Public Citizen

Buyers Up • Congress Watch • Critical Mass • Health Research Group • Litigation Group

Joan Claybrook, President

June 7, 1994

Representative Henry Waxman
Subcommittee on Health and the Environment
Committee on Energy and Commerce
U.S. House of Representatives
2415 Rayburn House Office Bldg.
Washington, DC 20515

Dear Representative Waxman:

We are writing to request that your Subcommittee hold a hearing, as soon as possible, to investigate charges of grave impropriety committed by U.S. Department of Defense' AIDS researchers. We have obtained internal memoranda, not previously made public, from the Department of Defense that allege a systematic pattern of data manipulation, inappropriate statistical analyses and misleading data presentation by Army researchers in an apparent attempt to promote the usefulness of the GP160 AIDS vaccine (VaxSyn; MicroGeneSys, Meriden, Connecticut), which is intended to prevent the progression of disease in persons with HIV infection. The Phase I and Phase II studies in which this alleged misconduct occurred were conducted by researchers at the Walter Reed Army Institute of Research (WRAIR), led by Lt. Col. Robert Redfield, M.D., Chief of the Department of Retroviral Research, and misleading results from these trials were reported in a variety of scientific fora, including the *New England Journal of Medicine* in June 1991, the journal *AIDS Research and Human Retroviruses* in June 1992 and the annual International AIDS Conference in Amsterdam in July 1992. In addition, overstated conclusions have been presented on two occasions at hearings before your Subcommittee.

Meeting on October 23, 1992 to discuss the allegations by two Air Force research physicians (see below) of scientific misconduct by Dr. Redfield, a subcommittee of the Institutional Review Committee at the Wilford Hall U.S. Air Force Medical Center, San Antonio, Texas reached the following conclusion (see Attachment 1):

The committee agreed the information presented by Dr. Redfield seriously threatens his credibility as a researcher and has the potential to negatively impact AIDS research funding for military institutions as a whole. His allegedly unethical behavior creates false hope and could result in premature deployment of the vaccine. The need for Phase II studies, which stand to answer questions raised in this controversy, could also come into question.

That meeting was called to review an October 21, 1992 memorandum (see Attachment 2) from Maj. Craig W. Hendrix, M.D., Director of the HIV Program in the Air Force, and Col. R. Neal Boswell, M.D., Associate Chief of the Division of Medicine in the Air Force, to Col. Donald Burke, M.D., Director of the Division of Retrovirology at WRAIR and Dr. Redfield's immediate supervisor. The memorandum decried "The problem of misleading or, possibly, deceptive presentations by Dr. Redfield, which overstate the GP160 Phase I data . . ." and recommended that the following action be taken:

(1) publicly correct the record in a medium suitable for widespread dissemination to our civilian scientific colleagues;

(2) censure Dr. Redfield for potential scientific misconduct which should at least include temporarily suspending his involvement on the current immunotherapy protocols; and

(3) initiate an investigation by a fully independent outside investigative body, such as the Office of Scientific Integrity [now the Office of Research Integrity] of the NIH, to evaluate the facts of the case and recommend appropriate actions.

Senior Department of Defense scientists have known of this misconduct since at least October 1992, and Dr. Redfield has acknowledged that his analyses were faulty on at least three occasions to internal Department of Defense audiences (the earliest admission was on August 28, 1992). A year and a half after Drs. Hendrix and Boswell made their requests (which were endorsed by the Directors of the Clinical HIV Programs in the Army and Navy, Col. Charles Oster and Capt. Walter Karney, respectively), none of their three demands has been met. Instead, the faulty analyses have never been publicly retracted, Dr. Redfield continues to conduct trials of GP160 and only an internal Army investigation has been conducted. That "informal investigation," by the Army's Col. Harry Dangerfield, concluded that "Evidence does not support the allegations of scientific misconduct." The recommendations of the report were:

1. *There is no requirement for adverse actions.*

2. *In faimess to LTC Redfield, the HIV Research Program, the Army and the scientific community, a press release correcting the record is warranted.*

3. *Measures to enhance the effectiveness of communication are warranted.*

Col. Dangerfield's investigation lends new meaning to the term "whitewash." Massive parts of the testimony of key figures have been whited out in documents obtained through the Freedom of Information Act, purportedly because the excised section "would have a chilling effect on open agency communications and/or is personal in nature which, if released, would result in an invasion of an individual's personal privacy." We have attached (see Attachment 3) the full version of the statement to Col. Dangerfield by Dr. William McCarthy, Director of Biostatistics for the Henry M. Jackson Foundation, a non-profit foundation created by an act of Congress to work with Department of Defense researchers, and have indicated which portions have been removed in the copy obtained through the Freedom of Information Act. The specifics of Dr. McCarthy's concerns have consistently been whited out.

The testimonies of others who questioned Dr. Redfield's analyses have been similarly edited. Only the introductory paragraphs and signatures remain from a ten page statement by Dr. Hendrix and a three page statement by Dr. Boswell.

Hundreds of HIV-infected persons have been enrolled in extremely expensive trials at WRAIR as well as in Massachusetts, Connecticut, New York City, Montreal and Sweden. While there are obvious similarities between the issues raised here and the recent revelations that investigators in the breast cancer trials failed to retract results based on incorrect data, the scientific misconduct in this case is more egregious in that it significantly altered the study results and may have resulted in hundreds of people being given the vaccine.

As noted above, findings from the Phase I trial have been presented in the *New England Journal of Medicine*, before your Subcommittee on two occasions, in the journal *AIDS Research and Human Retroviruses*, at the Amsterdam International AIDS Conference in July 1992 and at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Summaries of the misleading aspects of these publications and presentations are presented below.

1. *New England Journal of Medicine*

To our knowledge, the misconduct in this case dates back to a June 13, 1991 issue of the *New England Journal of Medicine* (see Attachment 4). In that article, Dr. Redfield and his colleagues presented data purporting to show that the CD4 cell count (an index of damage to the immune system in persons infected with HIV) remained stable among those who responded to the vaccine, while it declined in a control group of non-responders to the vaccine, a result characterized in the paper as "encouraging."

In the aforementioned statement of Dr. William McCarthy to the Army's internal investigation -- in one of the many portions whited out in the publicly available version -- Dr. McCarthy, described his re-analysis using more appropriate statistical methods of the data in the *New England Journal* article (see Attachment 3):

> *Using this approach my department determined that there was no statistical[ly] significant difference between the responders and the non-responders CD4 count longitudinal profiles.*

Reviewing these published data in the *New England Journal* and subsequent oral presentations, Drs. Hendrix and Boswell stated in their October 21, 1992 memo (see Attachment 2):

> *Data analysis has been sloppy or, possibly, deceptive with use of inappropriately chosen "control" groups, unorthodox statistical methods that abuse the data to come up with the desired CD4 trend conclusions, failure to include appropriately performed analyses that fail to support the desired conclusion and badgering of statisticians and colleagues by Dr. Redfield, sometimes successfully, to agree to data analyses against their better professional judgment.*

2. Congressional Testimony

On June 6, 1991, Dr. Redfield appeared before your Subcommittee and testified, referring in part to the same data presented in the *New England Journal* article, that "the individuals that have been immunized appear not to have a fall in their CD4 cells as opposed to historical controls."

Dr. Redfield appeared before your Subcommittee again on February 24, 1992, this time accompanied by Dr. Burke and Mr. Sheppard Smith, President of Americans for a Sound AIDS Policy (ASAP), a group that raises funds for HIV research and medical care. At that time, Dr. Redfield was Chairman of ASAP's Advisory Board and Dr. Burke served on the Executive Committee; both Lt. Col. Deborah Birx, M.D., Dr. Redfield's assistant, and Col. (Ret.) Edmund Tramont have also served on the Board.

Dr. Burke stated that "What was most remarkable in this study was that blood counts of the CD4 positive T helper cells remained stable over the 1 year period of observation in study patients with boosted immunity." Dr. Burke also indicated that $10 to $20 million would be needed to conduct the requisite follow-up studies. Dr. Redfield indicated that Army researchers were "within 12 to 19 months" of determining whether GP160 could prevent progression of disease. Mr. Smith, who is not a scientist by training, added that "Undoubtedly, any military witnesses today will understate the significant advances being made in regard to vaccine therapy at Walter Reed Army Institute of Research."

In October 1992, several months after the Amsterdam AIDS meeting (see below), Congress appropriated $20 million for a Phase III trial of VaxSyn to be conducted by the Army. That appropriation was modified on January 4, 1994 after it generated considerable controversy, including opposition from the NIH, the Food and Drug Administration and leading AIDS researchers. Army researchers will now use the funds for a variety of different types of HIV vaccine research.

3. *AIDS Research and Human Retroviruses*

In June 1992, Drs. Redfield and Birx published an article in the journal *AIDS Research and Human Retroviruses* (see Attachment 5) that stated:

> *Although the study was not designed to assess efficacy, CD4 counts were carefully monitored throughout the trial. It is extremely intriguing that at the time of analysis original vaccine responders experience 2.8% decline [in CD4 counts], and all trial volunteers 8.5% in contrast to historical natural history experience of a 26.1% decline. These data demonstrate long-term (2-3 year) safety and hint at clinical benefit.*

The implication was that the decline in CD4 counts in non-vaccinated control patients was averted in those getting the vaccine.

4. International AIDS Conference

On July 21, 1992, Dr. Redfield presented updated data from the GP160 Phase I study at the International AIDS Conference in Amsterdam. Dr. Redfield presented slides (see Attachment 6) purportedly demonstrating statistically significant decreases in the amount of HIV in the patients' blood (viral load) among vaccinees compared to a control group. In a presentation at the Amsterdam Conference, later aired on CBS TV, Dr. Redfield described the reported decrease in the viral load among vaccine recipients compared with people not getting the vaccine: "The virus [load] goes down. These are quite strong, significant, real, reproducible observations." However, although he had been given data for all 26 patients with viral load analyses prior to the conference (see Attachment 3), the data presented for the vaccinated patients were

REDFIELD/BIRX CHERRYPICKED THE 7 OF 26 CONTROLS WHOSE DECLINES SUPPORTED VACCINE EFFICACY + FAILED TO REPORT THE 19 WHO DID NOT. FRAUD!

for only 7 subjects in one slide and 15 subjects in another. Dr. Redfield was also quoted in the *New York Times* (July 26, 1992) and the *Wall Street Journal* (July 15, 1992) as saying that there was stabilization of the CD4 cell count among vaccine recipients.

It was the July 1992 Amsterdam presentation that first raised questions about the Phase I trial data. In August 1992, Dr. William McCarthy and Lt. Col. John Brundage, head of Epidemiology at WRAIR, were called in to separately reanalyze the raw Amsterdam data but were unable to replicate Dr. Redfield's results for the viral load.

Dr. McCarthy also informed Dr. Burke that "the CD4 count longitudinal profiles of the GP160 Phase I patients were not stabilizing" (see Attachment 3). Dr. Redfield agreed at a meeting on August 28, 1992 that his Amsterdam statements regarding viral load had been incorrect, that the control group used had been inappropriate and that the full data set should be used in the analysis. That meeting was attended by Drs. Redfield, Burke, Brundage, and McCarthy as well as Dr. Maryanne Vahey, who had performed the viral load analyses for Dr. Redfield and who had first questioned the validity of the Amsterdam presentation. At that meeting, Dr. Redfield agreed that an upcoming poster presentation by Dr. Vahey at the Advances in AIDS Vaccine Development conference in Chantilly, Virginia on August 31, 1992 should include the data on *all* subjects and the correct statistical analyses, without the inappropriate control group.

However, on August 24, 1992, shortly before the Chantilly meeting was to occur, Dr. Vahey received a telephone call from Mr. Sheppard Smith of ASAP. Drs. Hendrix and Boswell reported the following in their October 21, 1992 memorandum (see Attachment 2):

> *According to Dr. Vahey, Mr. Smith had intimate knowledge of the GP160 Phase I data and offered detailed suggestions for how Dr. Vahey should present the incomplete data with the control group, coincidentally as Dr. Redfield had done in Amsterdam, to favor further development of the vaccine. He also insisted that she needed to know of the increasing pressures on her due to: (1) the millions of dollars at stake, (2) Army-NIH vaccine competition, and (3) upcoming congressional testimony [on] GP160 vaccine studies. We are suspicious of Mr. Smith's access to GP160 data, his involvement at the most basic level of data analysis on this study, and his motivations in raising issues of financial and congressional pressure which are scientifically immaterial and have, on the surface, the appearance of a very gross impropriety.*

To our knowledge, Dr. Vahey did not alter her presentation as a result of the phone call.

5. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

On at least two occasions after Dr. Vahey's Chantilly presentation, Dr. Redfield again admitted before the Department of Defense's researchers that the presentation in Amsterdam had been incorrect and misleading. Following these admissions, however, Dr. Redfield made yet another misleading presentation at the ICAAC meeting in Anaheim, California on October 13, 1992 that, according to Drs. Hendrix and Boswell, "continued to present selected patients and made partially true statements to maintain the misleading message." In the published abstract from the meeting, Dr. Redfield and his colleagues report that:

> *the reduction of in vivo HIV expression supports an antiviral effect of this therapeutic strategy.* (see Attachment 7)

Phase II Trials

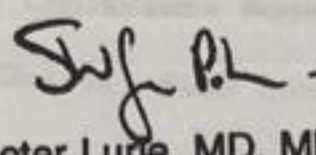
In addition to the concerns regarding the Phase I trials described above, Drs. Hendrix and Boswell also raised questions about the Phase II trial of GP160 being conducted at WRAIR and for which Dr. Redfield was also principal investigator. Although researchers are not supposed to know whether patients are in the vaccine or control group (blinding), according to Drs. Hendrix and Boswell "An unblinded laboratory investigator has been seeing GP160 patients for research visits" and "unblinded data on current Phase II patients has been presented to other clinical investigators on the study."

We strongly urge you to hold a hearing to further explore these issues and to request a full investigation of these events by a truly independent body. In addition to this investigation, a censure of all military and other personnel who are found to have engaged in scientific misconduct is critical. The scientific record, including publications and presentations, should be immediately corrected by requiring Dr. Redfield and his colleagues to issue prominent retractions.

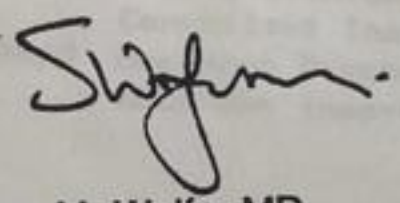
The events described here illustrate the increased potential for scientific misconduct when fame, financial reward and even a Nobel Prize await the discoverer of an effective HIV vaccine and suggest the need for special monitoring of research in this area. These incentives appear to have produced a campaign to promote GP160

that bears more resemblance to market research than it does to objective scientific research. The real tragedy here is that hundreds of HIV-infected persons have been recruited to get this vaccine, perhaps as a result of these misleading analyses. As Drs. Hendrix and Boswell stated at the end of their memorandum, "We cannot continue to deceive."

Sincerely,



Peter Lurie, MD, MPH
Assistant Adjunct Professor
University of California
San Francisco
Research Associate
Public Citizen's Health Research Group



Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group