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‘A delicate diplomatic situation’: Tobacco industry efforts to gain control of the Framingham study

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Abstract

The Framingham Heart Study (henceforth Framingham) is among the gold standards for epidemiological research. A prospective cohort study of 5,000+ men and women, it provided early findings about causes of coronary heart disease (CHD), following a cohort over 24 years. After US government funding ended, the tobacco industry-funded Council for Tobacco Research (CTR) provided continued funding for analyses related to smoking.

Objective—This study sought to understand the tobacco industry's motivation and activities in funding Framingham.

Study Design—We analyzed previously undisclosed tobacco industry documents, conducting iterative searches of the Legacy Tobacco Documents Library (<http://legacy.library.ucsf.edu/>), and assembled an historical case study.

Results—CTR funded Framingham to obtain full access to Framingham data. CTR planned for longtime industry consultant Carl Seltzer to reanalyze them to suggest that tobacco-related morbidity and mortality primarily resulted from “constitutional” factors such as age/ethnicity. Once data were obtained, CTR terminated funding for the Framingham principal investigator, who disagreed with Seltzer. Seltzer's critical analyses of subsequently-published work by the Framingham team created confusion about the association between coronary heart disease and cigarette smoking.

Conclusion—Researchers accepting tobacco industry funding risk losing control of data, analysis, and publication.

Keywords

Tobacco industry; Research ethics; Smoking; Cardiovascular disease

The Framingham Heart Study, initiated in 1948, has long been considered among the gold standards for epidemiological research [1]. A longitudinal study of some 5,000 men and women from Framingham, Massachusetts, the study provided some of the first findings about the causes of coronary heart disease (CHD). Administered by Boston University (BU) and directed for 30 years by Charles R. Dawber of the Public Health Service (PHS) and later BU, Framingham sought to identify risk factors related to the development of CHD. The prospective design included physical examinations and lifestyle interviews every two years. [1]

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Prior to 1970, Framingham had been funded by the National Heart Institute (NHI, now known as the National Heart, Lung and Blood Institute) and the American Medical Association (AMA). In 1970, however, the AMA decided to discontinue funding, [2] and a NHI committee recommended discontinuing Framingham's clinical examinations, believing that the major hypotheses had been adequately tested; new NIH funding was not approved. [3-5] Framingham was to be shut down June 30, 1970. [4] Dawber was urged to find private funds, and a campaign to finance additional follow-up for the cohort's bi-annual clinical evaluations was launched. [5] Support was forthcoming from several quarters, including "industrial enterprises, insurance companies and private individuals," and the study continued four more years. [5]

The tobacco industry was among the "industrial enterprises" that provided continued Framingham funding, through its tobacco industry-funded Council for Tobacco Research (CTR). [6] The tobacco industry has a long history of funding research and researchers in order to influence the questions asked, as well as the design, conduct and publication of studies related to the health effects of tobacco and secondhand smoke. [7,8] One way that the tobacco industry has manipulated the scientific discourse on smoking and disease has been to influence the science itself.

This paper analyzes internal tobacco company documents to examine the tobacco industry's efforts to gain control of and influence publications from Framingham data about smoking's effects on CHD.

Methods

Between January 2007 – March 2009, we searched, using snowball sampling, an archive of previously undisclosed tobacco industry documents, made public following the Master Settlement Agreement. [9,10] The Legacy Tobacco Documents Library (<http://legacy.library.ucsf.edu/>) holds more than 10 million documents. Searches expanded from keywords "Framingham Heart Study" and "Dawber" to other terms identified in reviewed documents. EndNote software was used for data management. Initial searches produced 13,757 "hits". After screening documents based on index entries, 1403 were selected for review. After eliminating duplicates and those irrelevant to our study focus, 390 documents were analyzed, cited here representatively rather than exhaustively. [9] We also reviewed papers based on Framingham data authored by key actors in the events studied, and conducted searches for media reports about these publications. Documents were analyzed using an interpretive case study approach, [11,12] iteratively and comparatively reviewing them and attempting to appraise the meaning of the material within the context of the time and place in which it was produced. The analysis was assembled into a chronologically organized case study.

Results

Exploring funding possibilities with the tobacco industry

After the 1970 loss of funding, [2] Dawber contacted R.C. Hockett at the Council for Tobacco Research (CTR). [13] Dawber wrote:

"Those of us connected with the Framingham Study have interpreted the Framingham findings as exonerating pipe and cigar smoking as factors related to coronary heart disease. Cigarette smoking appears to relate to the precipitation of an ischemic episode rather than to the development of atherosclerosis. Presumably in those persons with no major risk factors the added risk of cigarette smoking may be of little importance... the tobacco industry should support a study... to

determine the several factors related to coronary heart disease development. Documentation of the effect of cigarette smoking in persons with and without these risk factors is needed... in the absence of other important risk factors cigarette smoking may be relatively unimportant.” [3]

Hockett noted in a memo to CTR'S advisory board: “we will probably all agree that this study ought by all means to be continued.” [13] Funding it, Hockett noted in a July letter to RJ Reynolds General Counsel, Henry Ramm, “would have considerable public relations value in the scientific world.” [14] Tobacco companies were particularly interested in research that might suggest a “constitutional hypothesis”—that is, that some people were genetically predisposed to take up smoking and to develop disease. [15]

Hockett asked Ramm about funding Framingham as a “special project”. [14] “Special Projects” at CTR did not go through peer review by the independent scientists known as the Scientific Advisory Board, but were instead selected by tobacco industry lawyers. Previous research has shown that scientific merit played little role; the results of these projects were used to generate good publicity for the industry, to deflect attention away from tobacco use as a health danger, and to attempt to influence policymakers. [16] Their primary purpose was to produce research that could be used to defend the industry in court or legislative arenas. [15,17] Ramm replied, for reasons which remain unclear, that the tobacco companies would not support Framingham as a special project, but encouraged him to submit a regular proposal. [18]

Dawber's CTR research proposal

In March 1971, Dawber submitted his first proposal, entitled, “Smoking classes, risk factors and cardiovascular disease” and listed as investigators Charles Dawber, Thomas Emerson and Carl Seltzer. [19] Dawber and Emerson of BU were investigators previously on Framingham. Seltzer was at the time a professor (of anthropology) at Harvard School of Public Health, who had consulted for the tobacco industry since 1968 [20] (his later tobacco industry consultancies have been previously documented). [15] The final grant, however, included only Dawber and Seltzer [21]. Hockett noted:

“The consensus of the Board was that...if developments made it feasible, a grant targeted toward analysis of data specifically interesting to the Council might be considered. This possibility has developed even beyond any expectation.” [21]

In June, 1971, Dawber accepted funding for the first year of a study to analyze the association of smoking and coronary heart disease (CHD). [22] The following month (July 1971), the tobacco industry's Zahn Public Relations firm released statements to the press, claiming CTR funding would “revive” Framingham. [23] Besides being good public relations, the industry anticipated findings disputing the contention that cigarettes were implicated in heart disease. CTR physician Sheldon Sommers suggested:

“In epidemiology the Framingham material occupies a key position with reference to factors related to coronary disease. If it is possible to reevaluate this material and to publish the findings, there are going to be revelations of importance...we should take advantage of this opportunity.” [24]

The first year apparently went well; in 1972, Dawber submitted a renewal to “especially consider the age at which a particular manifestation of cardiovascular disease develops in the several smoking categories and in non-smokers.” [25] A CTR summary noted: “this study has made substantial progress and has presumptively achieved some ‘quite startling’ observations”, [26] although these were unspecified. A second-year award was approved. [27,28]

Access to data free of NIH restrictions

CTR was interested in acquiring the Framingham data in order to reanalyze it and publish without restrictions from NIH. In a “confidential” December 1972 letter to Seltzer, Dawber sought permission to transfer the previous year's remaining funds, noting that the head of the computer center had agreed to expedite Framingham data processing. [29] Three days later, Seltzer told Hockett:

“In my opinion, the appropriate course is to permit Dr. Dawber to carry-over these funds. I do not wish to disturb the situation at this time. The moment of truth will come soon after the first of the year...when he claims with the help of these monies he will hasten the copy of the original Framingham data. At that time, he asserts we will then be free of the NIH...restrictions. I prefer you allow matters to rest as they are...so that there will be no excuse for any untoward action.” [30]

CTR was apparently under pressure to account for the funds. [31] In January, 1973, Frederick Nordsiek, the CTR Associate Research Director, who managed budgets and contracts, asked Hockett:

“When do we write to Dawber and ask for an accounting of his funds for the period ending 6/30/72? Dr. Seltzer says ‘The moment of truth will come soon...’ – very poetic, but in hard figures, what date is that?” [32]

Hockett responded: “I have written to Dr. Seltzer about this. Hold this pending reply.” [32] Meanwhile, Dawber had applied for a third year of funding. [25,33] Seltzer strongly recommended continuation, telling Hockett:

“...a copy of all the data (on all exams) for each subject is in Dr. Dawber's possession. I have been shown these data. This means that now Dr. Dawber is independent of the PHS [Public Health Service] for the original and earlier data... without which most of the projected projects would not be possible...Framingham original data is now being punched into IBM cards and transferred to computer tape...when this is completed, the original Framingham data will now be available for use in analysis with various projects by all of us concerned...and no longer will be dependent [sic] on the PHS for this material.” [34]

Up to the 22nd year of data collection, all Framingham publications apparently had to be cleared by the PHS, the parent entity of the NIH. [34] The 22nd year would be completed by September, 1973; Seltzer anticipated that at that point, the information would be the “private property of Boston University” [emphasis in the original], assuring Hockett that the data would contain CHD status: “just the data we are most interested in”. [34]

Another benefit to these data, according to Seltzer, was that preliminary analysis seemed to support the tobacco industry's premise that any suspected health consequence of smoking was due to constitutional factors (i.e. gender, aging, ethnicity). Rather than smoking causing illness and death, the industry held that certain people who smoked were predisposed or susceptible to CHD:

“Dr. Dawber has informed me that the preliminary analysis of this material shows that although young cigarette smokers develop myocardial infarcts at an earlier age than non-smokers, that after the age of 55 there is no essential difference in age of onset of infarction between smokers and non-smokers. This confirms my own observations...of the absence of differential risk in elderly smokers...”[34]

Seltzer's efforts were apparently persuasive; CTR awarded Dawber a “terminal grant” for the period of July 1973-June 1974. [35] The project objectives were to:

“study the relationship of cigarette smoking practices to the development of coronary heart disease, stroke, and peripheral vascular disease, in the Framingham study... Re-analyses of data... will be carried out with the objective of pinpointing the actual changes in terms of life expectancy and disease development... Comparison is being made between cigarette smokers and nonsmokers in terms of the age of myocardial infarction, sudden death, coronary insufficiency, and angina pectoris”. [36]

In early 1974, Dawber submitted a new 2-year proposal, writing:

“The reported effect of cigarette smoking on the development of coronary heart disease, stroke and peripheral vascular disease is not one related to atherogenesis but to other factors... e.g. thrombosis or arrhythmia. Persons susceptible to these events develop them earlier if they smoke cigarettes. The net effect is to cause clinically overt disease to appear earlier in cigarette smokers than non-smokers. Ex-smokers will be at an even lower risk than those who never smoked. A third observation should be the disappearance of the effect of cigarette smoking with increasing age as susceptible persons are removed from the population”. [37]

This finding could be helpful, as the industry worried about aging smokers wanting to quit and sought to reassure them that quitting wasn't necessary. [38] However, Framingham data had still not been turned over. A handwritten summary of a February 1974 CTR meeting regarding the “Dawber Project” noted “Consensus [sic] against continuing at all [sic] unless we get the data” [emphasis in the original]. [39] Seltzer continued to urge patience:

“Yesterday, in Dr. Dawber's office I was shown a listing of CHD outcomes... according to the various manifestations of CHD events – AP, CI, MI, Sudden death and non-sudden death ... This is just the data I have been waiting for so long. With this information and a listing of the subjects who are still under surveillance, I will be able to make my first analysis of smoking habits and CHD... Dr. Dawber told me that he is not giving me this listing yet because it has to be checked... However... it is just a matter of time now when I will have in my possession the data I need for my analysis... Accordingly, I recommend the approval of the grant request”. [40]

CTR held funding approval pending further consultation with Seltzer; [41] minutes of March 13, 1974 list Dawber for only a \$15,000 award. [42] Apparently, CTR's funding offer was made contingent on producing particular reports. In a letter to Vincent Lisanti of CTR, however, Dawber refused to commit:

“I do not wish to receive any funds contingent upon guarantees of producing reports from Framingham... I would rather seek other sources of assistance than commit myself further regarding a timetable for completed reports from our Study [sic]” [43]

However, this did not end the matter. CTR was apparently planning to terminate Dawber's funding, but only after obtaining the data. A May 23, 1974 CTR memo noted:

“Carl Seltzer suggested delay to the end of June before notification of termination... Seltzer has a letter on Dawber's desk to which he wants a reply before notification is sent... He concurs in termination. He would like to get a commitment about the data that he himself has available before”. [44]

Pressuring Dawber

Seltzer apparently continued to strike a delicate balance, trying to extend funding long enough to encourage Dawber to turn over the data and negotiate agreement on a statistical

plan and publications content. [45] Dawber, however, resisted. In a letter to Seltzer, he asserted:

“With regard to our understanding on the analysis... I have indicated previously that as the principal investigator in the Boston University – Framingham Study I am responsible for the publication of such reports as I consider desirable. I have always stated a willingness to your participation [sic] in such reports. It is my intent to provide the necessary data for a paper on smoking and coronary heart disease based on the 22-year follow-up... the paper in question... must come out from my department. I have no objections to you being the senior author but the interpretation of the data must reflect my views as well as yours... as soon as we have the completed data we should get together and discuss just what analyses should be completed. Meanwhile, you are free to use the data you have with the understanding that it will be updated... I assume that the CTR will not renew our grant. This is unfortunate as it will probably curtail the time period that we can continue... However, with multiple sources of support it is not possible to allow one tail to wag the dog. For this reason I did not take kindly to suggestions regarding how I should conduct the Study. If the CTR does not have sufficient confidence in my ability to do the job I am happy to have them keep their money. I am hungry but not starving”. [46]

Seltzer responded, reconfirming interest in a joint paper on precursors of smoking and coronary disease, and noting his intention to continue “tentative” analyses. He wrote reassuringly, “When you indicate to me that the verified and updated data are available, I will make arrangements to meet with you to discuss what analyses should be completed... It goes without saying that the interpretation of the data must reflect your views as well as mine. The paper should reflect our joint view.” [47]

In July, 1974, CTR informed Dawber that it approved additional funding of \$15,000 [48] “to assist you and your co-investigator in completion of data analysis and preparation of publications on the topics originally agreed upon.” [45] By September 1974, Dawber accepted the funding and had given Seltzer the long-sought data. A handwritten note from CTR files noted:

“Dawber has given Carl [Seltzer] the CVD data he has been wanting. Next the manuscript [emphasis in the original]. Seltzer will immediately begin data analysis... Will work with Dawber closely – step by step- so that he (D.) will be familiar with the findings as they emerge. D [Dawber] will retire in two years and therefore may not be as concerned with political aspects of his work.” [49]

In March, 1975, the CTR accounting office asked Hockett about the \$6781 remaining balance of Dawber's grant, asking whether he should be requested to return unspent funds.

Hockett responded:

“...There is a delicate diplomatic situation and I must explore the current status of the work with Seltzer and Lisanti... We cut his request... to a \$15,000 terminal grant for wrapping up the information we wanted from the project. We gave this a six-month time period in the hope of stimulating activity...” [31]

In a handwritten April 10, 1975 note, titled “Notes on Seltzer's visit, “the Dawber situation” is referenced:

“Dawber situation--D say mos. [months] – would supply a few more “final” figures + check on CS [Carl Seltzer] figures. Plan CS will complete the paper and discussion and present a complete paper with both names on it. High Priority

Rather simplistic discussion to get data out– ask D. [Dawber] for criticisms within a reasonable time – OK will publish.”[50]

It was apparently decided to delay requesting return of the unused funds from Dawber until the paper issues were “settled.” [50] Dawber requested to use the unexpended funds in June 1975, [51] but the request went unanswered until September, 1976, when it was denied. [52] Dawber continued to emphasize:

“...Not only must the data be accurate but the conclusions that are reached from this data must represent the interpretation of all of us who are concerned in producing it... What I believe we must have is

1. Crude incidence rates for non-smokers and various types of smokers (we have this)
2. Corrected rates to take care of the actual population still at risk (we have this)
3. Corrected rates to take care of changes in smoking habits (as yet we do not have this completed)
4. Corrected rates or possibly stated figures that show not only the incidence rate but the average age at which the various subgroups actually develop the disease (we don't have this yet but I'm working on it)...” [53]

Seltzer responded, agreeing with the need “for the final manuscript from us to be ‘unbiased’ for the NHLI and anyone else.” [54] However, documents suggest that a struggle continued over analysis and presentation. A February, 1976 handwritten note[55] [Figure 1] suggests that CTR may have been reluctant to publish a mortality ratio and reveals concern that Dawber would insist on a causal interpretation. Seltzer “would go along just with a data presentation,” but the note warned: “there will be difficulties about a joint paper.”[55]

A three page handwritten note, titled, “Seltzer... April 6, 1976...visit” reported that the Dawber data had been analyzed by incidence. [56] The note demonstrates how “Seltzer would create bar charts for age groups” which would show “no regular pattern”, instead of using mortality ratios. The note also focused on constitutional factors:

“Why the high ratio in the younger age groups? Native born [and] foreign born (In Framingham about 40% of foreign born are Italians)...Analysis by native born vs foreign born. (Using incomplete earlier cycle data)... Conclusions- 1. No CHD increased risk in smokers over 50. 2. The youngest group show high risk. 3. No association at any age in the females. 4. The place of maturity seems toor are thereSeltzer suggested a series [emphasis in the original] of papers...men, women, young, old etc. ...Dawber disagrees – wants to do one overall ... paper.” [56]

Struggles continued, with Seltzer apparently wanting to claim that the data did not support a causal relationship between smoking and the myocardial irritability associated with sudden cardiac death. Eliminating the overall mortality data and presenting the data merely stratified by age and ethnicity would have made it possible to support the constitutional hypothesis and avoid the conclusion that smoking caused CHD.

In May, however, Dawber wrote Seltzer:

“There is good reason to believe that the relationship of cigarette smoking to sudden death may well be causal. I have not calculated the p value of the difference but I'm sure it is highly significant. To discard the known effect of cigarette smoke in producing premature beats and other evidence of increased myocardial

irritability is not reasonable. To say that the data do not support a causal relationship makes it incumbent to provide some evidence to support such a conclusion. I know of no such evidence in the Framingham data.” [57]

In September 1976, after having received \$172,888 from CTR from June 1971 to June 1975, Dawber was asked to return all remaining funds (\$6,691.58). The decision appears to mark the end of the Dawber-Seltzer collaboration; searches of the Legacy archives, Pubmed and the Framingham Study website located no papers with both listed as authors. However, they continued to contend over issues of data analysis and interpretation (See Tables 1 and 2). In 1977, Seltzer wrote a letter to *Lancet*, challenging a 1974 report by Dawber and colleagues. Seltzer argued that intrinsic “biological and psychological characteristics” were the best explanation for differential disease rates.[58] A response from the Framingham team, including Dawber, pointedly observed:

“While we think Dr. Seltzer's graph is misleading we can vouch for its accuracy: we gave him the data on which it was based. But more to the point we gave essentially the same facts to your readers...The question is how to interpret the facts?” [59]

The response stated that,

“Dr. Seltzer apparently adjusted for age by averaging the three age-specific rates. If you do the more usual thing and age adjust to the age distribution of the total population the impression is vastly different.” [59]

In 1980, Seltzer published an editorial in *American Heart Journal*, titled “Smoking and coronary heart disease: what are we to believe?” He concluded:

“For the present, then, it is reasonable to believe that stopping smoking does not reduce the risk of CHD, and that there is no established proof that cigarette smoking is causally related to coronary heart disease.” [60]

As late as 1984, he continued to publicly criticize the Framingham study, claiming inaccuracies (without revealing his tobacco industry ties). [15] His efforts bore fruit in media coverage [61,62] perpetuating the idea that whether smoking caused CHD was still an open “controversy.” [16]

Discussion

Open discourse about scientific disagreements is common among scientists. However, the CTR's references to the “political” aspects that Dawber might be less concerned about post-retirement, and Hockett's discussion of the “delicate diplomatic situation” (particularly when understood within the subsequently-exposed larger context of the CTR's work), suggest that these disputes were not merely scientific in nature, but were about controlling the analyses and interpretation of results potentially unfavorable to industry. This case illustrates why researchers who accept tobacco industry funding risk losing control of data, analysis, and publication. CTR clearly sought to fund research aimed at exonerating cigarette smoking as a cause of disease, providing funding for the primary purpose of gaining full control of the data for re-analyses aimed at supporting the “constitutional hypothesis.” Once the data were obtained, Dawber was no longer needed, particularly after he apparently resisted the post hoc subgroup analyses and interpretations that the industry sought (Fig 2).

As a scientist anxious to continue his work and constrained by lack of funding, Dawber's position was not unlike that of many scientists today. Epidemiological studies, with their long time frames of decades or more, are particularly vulnerable to changes in funding. A lack of stable funding can jeopardize earlier investments in research by hindering the

publication of the full results of an epidemiological study. Industry funding, often encouraged by academic-business “partnership” arrangements increasingly embraced by many universities, can allow important scientific work to begin or continue that otherwise might be delayed or never done. However, this study illustrates how such arrangements risk pressures to compromise scientific independence for the benefit of a sponsor. Funding source can introduce biases related to data control and publication in epidemiological studies as well as experimental studies.[63]

Many questions remain about the best models for corporate-academic research relationships. These models must protect not only against bias in the design, conduct and reporting of research, but also guard against the unethical use of researchers and study data to support industry objectives. [64] Consortia of funding from industry have been suggested [65] as one model that can reduce the influence of a single sponsor, in line with Dawber's comment that “with multiple sources of support it is not possible to allow one tail to wag the dog.” However, it has been difficult to get corporate sponsors to participate in such consortia. [64]

Dawber's role in this case is complex. As many scientists have likely done, he appears initially to have dangled before CTR the “carrot” of a potentially industry-favorable finding in order to secure funding. In two papers published during the period during which CTR funding was received, he referred to “susceptible” and “predisposed” persons in discussing effects of smoking on heart disease [66,67]--terms he did not use in his later work. These terms are consistent with the industry's favored “constitutional hypothesis.” However, as pressure increased to conduct analyses he felt were inappropriate, Dawber proved unwilling to compromise on analyses he must have felt could undermine his integrity as a scientist—and lost funding and control of the data as a result.

The tobacco industry has sought researchers' data through requests, lawsuits, and policy changes to require its availability. [68] A unique aspect of epidemiological research is that a corporate sponsor does not need to control the design and conduct of the study in order to influence the findings. A sponsor can obtain the data after they are collected and re-analyze them in a way that is different than what the original investigators intended. The tobacco industry, for example, attempted to obtain and reanalyze data from Elizabeth Fontham's multi-center case control study of the effects of secondhand smoke.[69]

This study explores industry activities related to one of the major epidemiological cohort studies of the 20th century. Seeking access to data merely to reanalyze it to fit a self-serving interpretation is scientifically and ethically inappropriate. Seltzer's subsequent use of Framingham data for analyses completely independent of (and attacking) the original Framingham investigators violated the spirit of authentic scientific collaboration, which requires researchers to be open about disagreements and to make their case for reviewers and readers. In addition, many of Seltzer's attacks took the form of opinion pieces, letters, and editorials [58,70-73] which were used for industry public relations, rather than peer-reviewed research papers. [74-79]

This case study also has implications for contemporary publication practices. It points to the inadequacy of conventional journal policies related to disclosure of funding sources.[80] Newer policies may require disclosing the “role of the sponsor,” typically asking for explicit disclosure of whether any funder was involved in study design; data collection, analysis, and interpretation; writing; and/or decisions about submissions. However, even this level of disclosure can be insufficient to ensure that editors and readers understand how decisions about data analysis and presentation may strategically mask more important findings or why such decisions were made. Authorship and contributorship statements can also help define the role of the sponsor by asking authors about who controls the data. [81] Publishing

competing interest statements in addition to funding sources, role of sponsor statements and authorship contributions could provide more information about sponsor control of data. For example, some journals now require disclosure of any nonfinancial ties that might influence the work.[81] Lastly, disclosure may never be sufficient to protect against influence of a research sponsor, so sponsored studies should be viewed with skepticism.[82,83]

More broadly, this study raises the question of how legitimate science—even large studies like Framingham—may be misused to serve corporate interests and thereby harm public health. Part of Framingham's attractiveness for tobacco companies was the study's near-legendary status among researchers, the media and the public. This lent legitimacy to publications referencing its data, which would likely be picked up by mainstream media. CTR's concern about being able to publish its re-analyses independent of NIH oversight suggests that it was trying to avoid addressing questions of bias in analyses and data presentation that NIH might have raised, while benefiting from the cachet of the Framingham name. Ultimately, CTR's efforts to control and use Framingham data via Seltzer's publications likely had the effect of confusing and delaying for several years full appreciation of Framingham's important findings that smoking tobacco causes CHD.

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Seltzer call Feb. 20 1976
 We need a conference
 with him HK 1716007

Dawber
 72 yr. data - person yrs. smoking
 incidence - of disorder
 disease
 Angina
 M.I. inf.

Finds - 3 age categories up to 40
 40-50
 50+

2 to 3% incidence for smokers over non-smokers
 about 2% 40-50
 no increase over 50 1 of Carl's age

No assoc. with age & age
 smoking

dose response relation
 duration - no relation
 little re Angina
 mostly M.I. & sudden death

Q degree of Seltzer involvement?
 this will be difficult
 about a joint paper
 the diff.

duration dose response
 not clear.

Overall mortality ratio 1.3
 This would
 D insists on a causal interpretation
 S. would go along just with a data presentation.

Figure 1.

February 1976 CTR hand written note: "overall mortality ratio 1.3"; "mortality ratios out"; "D [Dawber] wants causal interpretation; S [Seltzer] would go along just with a data presentation".

Table 1
Publications by Charles Dawber on Smoking and CHD 1959-1982

Authors	Date	Title	Journal	Type of Article:	(FS) YES or NO	Conclusion about smoking and CHD :
Dawber, T.R., William, W.B., Revotskie, N., Stokes, J., Kagan, A., & Gordon, T. [84]	Oct 1959	Some Factors Associated with the Development of Coronary Heart Disease	American Journal of Public Health	Data based Article analysis of 6 years of follow up	FS Yes	"..... Smoking was associated with an increased incidence of nonfatal MI and of death from CHD in men 45-62"
Katz, L.N., Allen, E.V., Cherkasky, M., Davis, F.W., Dawber, T.R. [85]	July 1960	Cigarette Smoking and Cardiovascular Diseases: Report by the American Heart Association	Circulation	Review	No	"Up to the present, a number of medical studies have been made, nearly all demonstrating a statistical association between heavy cigarette smoking and mortality (death) or morbidity (illness) from coronary heart disease."
Doyle, J.T., Dawber, T.R., Kannel, W.B., Heslin, A.S., Kahn, H.A. [86]	April 1962	Cigarette Smoking and Coronary Heart Disease	The New England Journal of Medicine	Data based article	Yes FS and Albany Medical College group	"...the Heavy cigarette smokers experience a threefold increase in the incidence of [MI] and in death from all causes as compared to nonsmokers ..."
Kagan, A., Dawber, T.R., Kannel, W.B., Revotskie, N. [87]	July-Aug 1962	The Framingham Study: a Prospective Study of Coronary Heart Disease	Federation Proceedings	Data based Article analysis of 8 years follow up	Yes FS	"Another potent risk factor which has appeared is that of cigarette smoking. Our data would indicate that cigarette smoking ... is strongly correlated with the risk of developing the more disastrous manifestations of [MI] and sudden death."
Dawber, T.R., Kannel, W.B., McNamara, P.M. [88]	1964	The Prediction of Coronary Heart Disease	Proceedings at National Cardiovascular Conference	Data based Article analysis of 10 years follow up	Yes FS	"It is now becoming evident, that the smoking of cigarettes is related to certain manifestations of coronary heart disease...the risk of developing a [MI] is significantly increased."
Doyle, J.T., Dawber, T.R., Kannel, W.B., Kinch, S.U., Kahn, H.A. [89]	December 1964	The Relationship of Cigarette Smoking to Coronary Heart Disease	Journal of American Medical Association	Data based article	Yes FS and Albany	"It was found that in men who report habitual consumption of 20 or more cigarettes per day the risk of [MI] was about three times greater than in nonsmokers...It is inferred that stopping cigarette smoking lessens the risk of CHD."
Dawber, T.R., Kannel, W.B., McNamara, P.M. [90]	Jan 1966	Detection of the Coronary-Prone Adult: The Framingham Study	Journal of the Iowa Medical Society	Data based article	Yes FS	"...Cigarette smoking deserves special comment as a habit contributing quite significantly to the development of CHD. As compared to non-smokers, heavy smokers were far more likely to die from CHD."
Dawber, T.R., & Thomas, H.E. [91]	Jan 1971	Prevention of Myocardial Infarction	Progress in Cardiovascular Diseases	Review	Yes FS	The low incidence rates of all forms of coronary heart disease in ex-cigarette smokers suggests that abandoning this habit is one of the most effective means at our disposal of preventing [MI] and sudden death."
June 1971 Dawber Accepts First Funding From Tobacco Industry						

Authors	Date	Title	Journal	Type of Article:	(FS) YES or NO	Conclusion about smoking and CHD :
Kannel, W.B., Dawber, T.R. [67]	Nov-Dec 1972	Contributors to Coronary Risk Implications for Prevention and Public Health: The Framingham Study	Heart and Lung	Data based article analysis of 12 years of followup (FS)	Yes FS	"These data suggest that cigarette smoking has a relative immediate effect, triggering coronary attacks in susceptible persons** rather than an influence which promotes atherosclerosis." **prior to this article there was no reference to "susceptible persons" a linch pin in the "constitutional hypothesis" promoted by the tobacco industry.
Dawber, T.R., Kannel, W.B. [66]	Dec 1972	Current Status of Coronary Prevention	Preventive Medicine	Review	Yes FS	"From our observations in the Framingham Study we are of the opinion that the cigarette habit [emphasis in the original] does not promote accelerated atherogenesis but rather triggers coronary attacks in persons predisposed by a sufficient degree of coronary atherosclerosis"
Tobacco Industry Funding of Framingham Study is Discontinued No further mention of susceptible or predisposed persons						
Gordon, T., Kannel, W.B., McGee D., Dawber, T.R. [92]	Dec 1974	Death and Coronary Attacks in Men after Giving Up Cigarette Smoking	The Lancet	Data based article on 18 years of observation	Yes FS	"The data reported reveal for the first time in this prospective study that when men under the age of 65 who smoke cigarettes give them up they reduce their risk of CHD, on average, by a half ..."
Gordon T., Kannel, W.B., Dawber, T.R., McGee, D. [93]	Sept 1975	Changes Associated with Quitting Cigarette Smoking: The Framingham Study	American Heart Journal	Data based article on 10 and 18 years of observation.	Yes FS	"no difference in blood pressure trends for those who continued to smoke to those who quit despite a greater weight increase in those who quit... the impact of quitting on the major cardiovascular risk factors appears to be trivial so that the cardiovascular advantage of quitting cigarette smoking should be straightforward."
Gordon, T., Kannel, W.B., McGee, D., Dawber, T.R. [94]	Feb 1977	Stopping Smoking and C.H.D	The Lancet	Letter to the Editor Rebuttal to Seltzer from FS team		"While we think Dr. Seltzer's graph is misleading we can vouch for its accuracy; we gave him the data on which it was based...since CHD is a major source of total mortality it is not surprising to find ...inversions in the mortality trends by level of smoking. We think this is explained by sampling variability... We do not pretend that the Framingham data are definitive: they simply provide another set of facts to consider. As for satisfying the skeptics we can think of no evidence that would do."
Sparrow, D., Dawber, T.R., Colton, T. [95]	1978	The Influence of Cigarette Smoking on Prognosis After a First Myocardial Infarction	Journal of Chronic Disease	Data based on 22 years of observation	Yes FS	"The benefit [of quitting smoking] appears to be in overall survival and not due specifically to a decreased rate of recurrent MI... indicating the need to give up the smoking habit early in life..."
Wolf, P.A., Kannel, W.B., Dawber, T.R. [96]	1978	Prospective Investigations: The Framingham Study and the Epidemiology of Stroke	Advances in Neurology	Data based 24 years of observation	Yes FS	"The impact of cigarette smoking on ABI [atherothrombotic brain infarction] is considerably less than on PVD [peripheral vascular disease] or CHD. In these latter two atherosclerotic diseases, incidence is increased in cigarette smokers, particularly among younger men who smoke heavily."

Authors	Date	Title	Journal	Type of Article:	(FS) YES or NO	Conclusion about smoking and CHD :
Castelli, W.P., Garrison, R.J., Dawber, T.R., McNamara, P.M., Feinleib, M., Kannel, W.B. [97]	July 1981	The Filter Cigarette And Coronary Heart Disease; The Framingham Study	The Lancet	Data based on examination in year, 1, 7, and 14.	Yes FS	"There is no evidence that the filter cigarettes of the 60s and 70s conferred any protection from coronary heart disease for men in the Framingham Study..."
Dawber, T.R., and Thomas, H.E. [98]	July 1979	Smoking and Heart Disease: Current Thinking	Comprehensive Therapy	Review	Yes FS	"...cigarette smoking is an important risk factor for all coronary heart disease manifestations and congestive heart failure...Discontinuation of smoking has a very favorable impact on the risk of subsequent coronary heart disease on both those who are free of this disorder and those who have already developed serious clinical manifestations."
Kannel, W.B., Dawber, T.R. [99]	Jan-Febr 1982	Contributors to Coronary Risk: Ten Years Later	Heart and Lung	Review	Yes FS	"we wish to reassess the evidence previously presented and the conclusions reached in the light of an additional 10 years of observation...cigarettes smoking...continues to be a major factor in the development of myocardial infarction...the cigarette smoking effect is independent of other risk factors... evidence is accumulating to indicate a benefit of quitting cigarette smoking..."

Table 2
Framingham Study and Tobacco Industry Funding Timeline

Date	Event
1948	Framingham Study (FS) initiated
1948-1970	FS funded by National Heart Institute (NHI) and American Medical Association (AMA)
Apr-May, 1970	NHI and AMA discontinue funding
Apr 14, 1970	Dawber contacts Council for Tobacco Research about possible funding
June 30, 1970	Due to lack of funds FS slated to be shut down
July 24, 1970	CTR encourages Dawber to submit proposal
March, 1971	Dawber submits first proposal: "Smoking classes, risk factors and cardiovascular disease" with Seltzer as co-PI
June, 1971	Dawber accepts funding from CTR for first year for \$48,925
July, 1971	Tobacco Industry public relations press release: CTR funding will "revive" FS
May 3, 1972	Dawber submits renewal application for 1/1/72-6/30/72: "Smoking classes, risk factors and cardiovascular disease" to "especially consider the age" of disease manifestation for \$54,338
Dec, 1972	Dawber requests transfer of previous year's remaining funds
Dec, 1972	Seltzer suggests CTR approve funds to allow Dawber to provide copy of data "free of NIH...restrictions"
Jan, 1973	Dawber submits renewal for third year of funding for 7/1/73-6/30/74 "Smoking classes, risk factors and cardiovascular disease", adding investigation of stroke and peripheral vascular disease and effect of "tobacco usage habits on these disorders" for \$54,625
Feb 28, 1973	Dawber has all data and is free of PHS restrictions. Seltzer assures CTR that FS data will include data suggesting health consequences of smoking are due to constitutional factors (gender, aging, ethnicity)
April, 1973	Dawber awarded "terminal" grant for 07/73-06/74
Jan 24, 1974	Dawber submits new proposal, "Epidemiologic Study of Cigarette Smoking and Cardiovascular Disease" for 07/01/1974-06/30/1976
Feb 05, 1974	Dawber has still not turned over data to Seltzer. CTR against continuing "unless we get the data"
Feb 20, 1974	Seltzer urges patience: "it is just a matter of time now when I will have in my possession the data I need". He urges approval of the grant request
March, 1974	CTR holds up funding approval pending further consultation with Seltzer
March 13, 1974	CTR approves Dawber for only \$15,000 award, contingent on producing specific reports
May 15, 1974	Dawber refuses funds "contingent upon guarantees of producing reports from [FS]"
May 23, 1974	CTR plans to terminate FS funding after obtaining data
June 20, 1974	Seltzer continues trying to extend funding long enough to encourage Dawber to turn over data and negotiate agreement on statistical plan and publication content
July, 1974	CTR awards Dawber \$15,000 to assist in the "completion of data analysis and preparation of publications on the topics originally agreed upon".
Sept, 1974	Dawber accepts funding, gives Seltzer the data
Sept 19, 1974	Seltzer begins data analysis and says he will work with Dawber "closely"
March, 1975	CTR accounting office asks when Dawber will return \$6781 unspent funds
March 19, 1975	CTR delays request because of "delicate diplomatic situation", waiting until publication issue settled
June, 1975	Dawber requests to use unused funds
Feb, 1976	Struggle continues over analysis and presentation- CTR reluctant to publish a mortality ratio and concerned that Dawber would insist on causal interpretation
April, 1976	Seltzer reports that Dawber has analyzed by incidence but Seltzer willing to "create bar charts for age groups" for publication which would show "no regular pattern"

Date	Event
May, 1976	Dawber tells Seltzer “there is good reason to believe that the relationship of cigarette smoking to sudden death may well be causal”
June, 1976	Dawber's request to use unused funds denied
Sept, 1976	After having received \$172,888 from CTR over 3 years, Dawber asked to return the remaining funds (\$6,691.58)