen (1988)	1	Angiography	No evidence of benefit
Wirebaugh [*sic*] (1990)	1	Angiography	No evidence of benefit
Deycher (1992)	215	Symptoms	70% improvement
Hancke (1992)	42	Need for surgery	39 canceled surgery
Hancke (1993)[269]	470	Symptoms	Significant improvements

ECG = electrocardiogram
**Described in text*
From the 2003 TACT protocol.[5] The asterisks, designating "described in text," are present in the original and refer to descriptions of 3 of the reports on pages 7-8 of the protocol. Reports with reference numbers in superscript are discussed in this article.

Evers (1979)[256]: This is an unpublished "review of a six-year report of chelation therapy given to about 3,000 patients..., which has primarily been directed at the treatment of vascular insufficiency due to atheromatous vascular involvement." Inclusion criteria appear to be only what can be gleaned from that statement; Evers did not report how many subjects were considered to be in each of the several possible subcategories. Diagnostic criteria, when mentioned, and outcomes were described only retrospectively:

> In arteriosclerotic obliterans cases, specific changes include: definite improvement of pedal artery pulsation, gain in color, return in normal temperature and improvement in tissue quality of the feet. We find that ninety percent of these problems in the lower extremities make significant gains including regaining the ability to walk long distances comfortably, freedom from claudication and evidence of improved distal circulation. Those whose cerebral vascular system is severely damaged by arteriosclerosis and/or micro-circulation thrombosis, suffering from amnesia, confusion, aphasias, and motor coordination have improved [*sic*]. There has been a notable improvement in coronary circulation in all cases of angina, characterized by the patient having no need for vaso-dilators after about the fifth infusion. An interesting, but not predictable dividend in some cases consist [*sic*] of improved renal functions, [*sic*] reduction of prostatic obstruction by calculi, decrease in the degree of insulin required by the diabetic, almost normal breathing in emphysematous patients, great improvement in arthritic patients and even in Parkinson's Disease sufferers.[256]

Evers offered no other evidence for his claims of clinical benefits. Thus Dr. Lamas' implication, that Evers' 3000 cases constitute a significant portion of those that challenge the negative findings of controlled trials, must depend not on rigorous data, because Dr. Evers did not supply any. Rather, it must depend on Dr. Evers' credibility, which we now examine.

In this case series Dr. Evers denied complications more serious than "simple drug sensitivity," and in a late 1970s brochure for patients he stated: "We have never had a case yet where there were any adverse reactions and there have been no deaths from it.[257]" However, in a 1976 trial in federal court, expert witnesses testified that at least 13 patients, and possibly as many as 21, had died as a direct result of Na_2EDTA administered by Evers at his own hospital (Meadowbrook Hospital in Belle Chasse, Louisiana) over a 2-year period from 1973 to 1975.[18] He had neglected to seek consultations for patients with renal failure and other life-threatening complications, treating them instead, for example, with "Myoflex": a tiny electric current applied to the skin, which, according to Evers, "increases blood flow to the kidneys.[65]"

One of the government's expert witnesses was Dr. J. David Spence, now Professor of Neurology and Clinical Pharmacology at The University of Western Ontario, London, Ontario, Canada, and Director of the Stroke Prevention and Atherosclerosis Research Centre at the Robarts Research Institute. He concluded his report to the Bureau of Health Insurance of the Department of Health, Education, and Welfare with these words:

> The total picture is so appalling that I strongly urge the Bureau of Health Insurance not only to withhold certification for Medicare, but to take all steps possible within the law to expedite the closing of this hospital and to protect future patients from being subjected to these dangerous practices.[65]

In 1975 Evers had been found "medically incompetent" by the Louisiana State Board of Medical Examiners.[258] In 1986 the Alabama State Board of Medical Examiners revoked his license after he had

> ...represented to...a patient under his care that a proposed treatment for malignant carcinoma of the breast using Ointment A and Ointment Z would cause the malignant tumors to come out through the skin when in fact the Respondent knew or reasonably should have known that such representation was false, untrue, or deceptive.[259,260]

The Alabama Board also found that Evers had

> ...caused to be performed or ordered numerous x-rays, laboratory and diagnostic tests [and] medical services including hyperbaric oxygen treatments, hydrotherapy, coffee enemas, chelation, accupath 1000 & iridology, electrical muscle stimulants, massages, mineral sit baths, ozone therapy, and spinal checks which the Respondent knew or reasonably should have known were not medically necessary in the diagnosis and treatment of the medical condition from which the patient suffered.[259,260]

The Alabama Board also asserted that Dr. Evers had "wrongfully conducted medical experiments upon his patient...without adequately informing the patient of the risk of harm to her health by the use of untested and unproven drugs, medicines and therapies.[259]" Dr. Evers' "Agreement Between Physician and Patient" included language such as this:

> For, and in consideration of, medical care rendered to me by Dr. Ray Evers (herein referred to as Physician)...

Should the government's insurance carriers or intermediaries or third parties find reason to deny me insurance benefits because of supposed "lack of medical necessity," I shall not hold my Physician responsible for any of my expenses for clinic treatment...

I specifically request that you, as my attending Physician, prescribe for my diagnosis and treatment based upon your individualized judgment and discretion, and not upon numerical averages in rulebooks or so-called "norms", "criteria", or "standards", or by whatever name, as established by any individual, group, agency, insurance company, or "service corporation", government agency, program, union, fraternal body, or any other organization or person...

I understand that the type of therapy given at RA-MAR CLINIC may not be in perfect agreement with the so called orthodox methods of treatment as approved by the AMA, FDA, or HEW. I understand that the type or therapy given here is the type that the Physician and I both agree is the correct future of medicine. (By the use of nutrition, enzymes, physical therapy, magnetic medicine, use of pyramids, etc. or any other modalities that may be used to benefit mankind)....[261]

Dr. Spence, after interviewing several of Evers' patients at Meadowbrook Hospital, wrote: "These interviews indicate clearly that the patients, in signing the so-called informed consent form, are not giving informed consent, and that they are not properly informed of the adverse effects of chelation therapy.[65]"

Evers was not pleased with those who disagreed with him or who inconvenienced him. He brought $1 million libel suits against Dr. Spence and at least one other expert witness in the 1976 case (Spence JD. Personal communication. 2006).[56] In the same year he was convicted of "intimidating and impeding two officers of the Internal Revenue Service" (IRS) after he had threatened to "get my gun and blow your brains out," had driven his car straight at one of the officers, and had called that officer a "yellow son-of-a-bitch" and the other officer a "black bastard.[62]"

The TACT protocols mention none of these facts with regard to Evers. Otherwise, it would have been evident to naive readers, such as members of the NIH Special Emphasis Panel[39] and human studies review boards, that Evers' "3000 cases" provide evidence only of the dangers of chelation and chelationists.

Casdorph (1981)[255]: This article, from the *Journal of Holistic Medicine*, reported an increase in ejection fractions (EFs) in 17 of 18 subjects who underwent chelation. The study was uncontrolled. There were no rigorous inclusion criteria; the author asserted, without documentation other than a history of coronary artery bypass graft in 4 subjects, that all subjects "had documented evidence of arteriosclerotic heart disease." Resting EFs were measured by radionuclide ventriculography before and after 20 Na_2EDTA infusions. The average increase was 5.8%, called "highly significant" by Dr. Lamas.[5]

It is not clear what this series has to do with evidence for chelation as a treatment for CAD, or even as a treatment for left ventricular dysfunction. (Congestive heart failure is an exclusion criterion for the TACT.[5]) Casdorph did not specify the timing of the post-treatment ventriculograms; if they occurred immediately after the final chelation infusion, increases in EFs likely resulted from increases in preload due to the sodium content of the chelation treatment (600 mg in 3 g of Na_2EDTA[65]), combined with afterload reductions that accompanied transient hypocalcemia. Thirteen of the 18 subjects had normal EFs to begin with, and only 1 subject had an EF below 46%; thus, the Frank-Starling relation predicts that an increase in preload alone would have enhanced systolic function. The mean increase of 5.8%, although perhaps statistically significant, can hardly be considered clinically significant in such a sample. That increase has also been reported in 20% to 30% of subjects in congestive heart failure who received placebo.[262,263]

Other aspects of the article cast doubt on the objectivity of the author. He cited the early Clarke studies as authoritative evidence for the ability of Na_2EDTA to remove "metastatic calcium deposits" and to provide "remarkable benefits and improvement in patients suffering from angina pectoris.[255]" He neglected to cite the Kitchell reappraisal or other references to misinterpretations of uncontrolled trials of treatments for angina pectoris. He begged the chelation question: "...it is not too surprising that the administration of agents which remove calcium from the arterial wall do bring about dramatic relief of signs of arterial insufficiency and angina pectoris.[255]" He blurred the distinction between that assertion and the action of calcium channel blockers: "This presumably takes place because of removal of metastatic calcification in the arterial wall as well as interference with slow calcium currents which were recently described.[255]" His final sentence reveals a grandiose opinion of his study and an ignorance of cardiac physiology: "Thus EDTA must be added to the other new drugs popularly referred to as calcium blocking agents which have been shown to be potent coronary vasodilators.[255]"

Dr. Casdorph has since changed his emphasis about chelation, from one stressing its effects on calcium and atherosclerosis to one claiming that it is the cure for "toxic metal syndrome," the major cause of dementia: "...no other persons with our combination of medical knowledge and writing skill are privy to this proposed book's information about the dramatically successful therapy to antidote Alzheimer's disease and allied forms of dementia [*sic*].[264]"

Casdorph, who was the ACAM's president from 1987 to 1989, has also authored a book proffering "indisputable evidence" for faith healing.[265] He was listed as a TACT co-investigator by ClinicalTrials.gov as recently as March 2007,[38] but was not so listed by the NCCAM as of July 26, 2007.[117]

Olszewer (1988)[90,91]: This is a retrospective report of 2870 subjects treated with Na_2EDTA between 1983 and 1985 and followed for 28 months in a clinic in Sao Paulo, Brazil. They were diagnosed mainly with CAD (844 subjects), PVD (1130 subjects), or cerebrovascular disease (504 subjects). Subjects with CAD were diagnosed by a combination of history, ECG, and the "stress test." Outcome criteria seem to have been assigned only retrospectively. A subject with "marked improvement" was defined as "a patient whose stress test was previously positive and became negative, and who was previously symptomatic, and became asymptomatic, while off all drugs, after a course of 20-30 treatments." A subject with "good improvement" was defined as "a patient who had an improved stress test, with a normal ST segment, and who became asymptomatic, off all drugs, but who still had evidence of arrhythmia or hypertension."

Among CAD subjects, after treatment 649 (77%) were judged to have made a "marked improvement" and 140 (17%) were judged to have made a "good improvement." Only 1 subject was judged worse. In the PVD group, the results were even more dramatic: 91% of subjects were judged to have made a "complete recovery."

The authors reported that 120 subjects were "lost to follow-up and...not included in this report.[90,91]"

Like the early series, the report lacks rigorous inclusion, diagnostic, or outcome criteria, but there are more serious problems. The number of reported deaths over a period of 28 months was 7; 2 were in the CAD group. This is not credible for 2870 subjects with life-threatening cardiovascular diseases, followed for 28 months in the early 1980s, most of whom were eventually "off all drugs." It remains not credible even if all 120 subjects "lost to follow-up" are assumed to have died.[266] It suggests a departure from the rigor that is required of any study, but especially a human trial of a purportedly lifesaving treatment. For example, many subjects may have been misdiagnosed, or the reporting of outcomes may have been biased in the extreme. The authors may argue that the results demonstrated that chelation is a miracle cure for atherosclerosis, but if so this should have been evident in the more recent RCTs.

Bias or naiveté is evident in other parts of the report. The authors cited the early Clarke studies with approval, but ignored the Kitchell reappraisal and Soffer's negative report. They argued that their own "clinical response rates...are much too high...to be attributed to placebo-effect alone...." They added that their results "are remarkably similar to those obtained by Clarke...," implying that this enhanced the validity of that assertion. They were apparently unaware that Clarke's and their own "clinical response rates" were remarkably similar to the "constant and predictable placebo

effects" found in other reports by "enthusiasts.[251,252]" The glaring difference in death rates between their own study and Clarke's, however, renders the Olszewer study invalid unless it can be satisfactorily explained.

In this article, Olszewer and Carter also reported the "preliminary results" of "a randomized, double-blind, cross-over study...on a small group of 10 patients with peripheral vascular disease." The subsequent report of that study, published in 1990,[92] offered more specific inclusion and outcomes criteria than the authors' previous case series, including objective measures of walking distance (whether "pain-free" or maximal is not clear); the Master's 2-step exercise test; and a bicycle stress test, although it seems unlikely that "the Bicycle Stress Test included patients with claudication before 3 minutes at 50 kilometers per hour.[92]" The methods of randomization, allocation concealment (if any), and blinding were inadequately described, as was a comparison of baseline characteristics of the treatment and control groups. The dose of EDTA was 1.5 g per infusion; the frequency was not reported. In the authors' retrospective series, the dose had been 3.0 g per infusion, given 2-3 times per week.

The reported results were striking. After "active" and placebo groups of 5 subjects each were given the first 10 of 20 planned treatments, 5 subjects had improved so much -- had, on average, doubled their walking distances -- that the authors "therefore decided to break the code." All of those who had improved had received EDTA; those who had received placebo had not improved at all. The authors proceeded to give all subjects EDTA for the final 10 treatments, and by the end the original placebo group had experienced improvements comparable to those of the active group after its first 10 treatments. The original active group also continued to improve: The mean walking distance for those who received all 20 EDTA infusions increased from 160 to 602 m, or almost 400%. By comparison, in 2 subsequent controlled trials of chelation for PVD, involving a total of 181 subjects and using twice the EDTA dose, those in the placebo and active groups each increased pain-free and maximal walking distances by 20% to 50%.[21,25]

Because the sample size was so small, Olszewer, Sabbag and Carter's "double-blind" results have reasonably been dismissed as evidence for chelation being an effective treatment for cardiovascular disease. In the first TACT protocol, Dr. Lamas appears to do this without citing the article: "...two additional very small trials of 9 and 10 patients are not interpretable and not reviewed here.[4]" However, there is a reason for examining the trial despite its small sample size: to help determine whether Olszewer and Carter's previous case series, which reported the results of 844 subjects with CAD and 1130 with PVD, warrants inclusion among the references cited by Dr. Lamas as evidence for "thousands of patients with successful outcomes."

We have already argued that "Olszewer (1988)" ought not to be included, because of its inadequate methods, its bias, and its implausible death rate. Dr. Lamas did not acknowledge those problems in the text of page 7 of the 2003 TACT protocol, where he summarized the report.[5] The 1990 double-blind report gives more reasons to question any report by Olszewer and Carter. The small sample size notwithstanding, the results were highly improbable, as others have also concluded.[267] Bias continued to be evident in the authors citing the early Clarke articles but failing to cite the disconfirming reports of Kitchell and Soffer. Most telling, however, was their assertion that EDTA's

> ...safety, when administered according to the American College for Advancement in Medicine protocol, is no longer a major concern, in view of the fact that more than 500,000 patients have been treated in the US alone, without a single reported incident of renal failure or death since 1960.[92]

That statement was false. Co-author Dr. James Carter, who lives in Louisiana, was fully aware of Dr. Evers' cases of renal failure and of his deaths. In 1992 Carter published a book alleging a conspiracy of the American Medical Association, the FDA, the US Postal Service, the FTC, the IRS, the NIH, Medicare, Blue Cross Blue Shield, other private health insurers, drug companies, the American Hospital Association, the American Cancer Society, the AHA, medical journals, medical schools, state licensing boards, and other entities.[94] These institutions, according to Carter, were in collusion to "suppress" *Laetrile*, krebiozen, chelation, chiropractic, homeopathy, antineoplastons, "body detoxification," "immune system stimulation," "herbal medicine," coffee enemas, numerous other "alternatives," and even the Church of Scientology. In his book, Carter argued that there is no question that "chelation works," citing "published medical evidence" (eg, the articles reviewed here) and using phrases, such as "beyond a shadow of a doubt" and "the case against EDTA chelation therapy, on the basis of lack of efficacy and scientific medicine, is closed!"[94]

Carter discussed "pioneering chelation doctor Ray Evers" at some length, arguing that the deaths reported in the 1976 federal case had been due not to EDTA, but to "underlying progressive illness.[94]" He also suggested that Dr. Evers may

> not have been strictly following the [ACAM] chelation protocol developed in the 1970s....Dr. Evers was aware, however, that if there was any suggestion of impaired or reduced kidney function, the patient was not a good candidate for chelation therapy; if it were administered under those circumstances, the patient should be monitored closely.[94]

Carter attributed Evers' legal troubles, in part, to the chairman of the Louisiana Medical Board who, according to Carter, may have held a grudge against Evers because the two had interned together and had, at the time, "dated a mutual woman friend." Finally, "Dr. Evers, a devout Christian, never turned away any patients who came to him for help."

Dr. Evers, however, was a member of ACAM, then called the AAMP. His "3000 cases" article had described Na_2EDTA dosing essentially similar to that of the current ACAM "protocol.[33,256]" Dr. Spence, the expert witness, reported: "These patients were receiving chelation therapy in the manner advocated by the AAMP, under the direction of a member of the AAMP, who had on his office wall a certificate of merit from the AAMP.[66,268]"

In evaluating Evers' deaths, Dr. Spence was careful to distinguish the effects of EDTA treatments from "underlying progressive illness." Commenting on Dr. Evers' having neglected to seek expert consultations for complications of EDTA, Dr. Spence wrote:

> If the patients were all very advanced in age, and had died of hopeless diseases for which they were receiving no therapy, a consultation rate of one in twenty-one deaths might be considered within the realm of acceptable medical practice...however, patients as young as 47 years of age are permitted to die in congestive heart failure, and patients as young as 24 years of age are allowed to die of renal failure... [emphasis in the original].[65]

In a letter to the California State Department of Health, Dr. Spence wrote: "The causes of death included...renal failure, which, in a number of cases, was not present before administration of EDTA.[66]"

Elsewhere in his book, Carter called Evers "the eminent Dr. Ray Evers[94]" and revealed that he, Carter, had his own grudge against the Louisiana Medical Board, which he referred to as a "kangaroo court.[94]" The Board, curiously, dropped an apparently strong case against Carter after it had discussed the matter with the Tulane University School of Public Health and Tropical Medicine, where Carter was Chairman and Professor of the Department of Nutrition.[258] In regard to Dr. Evers being "a devout Christian" who "never turned away any patients," one need only review his threats to the 2 IRS officers and his "Agreement Between Physician and Patient" to wonder about the integrity of such assertions.[62,261]

It is reasonable to conclude that the cases reported by Olszewer and Carter, like those of Evers, have no place in a body of evidence purporting to justify an NIH-sponsored, phase 3 trial exposing 2000 subjects to a dangerous drug that certainly doesn't work as claimed by its advocates. Carter, who was the Chairman of the GLACM IRB that approved Henry Heimlich's "induced malaria therapy for HIV" trial,[133,134] is now a TACT co-investigator.

Hancke (1993)[269]: This is a report from Denmark of a retrospective series of 470 subjects with "claudication and/or angina pectoris" who "usually required 30 [chelation] treatments over a period of 3-4 months." They were assessed "on completion of treatment and again 2 months later." The authors might have followed the subjects for a longer period, because they also reported that "our experience covers a period of 6 years and we saw no severe side-effects or casualties arising from the treatment."

Inclusion criteria are absent. Diagnostic criteria are more specific than in most reports, but the reader can't tell whether they were assigned prospectively or retrospectively:

> Patients with claudication had their ankle-arm index, walking distance, foot temperature, pain at rest, skin color of feet and healing of wounds assessed and registered. Subjective judgement [*sic*] of resting pain was rated on a scale of 1-3. Patients with angina pectoris had their working capacity measured on a treadmill, and ST depression by electrocardiogram....The subjective judgement [*sic*] of results was rated on a scale from 1 to 3 with regard to the number of attacks of angina pectoris and consumption of nitroglycerin (1:worse, 2: unchanged ± 10%, and 3: improved).[269]

The results were similar to those of other reports by enthusiasts: Of 265 subjects with "myocardial ischemia," more than 90% "improved" and only 2 worsened. Eighty-five percent had improved "working capacity"; more than 90% "reduced their consumption" of nitroglycerin; 91% with angina pectoris "improved," as did 69% with "ST-depression" and 62% with "arrhythmia." Further, "of 65 patients referred for bypass surgery, 58 did not require it after their course of chelation.[269]"

In 262 subjects with claudication (some subjects were in both groups), the authors reported "improvement in 82%," including 31 of 44 who had "problems with wound healing" and 110 of 137 "who complained of cold feet." The ankle/arm blood pressure ratios improved in 82% and walking distance improved in 87%. Unfortunately, the report lacks raw data to compare these results with those of other, plausible trials. One statement, however, described individual results more impressive than even those reported by Olszewer, Sabbag, and Carter[92]: "Some patients with claudication who were unable to walk more than 100 feet could walk painlessly for 2 miles or ride several miles on a bicycle after their treatment.[269]" "Of the patients referred for amputation, 24 of 27 legs were spared following their course of chelation.[269]"

The authors reported no deaths. They concluded that:

> ...the beneficial results that we observed were far in excess of the 10-15% improvement that is usually seen in the placebo group of a controlled study....Our results are identical with those of other similar studies....On the basis of such well published data, it seems to us that it is unethical to wait for a randomized, double-blind, cross-over study to approve chelation for the treatment of arteriosclerosis....[269]

Ironically, and in rebuttal to Dr. Lamas' assertion that a properly controlled trial "leads to changes in clinical practice,[29]" such a randomized study had recently been done, right in Denmark.[21] It had failed to find evidence of a treatment effect for chelation. Hancke and Flytlie cited it only to dismiss it as "seriously defective" and as a manifestation of "the harsh attitude of the Danish vascular surgeons." Instead of changing their own clinical practices, Hancke and Flytlie filed a complaint against the trial authors to the Danish Committees on Scientific Dishonesty (DCSD).[153] The DCSD subsequently found "no evidence of scientific dishonesty on the part of the accused.[270]"

Other statements in the article by Hancke and Flytlie cast doubt upon their own integrity as investigators. In asserting that chelation "has been proved effective in a number of clinical trials," they cited 6 references. Two are the nearly identical reports of the same retrospective study of Olszewer and Carter[90,91]; one is the "double-blind" study of Olszewer, Sabbag, and Carter[92]; two are by Edward McDonagh, the chelationist who later admitted under oath that he had falsified his data.[44,89]

Hancke and Flytlie also wrote that "evidence for effectiveness of EDTA chelation therapy is cumulative over many years," citing 6 more references. One of these (and probably two others) was concerned solely with the common use of EDTA as an antioxidant for in vitro biochemical preparations[271]; it is barely relevant to the proposition of chelation therapy, and not at all relevant to the practice. Another reference was to an editorial in which Alfred Soffer unequivocally denied the existence of evidence for effectiveness of Na_2EDTA in treating cardiovascular disease.[9] It seems doubtful that Hancke and Flytlie could have read that article, which stated, in part: "There are several sites...where this therapeutic fad currently is in vogue and where the zealot peddles these wares to the nave afflicted. Symposia and miniconventions have been organized to extol its virtues....[9]"

Among those "zealots," of course, were Hancke and Flytlie.

Jorgensen, Guldager, and Jelnes (1992)[24]: This is another report notable for not being cited by the TACT protocols. It is by the authors of the Danish RCT cited above, working at the Hillerod Central Hospital, Hillerod, Denmark. It is a case report of a single subject, but provides at least as much useful information as the other reports in the later series. The full report is in Danish, but the abstract suffices to make the point:

> A 62-year-old man suffering intermittent claudication had 20 infusions of EDTA in a double-blind, placebo-controlled trial. No effect on symptoms or systolic ankle/brachial blood pressure index was found. Following the trial, he received 30 further infusions of EDTA in a private clinic. The systolic ankle/brachial index was unchanged throughout the total period as measured in Hillerod Central Hospital. However, the private clinic found a significant increase in the index following EDTA treatment. The reason for this discrepancy could be poor technique in the clinic or it could be due to bias or manipulation. The discrepancy explains the difference between the positive results claimed by the private EDTA clinics and the results of the double-blind, placebo-controlled Danish trial.[24]

Chappell (1993)[95]: This "meta-analysis" is not cited by the TACT protocols, but is pertinent because it is the article most frequently referenced by an article that is so cited: "Dayton 1995,[57]" which is summarized next. It is also pertinent because the first author, L. Terry Chappell, led the ACAM's mission at the hearing of Rep. Dan Burton's House Committee on Government Reform, discussed previously.[41] Chappell also sat on the NIH Special Emphasis Panel that passed judgment on Dr. Lamas' application for the TACT award[39] and was named, in that application, as one of the "prominent experts in chelation therapy" assigned to the "TACT Liaison Committee to the American College for Advancement in Medicine.[4]" Chappell is a TACT co-investigator.[7]

The article purported to demonstrate that in 19 studies, 87% of 22,765 subjects treated with EDTA "improved," with "a correlation coefficient of 0.88, which indicates a high positive correlation between EDTA therapy and improved cardiovascular function." There are numerous objections to

this article, beginning with its spurious claim to being a meta-analysis and including its reliance on a single unpublished "study" for the vast majority of its subjects (19,147). That study appears to have used only one, atypical outcome measure -- thermography -- and was apparently funded by the company that made the thermography device.[272]

Most troubling is how Chappell and his co-author dealt with the lack of control groups in the reports they reviewed:

> Even though placebo control has, for the most part, been absent in existing EDTA studies, this does not mean that the data collected are not valid or useful...
>
> For the purpose of this meta-analysis...simply consider the existing study data to be the data for the treatment group and compare the improvement in cardiovascular function of the treatment group to a control group defined to have no improvement in cardiovascular capability.[95]

As unlikely as it may seem, the authors simply added imaginary controls and assumed that had they existed they would have experienced "no improvement." One might imagine that this betrayed an ignorance of the natural history of disease and the design and interpretation of clinical trials. Not quite: "It needs to be shown that the assumption of a no-treatment group with no improvement is reasonable. This meta-analysis will use the blinded study by Olszewer, Sabbag and Carter to show this.[95]"

We agree with other reviewers that "the invention of a null-effect group in this way is clearly invalid and renders the meta-analysis meaningless.[267]"

Dayton (1995; revised in 1999 and 2006)[57]: On page 261 of the 2001 TACT protocol, Dr. Lamas cites this short, online book as support for "published case series suggesting clinical benefits.[4]" It is not a case series, but a sales pitch to potential consumers. It lists some 70 "conditions or combination of conditions which have been reported to improve following intravenous chelation therapy." It dismisses "criticisms of chelation therapy by doctors" with pithy, facile rebuttals, eg, "does a person need to have the education of a sky rocket scientist to admit rockets work?" It has a "frequently asked questions" section that ensures readers that chelation is "safer than aspirin," and "unlike surgical approaches, no strokes, deaths nor heart attacks have been reported to be due to intravenous chelation therapy, and fewer side effects are reported than with many pharmaceutical medical treatments.[57]"

Elsewhere it asserts:

> Although published scientific studies have proven chelation to be effective in regard to hardening of the arteries, the existence of such studies is still unknown to many physicians.
>
> In addition to being known as a treatment for metal toxicity, such as found in lead poisoning, chelation has been successfully used to overcome various conditions associated with aging. Impaired circulation due to hardening of the arteries and discomfort due to arthritis are among the most notable. Numerous scientific articles reflecting effectiveness and safety have been published. In one study evaluating over 22,000 patients, 87% demonstrated objective improvement. Millions of chelation administrations have been performed over 40 years, world wide. According to the American College for Advancement in Medicine not one fatality proven to be caused by chelation therapy has been reported when appropriate protocol is followed.[57]
>
> Chelation is often used as a safer method to replace much costlier conventional surgical and related medical procedures. Hardening of the arteries is a lucrative, multi- billion dollar industry. Generally those who profit from an industry, whether it be a surgical/medical industry or any other industry, tend to be antagonistic to changes that reduce profits.
>
> Chelation therapy is used in conjunction with programs, exercise, and stress reduction. It also complements standard medical and surgical therapy. With the improvement of health, the medical necessity for harmful and potentially harmful pharmaceutical drugs may be reduced. Although better known as a substitute for cardiovascular surgery, chelation also has been used as a strategy to prevent reclogging of arteries after surgical bypass and balloon angioplasty.[57]

The reader will by now recognize the usual gambits common to treatises by chelation advocates: "metal toxicity"; the conflation of Na_2EDTA and the safer CaEDTA (only the latter is approved for the treatment of lead poisoning, but it is overwhelmingly the former that is used for nonstandard treatments, including the TACT); invoking "published scientific studies" that are more accurately characterized as pseudoscientific studies (especially the Chappell "meta-analysis," presumably chosen because "22,000" is impressive to the scientifically naive); the false assertion of "not one fatality proven to be caused by chelation therapy"; the suggestion that chelation's lack of acceptance is due not to its lack of scientific support, but to the conflicting financial interests of cardiologists, surgeons, and drug companies; and finally, that chelation is a safer and less expensive alternative to cardiovascular procedures, surgery, and "potentially harmful pharmaceutical drugs."

In addition to the Chappell "meta-analysis," to which Dayton alludes several times, his book cites several of the other studies reviewed here and more than 10 articles by Edward McDonagh, the chelationist who admitted in a court of law that he had falsified data.[44] Dayton, like other advocates,[152-162] also claims that all negative studies of chelation, including all controlled trials, were actually positive.

The 2001 TACT protocol named Dayton the "Trial Chelation Consultant" and 1 of 9 "prominent experts in chelation therapy" who were to be members of the TACT Liaison Committee to the ACAM (Chappell is another).[4] According to the 2001 TACT protocol, Dr. Dayton is "the former Director of the Scientific Research Committee of the ACAM [and] has clinical experience with over 75,000 chelation infusions.[4]" At $100 per infusion,[58] "nutritional supplements in the range of $20 to $200 per month [and] diagnostic study costs and professional fees...ranging from a few hundred to several thousand dollars,[57]" such experience may have made Dr. Dayton rich.

But has it made him an expert? In a 2000 article extolling "detoxification," Dr. Dayton was quoted as saying that "dramatic increases in life span are found with chelation" and "chelation favorably impacts all four major causes of death in the United States (heart disease, cancer, cerebrovascular disease, and lung disease)." He recommended EDTA chelation for anyone over the age of 30 because "modern people are overwhelmed by pollutants." He claimed that the American College of Physicians "recommend[s] chelation therapy as a preferred treatment" for "unclogging carotid blockage.[234]"

Dayton's practitioner profile for the Florida Department of Health lists 2 federal criminal convictions: 18USC 371, "Conspiracy to commit offense or to defraud United States," and 18USC 1341, "Mail Fraud: Frauds and Swindles.[61]" Dayton is a TACT co-investigator.[36]

The later case series, which provide the vast majority of Dr. Lamas' "thousands of patients with successful outcomes," contribute nothing -- not even the "suggestive" evidence that might be granted to legitimate case reports -- to the assertion that chelation for CAD may have "a small or moderate benefit.[29]" The TACT protocols fail to acknowledge the complications and deaths of Evers[18] and fail to mention abundant, additional evidence of incompetence and/or bias, eg, the miniscule death rate reported in "Olszewer 1988[90,91]" or the inaccurate ankle/brachial index measurements performed by chelationists in Denmark, as reported by Jorgensen and colleagues.[24] The 2003 TACT protocol's characterization of such case series as "observational epidemiologic studies[5]" is unworthy of a document approved by the NIH.

The errors and misrepresentations in the TACT protocols are a serious problem. They are the basis for Dr. Lamas' argument that chelation for CAD is worthy of study in a large, human trial. Human studies review boards must have accepted that argument in order to approve a phase 3 trial of a drug that had failed in several phase 2-like trials, contrary to the usual policies of the NIH and to the US Code of Federal Regulations.[177,178]

Dr. Lamas does not appear to be the original author of , even if his cause has benefited from its errors. is almost an exact duplicate, albeit printed without attribution, of a table that appeared in the 2000 article by Edzard Ernst, in the *American Heart Journal*, that Dr. Lamas' editorial rebutted.[29,166] We reproduce that as .

Summary of Case Series (From the 2003 TACT Protocol)[5]

First Author (Year)	Sample Size	Outcome Measures	Result
Clarke (1955)[245]	22	Symptoms	Some improvements
Clarke (1956)[32]	20	Symptoms	19 improved, 1 died
Boyle (1957)[246]	20	Symptoms, ECG	Significant improvements
Meltzer (1960)[51]	10	Symptoms, ECG	9 improved
Clarke (1960)[50]	76	Symptoms	58 improved
Kitchell (1961)[248]	10	Symptoms	9 improved
Boyle (1961)[249]	10	Symptoms, ECG	9 improved
Meltzer (1961)[250]	81	Not stated	"Effective"
Kitchell (1963)*[54]	28	Symptoms, ECG	18 improved, [*sic*]
Lamar (1964)[52]	15	Symptoms	15 improved
Lamar (1966)[53]	3	Symptoms	1 improved, 1 died
Evers (1979)[256]	3000	Symptoms	> 90% improved
Casdorph (1981)*[255]	18	Ejection fraction	17 improved
Robinson (1982)	248	Symptoms, ECG	Significant improvements
Olszewer (1988)*[90,91]	844	Symptoms	821 improved
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Deycher (1992)	215	Symptoms	70% improvement
Hancke (1992)	42	Need for surgery	39 canceled surgery
Hancke (1993)[269]	470	Symptoms	Significant improvements

ECG = electrocardiogram
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From the 2003 TACT protocol.[5] The asterisks, designating "described in text," are present in the original and refer to descriptions of 3 of the reports on pages 7-8 of the protocol. Reports with reference numbers in superscript are discussed in this article.

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Uncontrolled Studies and Case Reports of Chelation Therapy for CHD (From Ernst [2000])[166]

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Clarke et al (1956)[32]	20	Symptoms	19 improved, 1 died
Boyle et al (1957)[246]	20	Symptoms, ECG	Significant improvements
Clarke (1960)[247]	700	Symptoms	87% improved
Meltzer (1960)[51]	10	Symptoms, ECG	9 improved, 5 improved [*sic*]
Clarke et al (1960)[50]	76	Symptoms	58 improved
Kitchell et al (1961)[248]	10	Symptoms	9 improved
Boyle et al (1961)[249]	10	Symptoms, ECG	9 improved
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AAMP = American Academy of Medical Preventics; ECG = electrocardiogram

All of the erroneous entries in Dr. Lamas' table are also present in Dr. Ernst's. There are a few differences; one is worth mentioning, if only for its absurdity: "Clarke (1960)" in Ernst's table, in which 87% of 700 subjects are said to have improved, is not present in Dr. Lamas' table. However, that article is not the report of a study at all; it is an editorial that we have previously cited.[247] ("Clarke 1960[50]" in Lamas' table is designated "Clarke et al 1960" in Ernst's). Nowhere in Clarke's editorial does the number "700" appear. We can only imagine, referring to the sentence that we quoted from the article, that someone changed "*several* hundred" to "*seven* hundred." A potential source for such a change is an abbreviation in a table on page 143 of Chappell's 1993 "meta-analysis," in which the Clarke editorial is listed as having presented the results of "sev hundred" subjects.[95] Chappell's table also misspells "Winebaugh" as "Wirebaugh," as does Lamas' table but not Ernst's.

That suggests that Dr. Ernst was also not the sole author of the erroneous table. Ernst, moreover, used it to argue against the efficacy of Na_2EDTA for CAD, so he would have had no reason to exaggerate positive data. In addition to the table in Chappell's article, another table may be pertinent. It is found in a 1993 article by Grier and Meyers in the *Annals of Pharmacotherapy*.[273] We reproduce it as .

Published Results of Chelation Therapy (From Grier and Meyers [1993])[273]

Reference	N	Disease	Outcome Measurement	Result
Case reports				
Clarke et al (1956)[32]	20	CAD	Symptoms	19 improved 1 died
Meltzer (1960)[51]	10	CAD	Symptoms ECG	9 improved 5 improved
Clarke et al (1960)[50]	76 31	CAD PVD	Symptoms	58 improved 27 improved
Kitchell et al (1961)[248]	10	CAD	Symptoms	9 improved
Kitchell et al (1963)[54]	28	CAD	Symptoms	18 improved

			ECG Exercise time	13 less segment changes [*sic*] 1 died 18 increased
Lamar (1964)[52]	15	PVD	Symptoms	15 improved
Lamar (1966)[53]	3 1	CAD PVD	Symptoms Symptoms	1 improved 2 died 1 improved
AAMP (1981)	18	CAD	Symptoms	17 improved
Robinson (1982)	248	Unspecified	Symptoms	not reported
Casdorph and Farr (1983)	4	PVD	Symptoms/signs	4 improved
Olszewer and Carter (1988)[90,91]	844 1130	CAD PVD	Symptoms, ETT Symptoms, signs ETT, Doppler	821 improved 1031 improved
McGillen and Mancini (1988)	1	CAD	Angiography	severe CAD
Godfrey (1990)	27	PVD	Doppler	25 improved
Winebaugh et al (1990)	1	CAD	Angiography	severe CAD
Deycher (1992)	623 215	PVD CAD	Symptoms Symptoms	70% improvement 70% improvement
Longitudinal studies				
Casdorph (1981)[255]	18	CAD	Ejection fraction	17 improved
Riordan et al (1989)	28	Unspecified	Symptoms	18% fewer symptoms

AAMP = American Academy of Medical Preventics; CAD = coronary artery disease; ECG = electrocardiogram; ETT = exercise tolerance test; PVD = peripheral vascular disease

Several of the errors in Drs. Lamas' and Ernst's tables (and , respectively) are present in the table of Grier and Meyers ( ), even if the 3 tables are not identical. Examples of common errors are the "58 improved" entry for Clarke et al (1960),[50] redundant entries for the original Meltzer/Kitchell cohort of 10 subjects,[51,54,248,249] and failure to include those 10 subjects in the entry for Kitchell (1963).[54] Nonsensical numerical entries in Ernst's table (Meltzer 1960,[51] Kitchell 1963,[54] and Lamar 1966[53] in) and in Lamas' table (Kitchell 1963[54] and Lamar 1966[53] in) can be explained as incomplete copies of the corresponding entries in the table of Grier and Meyers ( ). Drs. Lamas and Ernst each cited the article by Grier and Meyers, although neither cited it as a source for his own table. Ernst cited Chappell; Lamas did not.

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By the time the 2003 TACT protocol was issued, a total of nearly 300 subjects had been studied in 4, adequately designed RCTs and several useful substudies of Na_2EDTA for either CAD or PVD.[21-28] In no trial was chelation found to be superior to placebo.

Dr. Lamas reports having studied an additional 40 subjects, of whom 30 were to have been randomized to receive Na_2EDTA, in a "pilot study," PACT. According to the 2003 TACT protocol, the PACT should long ago have been completed.[5] We have asked the investigators and the NIH for its results, even if only in qualitative form, but they have denied us most of this information. We are concerned that there is no published report of the PACT. As previously stated, we suspect that this means that it did not demonstrate a favorable treatment effect.

Are the RCTs to date, even excluding the PACT, adequately powered to detect or exclude a clinically important benefit of chelation for atherosclerosis, contrary to Dr. Lamas' opinion? We think so. The Canadian PATCH study alone was designed to

> ...provide 90% power to detect a 60-second difference in mean change in exercise time from baseline to the 27-week follow-up, assuming an SD of 80 seconds within each group. The 60-second difference was based on a minimally important difference determined by a consensus of Calgary cardiologists.[27]

Independent reviewers from the United Kingdom agreed that the PATCH study was so powered, and called it "well designed and conducted.[267]" Those reviewers, who did not consider the case series at all, observed that it

> ...would require a very large number of participants to test the hypothesis that chelation is more effective than placebo. A study with these numbers is unlikely to be undertaken because it would require considerable funding; it is questionable whether the small effect sizes that may exist have any clinical significance.[267]

We agree that the hypothesis that chelation is merely more effective than placebo is not the correct question to be asking. The correct questions are two, and they are closely related. First, is there support for the standard claims made by chelation advocates over the last 50 years? If not, is there support for a lesser effect that is likely to be useful enough, ie, through a favorable combination of safety and efficacy, to warrant "add[ing] EDTA chelation to the armamentarium for clinicians who treat coronary disease?[2]" In hypothesizing the second question, Dr. Lamas ignored its dependence on the first.

Recall that the standard claims of advocates are that chelation dramatically improves symptoms, objective outcomes, and life expectancy in 80% to 90% of subjects with CAD (and 70 other conditions).[57,152,234] Dr. Lamas has conceded that those claims, at least in regard to cardiovascular disease, have been disproved by the existing RCTs.[29] However, what about the possibility that some lesser but still useful effect is the explanation for chelationists' perceived outcomes? If so we would expect that, among the many series, at least some would have reported such an effect. However, there have been no studies whatsoever -- no case series and no RCTs -- reporting the "small or moderate benefit" proposed by Dr. Lamas.[29] All studies by advocates and "enthusiasts" have been strikingly, implausibly positive; all studies by sober academics, including all credible controlled trials, have been unequivocally negative.

The authors of the PATCH report cautioned that their results "can be applied to fit only a similar population to that studied," and that there "was no difference [between the active and placebo groups] in the number of clinical events, but our study was not powered to detect any such differences." The authors also stated, "Larger trials with a broader range of patients will be needed to assess the safety and impact of EDTA therapy on clinical event rates.[27]"

Such caveats accompany every honest report of a clinical trial. They do not mean, unless the greater scientific and clinical question warrants it and it can be ethically justified, that there must be numerous, additional RCTs to cover every contingency. The PATCH authors, moreover, were referring to those caveats when they wrote that "larger trials...will be needed." If they had considered the low prior probability that chelation works as claimed, the low likelihood that a large trial would yield a clinically significant, as distinguished from a statistically significant, result, and if they had considered the case series and external evidence for toxicity of Na_2EDTA, they might have been more circumspect.

If, as the TACT investigators argue, the existing chelation data truly support pursuing a phase 3 human trial, what about numerous other health claims that have come and gone over the years? Certainly many of those have been disqualified by the same sort of "meager clinical trial data" that, according to Dr. Lamas, "Ernst and others over-interpreted...to come to [the] conclusion" that "chelation for CAD should be discarded.[29]" In fact, many have been so discarded, and rightly so. Two pertinent examples follow.

We have previously mentioned another failed treatment for CAD, bilateral internal mammary artery ligation, which enjoyed brief popularity in the United States at the same time as the early chelation series. It was a simple surgical procedure that could be done with small incisions and local anesthesia.[274] There was an anatomic rationale: Small vessels connect the internal mammary arteries to the coronary arteries. Flow from the former to the latter could, in theory, be enhanced by the increased pressure gradient resulting from downstream mammary artery ligation.[275] Uncontrolled case series involving hundreds of subjects with angina (thousands in the world literature) reported dramatic improvements.[251] Eventually, 3 controlled trials, totaling 47 subjects, reported no differences in outcomes between mammary artery ligation and sham operations, and the practice abruptly ceased.[251,274,276,277]

Thus the evidence against internal mammary artery ligation was similar in kind, but considerably less powered, than is the evidence against chelation. That is, responsible positive case series of mammary artery ligation involved thousands of subjects, whereas negative controlled trials involved only 47 subjects. In the case of chelation, responsible positive case series have involved a few tens of subjects at best. Negative RCTs of chelation have involved almost 300. Yet no competent physician or scientist would consider studying mammary artery ligation now, even though it is simpler, safer, and cheaper than coronary artery bypass grafting, and at least simpler and cheaper than coronary angioplasty -- characteristics frequently cited to justify chelation.[57,106]

Laetrile is the most notorious quack product of modern times.[70-76, 78] It is ineffective and toxic. Its purveyors, many of whom were and are chelationists, prey on desperate people. In justifying the existence of the NCCAM shortly after his appointment as director, the late Stephen Straus cited *Laetrile* as an example of a treatment whose public demand had "abated markedly only after competent studies showed it to be ineffective.[278]" By "competent studies," Straus was referring almost exclusively to a single, uncontrolled case series involving 178 subjects.[279] Laetrile apologists criticized the study for being uncontrolled,[280] but its design was similar to contemporary, preliminary studies of numerous chemotherapeutic agents that were consequently discarded because of no clear evidence of effect.[281]

Thus the trial evidence against *Laetrile* was considerably less rigorous than that against chelation. However, no competent physician or scientist would now call for more trials of *Laetrile*, although a Cochrane Review has done exactly that.[282] That is because its advocates made sensational claims, but as is the case for chelation, *Laetrile* lacked a scientific basis and the first credible case series showed no favorable effects -- only toxicity. It was obvious to ethical physicians at the time that *Laetrile* was fraudulent.[283-285]

Dr. Straus, moreover, was wrong about the demise of *Laetrile*. Its sales had abated markedly 2 years prior to the publication of the case series cited above, for the simple reason that it had become illegal -- against the formal objection of the ACAM.[71,73,76,77,286] Demand, however, persisted, as Straus ought to have known.[287,288] At least 2 TACT co-investigators, Michael Schachter and Jack Slinguff, have prescribed *Laetrile* within the past few years, and another, Stuart Freedenfeld, commends it on his Web site.[191,289,290] Slinguff's *Laetrile* business led to the suspension of his Ohio osteopathic license in 2004, but ClinicalTrials.gov still listed his Lake Cable Medical Center as a chelation study site as recently as March 2007.[38]

The Risks for Na

The established method for investigating the immediate and short-term risks for a drug, after sufficient animal studies have been completed, is the phase 1 trial, which measures responses to incremental doses in order to determine the threshold for toxicity while minimizing the risk for serious injury. There were several early studies of toxicity of Na_2EDTA in animals, but not all questions were answered, and there have been no formal phase 1 studies.

Early human studies, numbering a few hundred subjects, suggested that the most serious reported toxicities, hypocalcemia and renal failure, could be avoided by limits on dosing and rates of infusion.[250,291] Mucocutaneous lesions around the mouth, face, and scrotum were described as similar to lesions of "B complex deficiency," but were thought by some investigators to be due to zinc depletion caused by chelation.[245,291,292] These lesions were rarely reported after investigators lowered Na_2EDTA doses; nevertheless, some began giving zinc, pyridoxine, and riboflavin to subjects undergoing chelation. Burning at infusion sites was common in early studies, but chelation proponents argue that this has been minimized with reduced infusion rates, buffering, and the addition of procaine.[33]

Hypoglycemia in diabetics receiving exogenous insulin, especially insulin to which zinc had been added to reduce solubility, was reported in early studies. This was possibly due to zinc depletion leading to increased solubility, and hence more rapid action, of the exogenous insulin.[293]

Meltzer (1961),[250] which the 2003 TACT protocol erroneously cites as an efficacy series ( ), reported the side effects and toxicities of 2000 Na_2EDTA infusions in an uncontrolled series of 81 adults. Dosing consisted of 3.0 g Na_2EDTA in 500-mL normal saline or glucose solution, infused over 2.5-3 hours. This is similar to the TACT Na_2EDTA regimen, although Meltzer's group typically gave 3 infusions per week, whereas the TACT calls for 1 infusion per week. Unlike the TACT, Meltzer's group did not give zinc, B vitamins, or other additives. The findings are summarized in , reproduced from the original article. The most frequent side effects were burning at injection sites, hypotension (2 cases were "severe," defined as "a drop of systolic pressure of 30 mm or more with distinct hypotensive symptoms"; 23 cases were "moderate," defined as "a drop of systolic pressure of 30 mm with or without symptoms"), nausea, vomiting, abdominal cramping, and symptoms suggestive of hypocalcemia.

Summary of Case Series (From the 2003 TACT Protocol)[5]

First Author (Year)	Sample Size	Outcome Measures	Result
Clarke (1955)[245]	22	Symptoms	Some improvements
Clarke (1956)[32]	20	Symptoms	19 improved, 1 died
Boyle (1957)[246]	20	Symptoms, ECG	Significant improvements
Meltzer (1960)[51]	10	Symptoms, ECG	9 improved
Clarke (1960)[50]	76	Symptoms	58 improved
Kitchell (1961)[248]	10	Symptoms	9 improved
Boyle (1961)[249]	10	Symptoms, ECG	9 improved
Meltzer (1961)[250]	81	Not stated	"Effective"
Kitchell (1963)*[54]	28	Symptoms, ECG	18 improved, [*sic*]
Lamar (1964)[52]	15	Symptoms	15 improved
Lamar (1966)[53]	3	Symptoms	1 improved, 1 died
Evers (1979)[256]	3000	Symptoms	> 90% improved
Casdorph (1981)*[255]	18	Ejection fraction	17 improved
Robinson (1982)	248	Symptoms, ECG	Significant improvements
Olszewer (1988)*[90,91]	844	Symptoms	821 improved
McGillen (1988)	1	Angiography	No evidence of benefit
Wirebaugh [*sic*] (1990)	1	Angiography	No evidence of benefit
Deycher (1992)	215	Symptoms	70% improvement
Hancke (1992)	42	Need for surgery	39 canceled surgery
Hancke (1993)[269]	470	Symptoms	Significant improvements

ECG = electrocardiogram
**Described in text*
From the 2003 TACT protocol.[5] The asterisks, designating "described in text," are present in the original and refer to descriptions of 3 of the reports on pages 7-8 of the protocol. Reports with reference numbers in superscript are discussed in this article.

Side Effects of EDTA Administered With 2000 Infusions (From Meltzer [1961])[250]

Side Effect	Frequency of Occurrence
A. Renal Damage (increase in BUN, decrease in PSP excretion, cylindruria, hematuria, or persistent albuminuria greater than 1+	0

B. Burning at Injection Site or along course of vein:	
Initially only	30
Throughout infusion	68
C. Thrombophlebitis	1
D. Hypotension: Mild: a drop of systolic pressure of 20 mm without symptoms	8
Moderate: a drop of systolic pressure of 30 mm with or without symptoms	23
Severe: a drop of 30 mm or more with distinct hypotensive symptoms	2
E. Hypocalcemia: Mild: numbness, tinkling [*sic*] at circumoral area or leg cramps or muscle spasm	20
Severe: signs of tetany (Chvostek's sign, and others) or fall in serum calcium to 7 mg 100 mL	0
F. Systemic Reactions (febrile reaction, malaise, fatigue, headache, anorexia)	0
G. Histamine-like reactions (sneezing, lacrimation, nasal congestion)	0
H. Anemia or other hematopoietic changes related to treatment	0
I. Glycosuria or hyperglycemia	0
J. Dermatitis (presumably due to pyridoxine deficiency)	0
K. Nausea + vomiting: Mild	15
Moderate	1
Severe	2
Abdominal cramps or pain	2

Meltzer and colleagues also reported "a period of asthenia and lethargy described by several patients for 24 hours following an infusion.[250]" In 14 subjects whose hands and wrists were studied by "serial roentgenographic examinations using graded densities," the authors found no evidence of bone loss.

The only reliable, if incomplete, risk data from more recent trials come from RCTs. Guldager and colleagues gave 20 infusions of 3.0 g Na_2EDTA or placebo, 2-3 times per week, to 159 subjects.[21] Of 6 subjects who dropped out during the treatment period, 5 were in the EDTA group; one of these dropped out due to "impaired renal function," but no more information was given. Proteinuria occurred in 10 chelation subjects and 4 placebo subjects, but there were no overall differences in serum creatinine values between the 2 groups. There were some differences in other side effects: "Faintness" occurred in 11 chelation subjects and 1 placebo subject, but the authors did not report corresponding blood pressures or ECG findings. "Hypocalcemic symptoms" occurred in 6 subjects in the chelation group and 2 subjects in the placebo group, but only 1 subject -- in the chelation group -- "showed subnormal calcium levels." One subject in the chelation group had "Raynaud's phenomenon of two fingers" that persisted for 4 days. In a substudy of 54 subjects, there was biochemical evidence of bone loss in the chelation group.[23]

The van Rij trial, in which 15 subjects received Na_2EDTA, reported no differences between active and placebo groups.[25] That was also the case for the Hopf trial, in which 8 subjects received Na_2EDTA.[26]

In the PATCH study, with twice-weekly dosing for 15 weeks, 1 of 41 subjects in the Na_2EDTA group was withdrawn after 10 treatments because of a rise in serum creatinine from 1.5 to 2.1 mg/dL, for which "no other cause...was found.[27]" That subject's creatinine reverted to 1.6 mg/dL after 10 weeks. The PATCH reported no other toxicities suggestive of Na_2EDTA per se, but did not mention minor complications or side effects.

Dr. Lamas conducted a "pilot" trial, PACT, with a treatment regimen similar to the TACT, involving 40 subjects, 30 of whom received Na_2EDTA. He reported some of the safety results in the 2003 TACT protocol.[5] One subject developed "atrial fibrillation with a slow ventricular rate, and, secondarily, heart failure"; another had "a significant increase in AST and ALT"; another had an episode of "transient hypotension, which resolved within 15 minutes." There was "a benign course of creatinine levels.[5]" Lesser "adverse events" may have occurred, but the table reporting them was "withheld in entirety proprietary information" [*sic*] from the copy that we received through a FOIA request.[5]

Thus safety data from credible studies are limited to about 255 chelation subjects (175 from the RCTs, 80 from Meltzer), most of whom received 20-30 infusions of 3 g Na_2EDTA, given 1-3 times per week over 2.5-3 hours. Potentially serious complications occurred in at least 7 or 8 subjects: renal insufficiency in 1 or 2, elevated liver enzymes, hypocalcemia, and congestive heart failure in 1 subject each, and symptomatic hypotension in at least 3 subjects and possibly as many as 37. In the Meltzer study, 20 more subjects had symptomatic evidence of hypocalcemia, a potentially life-threatening complication, but this was not objectively documented. In the Guldager study, 11 subjects had symptomatic evidence of hypotension (faintness), but this was not objectively documented.

Episodes of discomfort in addition to faintness, including burning at the infusion site, gastrointestinal symptoms, and the "period of asthenia and lethargy" described by Meltzer, appear to be more common, but in the Guldager study -- the only RCT to report these in detail -- there was no real difference between the active and the placebo groups. A Guldager substudy suggested that repeated infusions of Na_2EDTA cause bone loss.[23] That could be of particular importance in postmenopausal women, who are certainly among the subjects in the TACT.

Overall, these data suggest that in well-monitored circumstances, the risk for a serious, but probably manageable, complication occurring at some time during a course of 20-30 infusions is in the realm of 1% to 5%; the risk for minor but annoying side effects is probably 5% to 20%; there is almost certainly decalcification of bone, because excreted calcium must be replaced from the body's stores, but it may be quickly replenished from dietary sources and hence inconsequential -- or perhaps not, especially in postmenopausal women. We simply don't know. The risks for other long-term or subtle complications, some of which are discussed below, are also unknown.

We are aware that these estimates are based on small samples from disparate sources and are therefore subject to error, possibly considerable error. The point, however, is that there is adequate reason to judge the risks for chelation, even when administered carefully in a monitored

research environment, to be substantially more than trivial. The onus is not on us to justify a precise number or range; the onus is on investigators to justify exposing human subjects to such risks.

In addition to trials, other sources provide ample evidence of risks for chelation. These include case reports in the medical literature; case reports not in the medical literature, such as expert witness reports in criminal and disciplinary cases; theoretical risks for Na_2EDTA that may be apparent only in certain circumstances; and risks, both theoretical and supported by previous studies, of the supplements used in the TACT.

We have previously cited deaths associated with the chelation practice of H. Ray Evers.[18] These were judged due to renal failure, congestive heart failure, and hypoglycemia. There is evidence that Dr. Evers could have prevented several deaths if he had identified and managed complications in a timely and competent fashion.[65] The initial complications would nevertheless have remained. The only significant difference between the dosing of Na_2EDTA in Dr. Evers' cases and that of the TACT is that Evers gave infusions 5 times/week for 3-4 weeks, followed by an indefinite rest period, whereas the TACT gives 1 infusion/week for 30 weeks. That difference may explain Evers' complications, but perhaps not: Dr. J. David Spence, one of the government's expert witnesses, reckoned that over a 2-year period at Meadowbrook Hospital, Evers had treated about 600-700 patients with chelation. The incidence of serious complications on the basis of only deaths -- as few as 13 or as many as 21 -- was thus 1.8% to 3.5%, similar to the incidence of serious, albeit appropriately treated, complications reported by the trials cited above.

At least 9 more chelation-related deaths have been reported in the past 15 years.[13-17, 19,20] Some occurred during or shortly after an infusion, or were found to be due to hypocalcemia, thus indicating toxicity of the drug. Others occurred the day after an infusion or at a time unspecified in the report. Those may have been due to drug toxicity or to "heart attack," as stated by a couple of the reports, suggesting another sort of complication: the "opportunity cost" of not having received an effective intervention. These reports are necessarily anecdotal because they occurred outside of human trials and were investigated after the fact by regulators or expert witnesses. It is thus unsurprising that advocates have excused such deaths as not having been due to chelation, or due to chelation administered not "in accordance with established guidelines.[30,92]"

In most cases, however, the practitioners have been members of the ACAM, which promulgates those guidelines.[33] One, Neil Ahner, is a "past director" of the ACAM and "board certified" in chelation therapy.[17, 294-296] Another, the late Dan Christian Roehm, was listed, in the 1986 membership roster, as a Director of the AAMP (the former name of the ACAM).[17,297] Another, Elmer Cranton, is a former ACAM president and one of the "prominent experts" named to the TACT Liaison Committee.[4,19]

The practitioner impugned in the 2005 hypocalcemic death of an autistic 5-year-old in Pennsylvania is an ACAM member and a self-styled expert in "mercury poisoning.[13,108,298,299]" There is now evidence that he infused 1 g of Na_2EDTA into the 20-kg boy over 5 minutes -- an extremely dangerous rate.[108] The naturopath involved in the 2003 hypocalcemic death of a woman in Oregon, who chelated her to "remove heavy metals," is also a member of the ACAM.[13,109,300]

Serious but nonfatal complications of chelation are likely to be at least as common as deaths, but for obvious reasons are less likely to be reported. According to a 2003 Board Action in Connecticut, 1 of 3 charts reviewed in an investigation of a chelationist's practice revealed that in 2002, "during an IV infusion of EDTA, [the patient] became lethargic and incoherent and developed rales in her chest.[301]" This suggests hypocalcemia and/or congestive heart failure, 2 well-described, life-threatening complications of Na_2EDTA infusions. The chelationist was Robban Sica, an ACAM member and a "Director" of the ABCMT, the ACAM's "certification" organization.[218] Between 1999 and 2001, Dr. Sica had been a defendant in 3 lawsuits alleging insurance fraud, racketeering, and sham ownership of medical professional corporations, each time settled by confidential agreement or consent agreement.[118] In 2005 she signed a Consent Order that placed her Connecticut license on probation for 1 year, pending correction of substandard and dangerous practices involving chelation, including erroneous diagnoses of "heavy metal toxicity.[302]" Sica is now a TACT co-investigator.[7]

A 2002 article reported 5 patients evaluated at the Emory University, Atlanta, Georgia, emergency department after they had become "ill 30 min to 2 h into iv chelation therapy at an outpatient clinic.[303]" The treating chelationist, who was not identified in the report, described an infusion regimen essentially similar to that of the ACAM protocol. All 5 patients had "gastrointestinal and musculoskeletal symptoms," fever, and hypotension. Four had leukopenia, proteinuria, and ketonuria. Three had hypocalcemia, hematuria, and transient rises in blood urea nitrogen (BUN) and creatinine. Two had hyaline casts in their urine. Four required admission to the hospital, 2 to the intensive care unit. After "3-5 d, all were discharged without permanent sequellae." The authors surmised that the complications were due to "errors in dosage or the rate at which the formulation was infused.[303]" Alternatively, the complications may not have been due to errors in dosing or infusion rates, but to Na_2EDTA or other agents in the chelation mixture given at the intended doses and infusion rates.

The same article reported that "the Georgia Medical Board has investigated several [other] cases related to complications of chelation therapy treatments.[303]" On the basis of the substantial experience of one of us (RSB) in reviewing chelation cases, we believe that complications from chelation "as practiced in the community" are fairly common but underreported.

All observers agree that the more rapidly Na_2EDTA is infused, the more likely it is to cause dangerous hypocalcemia.[5,55,291,304] Soffer and colleagues[55,304] reported that the only reliable, early sign of clinically important hypocalcemia in their series had been prolongation of the QT interval:

> Hypocalcemic tetany may appear with terrifying suddenness, even moments after Chvostek's and Trousseau's signs are noted to be negative. A rapid increase in heart rate and the appearance of an advanced hypocalcemic electrocardiographic pattern are the best signs of impending crisis.[304]

The Na_2EDTA (*Endrate*) prescribing information, mimicked by the ACAM and TACT protocols, stipulates a dose in adults of no more than 3 g to be infused over at least 3 hours.[5,12,33] Nevertheless, unintended variations in IV flow rates are inevitable, prompting one of the expert witnesses in the Evers case to argue that if Na_2EDTA were to be infused at all, it should be done with continuous nursing care, continuous ECG monitoring, and infusion pumps.[65,66] That was 30 years ago. Today, neither the ACAM protocol nor the TACT requires these safeguards.[5,33] Thus occasional episodes of hypocalcemia will continue to be unsurprising.

ACAM members acknowledge that

> ...there can be a febrile systemic reaction that may occur 4 to 8 hours after infusion of EDTA...characterized by a rapid onset of malaise, fatigue, and excessive thirst followed by the sudden appearance of chills and fever. This, in turn, is followed by severe myalgia, frontal headaches, anorexia, occasional nausea and vomiting, and rarely, increased urinary frequency and urgency.[33]

The prescribing information for *Endrate* warns, in addition to the complications already mentioned, of postural hypotension, generalized dermatitis, hyperuricemia, and more.[12]

At least 1 author has warned of the enhanced potential for chelation to injure the kidneys of occasional patients who genuinely have elevated levels of certain heavy metals, especially cadmium.[78] Although rare, such people are not excluded from the TACT, because there is no preliminary screening for heavy metals.

We have previously cited evidence for pro-oxidant effects of iron chelated by EDTA.[147-149] More recent work has replicated this finding.[236] There is also evidence that the pro-oxidant effects of iron are enhanced by ascorbate,[150,237,238] although the physiologic significance of this is unclear.[241]

In the absence of testing for markers of oxidative stress, pro-oxidant effects cannot be measured directly in the TACT. They can only be suggested by an excess of long-term, unwelcome clinical consequences in the active treatment groups, that is, only after some subjects have been harmed. In order to be eligible for the TACT, moreover, all subjects must have CAD, the result of a process that is thought to be accelerated by oxidative stress. Such an entry criterion is useful for detecting reductions in events that would typically be common for the entire study cohort. For the same reason, however, this entry criterion -- in effect, a "proxy" for oxidative stress -- hinders the study's capacity to detect increases in such events. Thus if the chelation regimen has harmful, pro-oxidant effects, the TACT cannot detect them before injuries have occurred, and perhaps not at all.

Antioxidant trials have not only failed to demonstrate efficacy,[305] but have suggested that some of the "high dose vitamin and mineral supplements" advocated by the ACAM and included in the TACT are dangerous. Vitamins E and A and beta-carotene have been associated with a small excess of congestive heart failure and all-cause mortality.[306,307] Vitamin A has been associated with reduced bone density and hip fractures,[308,309] which are of particular importance in postmenopausal women, and even more so in light of evidence that Na_2EDTA itself causes bone loss.[23] Vitamin C given orally in doses of 60-2000 mg/day appears to be harmless,[307] but as suggested above, the TACT regimen of 7000 mg given intravenously with Na_2EDTA may be a different matter.[4,5]

Vitamin C as administered in the TACT confers another risk that would not have been apparent in other antioxidant trials. Seven grams of ascorbate contain, according to the ACAM protocol, more than 600 mg Na+.[33] Together with 600 mg of Na+ in 3 g of Na_2EDTA,[65] this means that each chelation infusion has the same amount of sodium as 1 L of 3% NaCl or 3 L of normal saline. Thus the risk for volume overload is substantially increased by the addition of high doses of vitamin C.

An indirect risk for chelation, suggested by NCCAM Director Straus[2] but not specifically acknowledged in the TACT protocols, is that its advocates frequently denigrate proven interventions.[7,199, 228-230] The risk that subjects might not receive effective therapies must be judged greater in the TACT, in which the bulk of co-investigators are chelationists, than in other NIH-sponsored trials.

The TACT protocols ignore or minimize several of the risks described above. In regard to responsible trials, the 2003 protocol concludes: "...the data on adverse events are reassuring...; we expect a low rate of adverse events and an overall safe intervention.[5]" The first paragraph of the 2003 protocol, citing a 2001 "textbook" edited by Elmer Cranton,[310] states: "It has been estimated that in the last few years, over one million patients received over 20 million infusions 'with no serious adverse effects,' but this has not been well-documented.[5]" What have been well documented, but unstated in the protocol, are the serious adverse effects reported above. Cranton himself had a chelation-related death only a year before the publication of his textbook.[19]

The 2001 protocol, which was the application that the NIH approved in awarding the grant to Dr. Lamas, relies mainly on the ACAM's assessment of risk:

> ...safety considerations may lead to our suspending infusions on some patients; however, based on the clinical experience of the ACAM, we expect this number to be very small.... The chelation protocol used at present has been published by ACAM...is in use in hundreds of thousands of infusions yearly, and is thought to be safe.... The chelation protocol has been in use for years and has been found to be quite safe by chelation practitioners.... The DSMB [Data Safety and Monitoring Board] will remain independent, as it will be selected by the NCCAM.[4]

We wonder whether the NIH Special Emphasis Committee and the relevant IRBs were aware, when they reviewed that document, that the ACAM had consistently misrepresented Na_2EDTA and its dangers. It continues to do so, as typified by this press release:

> ...IV EDTA is an FDA approved treatment for lead toxicity in children and adults, with an excellent track record for safety. Millions of infusions have been administered over the last 30 + years, without any deaths being noted, when used in accordance with established guidelines.[30]

Na_2EDTA is not an FDA-approved treatment for lead toxicity.[12] Several deaths have been "noted," as documented above. The same press release claims that the very existence of the TACT shows that the NIH has deemed chelation safe:

> In fact, the TACT study (Trial to Assess Chelation Therapy), has been in progress, with a goal to assess the efficacy of Chelation Therapy in close to 2,400 patients. In launching this NIH sponsored study, the safety of IV EDTA was accepted to have been firmly established [*sic*].[30]

The 2001 protocol, however, states that "...assessment of safety is an important secondary endpoint of the trial.[4]" In pitching the TACT to prospective subjects, the NCCAM Web site does not assert that the safety of IV EDTA has been "firmly established." On the contrary, it states that the TACT "will assess whether EDTA chelation therapy and/or high-dose vitamin/mineral supplements are safe and effective in treating individuals with CAD.[3]"

The TACT is expected to have an independent Data Safety and Monitoring Board (DSMB). According to the TACT RFA: "At the time of award, the Awardee will be requested to nominate prospective DSMB members to the Director of NCCAM, who will select the DSMB members.[1]" We wonder whether Awardee Lamas told Director Straus that Robert Nash, who has identified himself as a member of the TACT DSMB,[47] is an ACAM board member and recent chairman of the ACAM's "credentialing" organization, the ABCMT. The ABCMT, like the ACAM itself, claims that "established detoxification techniques [e.g., chelation] have been proven safe and effective over time....[102]" Nash is the author of a 2004 letter admonishing all state medical boards to accept the "ABCMT Standard of Care for Increased Total Body Burden of Toxic Metals.[115]"

TACT Co-Investigator Robban Sica offered Nash as an expert witness in her failed 2004 federal lawsuit attempting to stop the Connecticut Bureau of Health Care Systems from disciplining her for substandard practices involving chelating agents.[119] Nash, Sica, Martin Dayton, Ted Rozema, James Carter, Terry Chappell, and other TACT co-investigators are fellow members or advisors of the ABCMT Board or the board of another close affiliate of the ACAM, the ICIM.[218,311] If Nash is a member of the TACT DSMB, that committee would appear not to be independent of pro-chelation activism.

Neither of the TACT protocols acknowledges reports of chelation-related deaths "in the last 30+ years," although such reports are easy to find. The protocols should have mentioned Evers' deaths in particular,[18] because his "3000 cases[256]" constitute a large fraction of Lamas' "thousands of patients with successful outcomes[29]" ( ). Evers' deaths also argue that nephrotoxicity is a more substantial risk than the TACT protocols admit. In minimizing that risk, Dr. Lamas cites an article co-authored by Edward McDonagh,[4,174] the chelationist who admitted under oath to having falsified his data.[44]

Summary of Case Series (From the 2003 TACT Protocol)[5]

First Author (Year)	Sample Size	Outcome Measures	Result
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Hancke (1992)	42	Need for surgery	39 canceled surgery
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ECG = electrocardiogram
**Described in text*
From the 2003 TACT protocol.[5] The asterisks, designating "described in text," are present in the original and refer to descriptions of 3 of the reports on pages 7-8 of the protocol. Reports with reference numbers in superscript are discussed in this article.

The TACT protocols concede that acute hypocalcemia is likely to occur when Na_2EDTA is infused too rapidly. Nevertheless, the only systematic safeguard is a recommendation to use "the smallest gauge catheter or a 25 gauge butterfly needle as this will limit the maximum infusion rate.[4]" This cannot be relied on to prevent rapid infusions. It may, however, result in inadequate IV access when emergency treatments become necessary.

The 2001 TACT protocol does not raise the possibility of bone loss; the 2003 protocol does, but dismisses it without citing the study that most convincingly suggests that it occurs.[23] Instead it cites another article, again co-authored by admitted defrauder McDonagh, that reported no evidence of bone loss by bone densitometry.[175]

The 2003 TACT protocol does not address evidence that chelation may have prooxidant effects. The 2001 protocol mentions that "iron...may remain in a redox active state when bound to EDTA," but does not elaborate on the clinical implications, and asserts that this doesn't happen "when there is a molar excess of EDTA, as is the case in plasma following high-dose EDTA infusion.[4]" In support of that assertion, the protocol cites an article describing in vitro Fe-dependent superoxide modification of low-density lipoprotein (LDL) in preparations containing smooth muscle cells and Fe at a concentration of 10 micromoles (mcM).[312] According to the article, however, "EDTA stimulated Fe-promoted modification [of LDL] in the 1-100 mcM range.[312]" Thus EDTA, even at a concentration 10-fold greater than that of the iron in the preparation, increased free radical damage -- contrary to the assertion in the 2001 protocol, but exactly as predicted by other, uncited articles.[147,148] The protocol does not justify its assertion about concentrations of Fe and EDTA "in plasma following high-dose EDTA infusion," nor does it define "high-dose EDTA infusion.[4]"

The protocols do not mention risks for the high doses of vitamins that are included in 2 of the 4 arms of the trial, although the authors should have been aware of reports suggesting excess mortality and bone loss.[308,309,313,314]

Dr. Lamas has repeatedly asserted that chelation for CAD is in a "state of equipoise" or a "state of clinical equipoise.[4,5,29]" "Equipoise," in regard to clinical trials, refers to the ethical requirement for "a state of genuine uncertainty...regarding the comparative therapeutic merits of each arm in a trial.[45]" For a number of reasons this requirement has been challenged, but it is not our intention to engage in that controversy here.[315-318] Rather, we respond to the use of the term in the context of the TACT.

According to the 2003 TACT protocol:

> In general, the timing of a trial is a delicate matter. On the one hand, there must be sufficient belief in a favorable benefit to risk ratio of the intervention to justify exposing half the subjects. On the other hand, there must be sufficient doubt to justify withholding the intervention from the other half. Thus a state of equipoise exists. From a clinical and public health perspective, chelation is in equipoise....[5]

But is it? Revisiting the "2 x 2" design of the TACT, a state of equipoise requires that current knowledge predict similar risk-benefit ratios for each of the 4 arms. However, the available evidence predicts that the 2 Na_2EDTA groups are at substantially greater risk, relative to potential benefits, than the 2 placebo groups. The 2 high-dose supplement groups appear to be at slightly greater risk, relative to potential benefits, than the 2 low-dose supplement groups. Thus there is no state of equipoise.

Paradoxically, the majority of co-investigators in the TACT also disagree with Dr. Lamas that chelation is in a state of equipoise: They are chelationists who profess a certitude opposite to what the available evidence warrants. In 1987 Freedman argued that requiring individual investigators to make judgments of equipoise is unreasonable, because they frequently prefer one treatment over the other(s). He proposed, instead, the "concept of 'clinical equipoise,' the requirement [for which] is satisfied if there is genuine uncertainty within the expert medical community -- not necessarily on the part of the individual investigator -- about the preferred treatment.[45]"

Thus if chelation for CAD is to be judged in a state of clinical equipoise, experts in cardiovascular disease and clinical trials should make that judgment.

Such experts, however, have consistently argued otherwise. In 2000 the NHLBI Advisory Council, chaired by NHLBI Director Claude Lenfant, rejected a proposed chelation trial in part because of "the paucity of scientific evidence" and "the potential long-term toxicity for bone disease, especially in post-menopausal women.[169]" That was prior to the publication of the Canadian PATCH trial, which would only bolster the scientific evidence against the method.[27,28] The AHA has written: "According to qualified scientists who are familiar with research in heart disease, there's only a very small chance that chelation therapy will work.[232]" The AHA, furthermore, would support a human trial only if, in a preliminary study, "EDTA had been proven successful in reducing arterial plaque without dangerous side effects.[232]" Because no such study has occurred, it follows that the AHA and "qualified scientists," ie, experts, do not favor the TACT.

Cardiologists in general seem to lack enthusiasm for the TACT. Chelationist Co-Investigator John Gannage reported that the recent expansion of the trial to "chelation sites" in Canada was necessitated by the failure of American cardiologists to recruit subjects.[195] Finally, it is reasonable to suppose that the many learned chelation skeptics writing in the 1970s and 1980s, prior to any controlled trials, would be all the more skeptical now that subsequent RCTs have uniformly failed to support the treatment.[9-11, 63,65,78, 124-128, 253]

We wonder whether Dr. Lamas' description of ACAM members as "prominent experts" was born less of naiveté or patronization, and more of cynicism: that to counter real experts refuting his claim of clinical equipoise, he would need to conjure experts of another sort.

Discussion

The argument made in the *American Heart Journal* and in the TACT protocols, that "case series encompass[ing] thousands of patients with successful outcomes[29]" are adequate to justify a large trial of Na_2EDTA chelation despite previous, negative RCTs with an aggregate sample size of 275, is not supported by a rigorous appraisal of those case series. The early case series were honest attempts to investigate a method that at first seemed promising according to the understanding of atherosclerosis and the clinical investigations at the time; within a few years it had become clear that the method was not useful. In regard to the later series, there is ample evidence, both in the articles themselves and in other sources, of implausible results and of bias in the extreme. The later series are not credible as case reports; they are better characterized, to quote Alfred Soffer, as the offerings of "pseudoscientific zealots.[9-11]"

Thus the few, credible case reports agree with the RCTs: There is no evidence that chelation is a useful treatment for cardiovascular disease. On the contrary, the weight of the evidence from both the case series and the RCTs argues that chelation is ineffective, even if this conclusion has not been proved beyond a shadow of a doubt -- as, logically, it can never be.

Nor has it been shown that "established guidelines" render IV disodium EDTA and megadoses of supplements safe. Responsible trials have reported a small but significant incidence of potentially life-threatening complications and a larger incidence of minor but uncomfortable side effects. There is ample additional evidence -- found predominantly in court opinions and newspapers, not cited by the TACT protocols -- of deaths and serious injuries associated with chelation given by ACAM members. There is laboratory evidence that the "standard" chelation solution may increase oxidative stress. In estimating risk, the NIH might reconsider its confidence in "the clinical experience of the ACAM,[4]" which has continually misrepresented the issue.

What, then, of the hypothetical "small to moderate benefit[29]" that has never been reported? This explanation for the chelation phenomenon -- in essence, that advocates' far-fetched claims are simple exaggerations of modest efficacy -- is unlikely. Far more likely are the classic errors in judgment that have encouraged advocates of every spurious therapeutic claim throughout history, eg, failure to recognize the variable course of symptoms, the post hoc fallacy, errors in diagnosis, confirmation bias, affirmation bias, selection bias, social and cultural biases, demand characteristics, and all of the rest.[319]

In the early years of chelation, "enthusiasts" exaggerated those judgmental errors because the usual primary outcome, a reduction in angina pectoris, was especially sensitive to a "placebo effect.[126,251,252,262]" Later, chelation zealots exaggerated them further, spurred by abundant financial rewards,[58,59] by other chelationists' flawed "studies"( ), and by fraud.[44] It is no mere coincidence that chelationists peddle myriad additional treatments, most famously *Laetrile*, that resemble one another only in being pseudoscientific and lucrative.[7]

Summary of Case Series (From the 2003 TACT Protocol)[5]

First Author (Year)	Sample Size	Outcome Measures	Result
Clarke (1955)[245]	22	Symptoms	Some improvements
Clarke (1956)[32]	20	Symptoms	19 improved, 1 died
Boyle (1957)[246]	20	Symptoms, ECG	Significant improvements
Meltzer (1960)[51]	10	Symptoms, ECG	9 improved
Clarke (1960)[50]	76	Symptoms	58 improved
Kitchell (1961)[248]	10	Symptoms	9 improved
Boyle (1961)[249]	10	Symptoms, ECG	9 improved
Meltzer (1961)[250]	81	Not stated	"Effective"
Kitchell (1963)*[54]	28	Symptoms, ECG	18 improved, [*sic*]
Lamar (1964)[52]	15	Symptoms	15 improved

Lamar (1966)[53]	3	Symptoms	1 improved, 1 died
Evers (1979)[256]	3000	Symptoms	> 90% improved
Casdorph (1981)*[255]	18	Ejection fraction	17 improved
Robinson (1982)	248	Symptoms, ECG	Significant improvements
Olszewer (1988)*[90,91]	844	Symptoms	821 improved
McGillen (1988)	1	Angiography	No evidence of benefit
Wirebaugh [*sic*] (1990)	1	Angiography	No evidence of benefit
Deycher (1992)	215	Symptoms	70% improvement
Hancke (1992)	42	Need for surgery	39 canceled surgery
Hancke (1993)[269]	470	Symptoms	Significant improvements

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Randomized, blind, controlled trials were devised to correct for such judgmental errors. Although RCTs may not be perfect, a few such trials from disparate sources, unanimously showing no advantage for chelation, carry far more weight than chelationists' opinions. In the historical context of chelation promoted as a treatment for atherosclerosis, such "absence of evidence of efficacy" constitutes substantial "evidence of absence of efficacy," contrary to Dr. Lamas' assertion.[29] Underpowered or not, the RCTs and the rest of the "totality of the evidence[5]" -- case series that are either disconfirming or not credible, implausible hypothesized mechanisms, evidence of substantial risks, evidence of pro-oxidant effects, and advocacy arising exclusively from biased, unreliable sources -- refute the claim of equipoise.

These are compelling reasons to limit any current investigations of unapproved uses of Na_2EDTA, if they can be justified at all, to laboratory and animal studies -- as stipulated, for example, by paragraph 11 of the Helsinki Declaration:

> Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.[176]

What, then, induced the NIH to proceed with the TACT, so shortly after the NHLBI scientific review panel had overwhelmingly rejected a proposal for a similar study?[169] The evidence suggests that the NIH solicited the trial only after extraordinary pressure from a powerful congressman and from the ACAM lobby.[41,42,168,171,173] Those applying the pressure must have been content to redirect it to the nascent NCCAM, because they knew that this NIH Center had been established exactly for that purpose: to provide a diversion for legislators who imagined that they and a few of their constituents were better than real scientists at distinguishing between the plausible and the implausible.[172]

That "the fix was in" is suggested by the ACAM's intimate involvement in the stated rationale, in the planning (even prior to the Burton Hearing),[4] and in the execution of the trial. It can also be inferred from the choice of the more dangerous disodium salt of EDTA -- otherwise pointless, given Dr. Lamas' rejection of decalcification in favor of the heavy metals hypothesis[4] -- and from the presence of 2 ideologues on key oversight committees: past ACAM President L. Terry Chappell on the "Special Emphasis Committee" that reviewed Dr. Lamas' original protocol,[39] and past ABCMT Chairman Robert Nash on the DSMB.[47] Each of these appointments violated formal NIH policies.[183]

Even so, it seems that it was necessary to fashion a scientific and social case for the trial. Thus the "lack of adequate prior research" and the "widespread use of chelation therapy in lieu of established therapies" made the TACT a "public health imperative.[2]" The results "will provide either a significant positive result or an informative null result,[4]" which will "lead to changes in clinical practice, ultimately benefitting patients.[29]"

Such a case could only be justified by misrepresenting the science and the tiny subculture in which chelation thrives. TACT literature includes numerous examples of factual errors, language distortions, and failures to cite "relevant sources of information.[176]" Some examples seem purposeful, eg, the misleading descriptions of case series on pp. 7-8 of the 2003 protocol,[5] or the erroneous portrayal of an article that reported pro-oxidant effects of iron in the presence of EDTA.[4,312] Others seem merely lazy: the duplications and other errors in that appear to have been copied from another source, or the recurrent citations, in both TACT protocols and in a 2006 editorial by Dr. Lamas in the *British Journal of Cardiology*,[49] of a 1982 article[320] as the source of a statement that could not have been made until at least 1993. The *BJC* editorial contains more inaccuracies.

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In his 2000 editorial in the *American Heart Journal*, Dr. Lamas inflated the number of patients who receive chelation in a year by a factor of at least 20.[29] Later the NCCAM and the TACT protocols offered a reduced estimate, but not plainly so: Rather than report the number of patients, they reported the number of "visits," only mentioning elsewhere that each patient typically makes at least 30 visits in the first year.[2-5] In the recent *British Journal of Cardiology* editorial, Dr. Lamas offered yet another estimate, 3-4 times the likely reality, on the basis of a survey that had warned that its chelation estimate did "not meet [the] standard of reliability or precision[321]" -- a point that Dr. Lamas failed to mention. Intentional or not, such obscurities have nurtured the myth of "widespread use," a chief rationale for the TACT.

Against all prior experience, Dr. Lamas initially declared that a large chelation trial would "lead to changes in clinical practice.[29]" Later the TACT protocols retreated from that position, but not so much that a naive reader might have suspected the truth: "a...result upon which rational clinical decision-making and health policy *can* be based[4]" [emphasis added]. By the time he wrote his *American Heart Journal* editorial, Dr. Lamas should have known enough to predict that no amount of scientific evidence would be likely to change chelationists' claims. The NHLBI Scientific Review Committee[169] had correctly made that observation just prior to the publications of the PATCH reports,[27,28] even though the committee lacked Dr. Lamas' advantage of having spent more than a year collaborating with chelationists and, ostensibly, researching chelation literature.[4]

TACT literature has repeatedly conflated Na_2EDTA and the safer CaEDTA, as typified by the false assertion that "EDTA...is approved by the U.S. Food and Drug Administration (FDA) for use in treating lead poisoning and toxicity from other heavy metals.[2]" More misrepresentations include the citations of several articles by a chelationist who had previously admitted under oath to having falsified his data[44]; failure to cite 2 substudies of the Danish RCT, one reporting evidence of bone loss[23] and the other demonstrating discrepancies between outcomes reported by academic researchers and those reported by chelationists[24]; the unexplained absence, in the 2003 protocol, of the "markers of oxidative stress" TACT substudy that had been stipulated by the RFA and included in the 2001 protocol[1,4]; and the failure to cite several biochemistry articles that reported pro-oxidant effects of EDTA and vitamin C.

Chelationists constitute a tiny, fringe group of practitioners who encourage a tinier fraction of the population to buy chelation and other dubious treatments, and to eschew established therapies. Their history is replete with pseudoscientific and unethical practices; it is also replete with regulatory and criminal investigations and sanctions, some involving TACT co-investigators even since the trial began.[200,201] TACT literature gives not the slightest hint of that sordid history: Only 3 years after the FTC had cited the ACAM for falsely advertising chelation, the prestigious NIH endorsed it as "the world's...most respected organization of physicians who employ chelation therapy.[4,163]" Only a year after the FDA had exposed the GLACM IRB as a ruse to shield quackery from the law, the NIH approved the TACT's description of its members as "prominent experts.[4,140,141]"

The TACT consent form reflects much of this misleading language.[6] It blurs the distinction between the 2 EDTA salts: It neglects to mention that the EDTA used for lead poisoning is typically infused in the hospital with continuous monitoring and nursing care, whereas the EDTA used in the TACT is both inherently more dangerous and is administered in a more dangerous way. The form omits the relevant scientific and social background of chelation. It lacks an honest appraisal of the prior evidence. It omits several reported risks. Its straight-faced reference to "a standard intravenous mixture established by the American College for Advancement in Medicine" suggests, to the unsuspecting subject, a promising investigational treatment endorsed by a professional organization comparable in legitimacy to the American College of Cardiology.

All in all, such misrepresentations have served to submit 2000 unwary subjects and $30 million of public money to an unethical trial of a dubious treatment that, had it been accurately represented and judged by the usual criteria, would certainly have been disqualified again.

Even if the TACT is completed, which it should not be, it is unlikely to reduce the promotion of reckless uses of Na_2EDTA. Whatever the outcome, chelationists have already positioned themselves to continue the practice: By virtue of ridding the body of toxic heavy metals, they claim, chelation is useful for more than 70 conditions. Without exception, chelationists have refused to accept previous results that contradict their beliefs.[57, 152-162] Their response to the TACT, should it yield definitive, negative results, is unlikely to be different.

The trial, moreover, is unlikely to yield "an informative negative result[49]" even though chelation is almost certainly ineffective for CAD. It is more likely to yield ambiguous results. There are multiple endpoints, including subjective quality-of-life measures, and several subgroup analyses.[4,5] The variety of trial settings increases the likelihood of heterogeneity of procedures and reporting. Promotions of chelation by TACT co-investigators have already introduced unacceptable bias into the trial.[7] There is ample, additional opportunity for mischief, and ample reason to think that several co-investigators are inclined to make it.[7] The statistical analyses will not be Bayesian.[322-324]

Thus, merely on the basis of chance and bias, it is likely that some outcome data in some subgroups will differ sufficiently, between those receiving Na_2EDTA and those receiving placebo, to reassure chelationists that chelation "works" and to sustain "lingering questions of efficacy[29]" in the minds of apologists. Dr. Lamas himself has made much of 2 or 3 "tantalizing positive secondary outcomes[29]" of a previous trial in which only 15 subjects received Na_2EDTA, and in which the remaining 30 secondary outcomes and all 7 primary outcomes were unequivocally negative.[25] The all-but-inevitable "tantalizing positive secondary outcomes" of the TACT would likely lead to years of additional, unnecessary trials or, at the very least, unremitting peddling of chelation by practitioners armed with fresh fodder in their perpetual battle against rational standards of care.

The NIH has hired nearly 100 unqualified co-investigators to care for nearly 2000 unsuspecting subjects.[7] In announcing the TACT, the late NCCAM Director Stephen Straus tacitly acknowledged that such soon-to-be co-investigators had been pushing chelation "in lieu of established treatments.[2]" The TACT consent form warns subjects to "continue to use proven standard medicines for heart attack patients,[6]" but the Declaration of Helsinki expects better:

> Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.[176]

It is the obligation of investigators to provide reasonable predictions of efficacy and assurances of safety, on the basis of all "relevant sources of information,[176]" prior to exposing human subjects to a phase 3 trial. The TACT investigators did not do that.

Most medical journals now subscribe to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors.[325,326] Because the Uniform Requirements include honoring the Helsinki Declaration, it appears that any report emanating from the TACT could not be published in one of the subscribing journals.

Conclusion

The many case series of chelation for cardiovascular disease provide no basis for nullifying the uniformly negative results of the several RCTs. The risks for chelation are more than trivial. The evidence against chelation is more than sufficient to disqualify it from further human trials. Experts in cardiovascular disease and in clinical trials, particularly those who are acquainted with the history and literature of chelation, agree with that assessment.

These points have been misrepresented by the PI, the TACT protocols, the NCCAM Web site, the 2003 TACT consent form, and by trade organizations that stand to gain from the NIH casting their members and practices in a favorable light. The trial appears to exist not because of a real scientific or medical need, but because a powerful congressman successfully manipulated the NIH through its most politically vulnerable appendage, the NCCAM.

There is little basis for predicting that the TACT will yield a reliable or definitive result, and even less for predicting a favorable effect on clinical practice. Numerous co-investigators are unfit to care for subjects in a human trial or to submit trustworthy information to the NIH.

The TACT is pointless, dangerous, unethical, and a waste of public funds. It should be stopped immediately and permanently, and its origin and nature subjected to an independent, comprehensive inquiry. If the NHLBI has assumed primary responsibility for the grant, we are optimistic that this now may happen.[184]

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