

Background Information for
The CFSAC Research Recommendations
“Fish or War?”
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Introduction

The Chronic Fatigue Syndrome Advisory Committee (CFSAC) was formed in August, 2003 for the purpose of advising the U.S. Secretary of Health and Human Services on how to proceed with the government's response to Chronic Fatigue Syndrome (CFS). The CFSAC will come forward with recommendations in the areas of disability, education and research. Recommendations in the area of research need to reflect the history of CFS funding, the present mechanisms employed for funding CFS research, and the possible methods of funding CFS research in the future. As discussed below, the federal government has spent approximately \$146 million on CFS research and we do not know its cause, can only treat its symptoms, and have not found a cure or method of prevention. Would a recommendation to continue funding CFS research with current funding mechanisms be the best way to proceed? How will the funding of CFS research through traditional mechanisms, or slight variations of it, bring about outcomes different from the present? The following information is provided to the CFSAC in the hope that a summary of the past, present, and possible future funding mechanisms for CFS research will be helpful in formulating the recommendations.

The Past

Since 1988, the National Institutes of Health and the Centers for Disease Control have conducted a range of research studies on CFS. The National Institutes of Health, according to its own budget office, has spent \$31.6 million on CFS studies between 1999 and 2003. The Chronic Fatigue Immune Deficiency Syndrome Association of America (CAA) places the total expenditure of NIH on CFS research from the year 1990 through the year 2003 at \$78 million. For the same period, the CAA places the expenditure of the Centers for Disease Control on CFS at \$68 million. If the CAA numbers are accurate, the federal government has expended \$146 million on CFS research.

A determination of the precise amount of money spent by the National Institutes of Health and the Centers for Disease Control on CFS research is difficult to determine because the monies spent on CFS research have not been accurately reported by the government. Some of the funding reported by NIH as having been spent on CFS research has actually been spent on research for other diseases. Some might argue that the tripling of NIH's allocation for CFS research between 1990 and 1995 illustrates its responsiveness to the need for an increase in CFS research. However, during the subsequent 7 years, NIH funding for CFS research fell by 16 percent. During that same 7-year period, NIH kept receiving increased appropriations in an effort to double its annual budget.

With regard to CDC spending, the Inspector General of the Department of Health and Human Services reported in 1999 that from 1995 through 1998 the CDC inflated its research figures in Congressional testimony each year (Inspector General's Report to Dr. Jeffrey Koplan, Director of the CDC, May 10, 1999.) Subsequently, the CDC restored 12.9 million to its CFS program.

Other factors may contribute to the Federal Government's less than aggressive response to CFS: (1) Government-sponsored prevalence studies of CFS estimate that close to 800,000 Americans have CFS. However, these prevalence data stem from studies of adult populations. There are little data on younger-than-adult populations in the United States or elsewhere in the world. Until definitive studies are performed on adolescent and pre-adolescent populations, the prevalence of CFS in the United States cannot be firmly established. Until the total number of individuals afflicted with CFS is known, the population-based urgency of a federal-government response to CFS will be less than appropriate. (2) Because the majority of CFS patients are women (men constitute an estimated 33 % to 25 %

of the patient population), and the person spearheading NIH's CFS research effort is also in charge of Women's Health issues, there is a false impression that CFS is a woman's disease. Breast cancer is an example of a woman's disease. The ratio of women:men with breast cancer varies from values of 139:1 to 66:1 (PubMed citation 12679975). While there is no precise definition of a woman's disease, a disease should be characterized as a women's disease when it affects women far in excess of men. Clearly, with a ratio of 2:1 or 3:1, CFS does not meet the "breast cancer" standard of being characterized as a women's disease. An accurate portrayal of CFS as an illness that affects men, women and children would result in greater support for greater funding. (3) CFS may have been given a low priority of diseases to fund because it is not life threatening. Mistakenly, physicians inform their patients that the good news of a CFS diagnosis is that they will not die of it. However, there are no mortality/morbidity studies of CFS patients. We do not know if these patients die prematurely, or of CFS-precipitated illnesses. Until such studies are done, it is premature to conclude that CFS is not a life-threatening or a life-shortening illness.

The Present

The CFSAC will most likely advocate an increase in funding for CFS research. How much money will they advocate? How will that money be spent? How will they justify their expenditure recommendation? To assist the Committee in its work, a Research Subcommittee has been formed to intensively study the subject of CFS Research. The Subcommittee will bring proposed recommendations to the CFSAC for its consideration. Several Research Subcommittee members are experienced researchers in the area of CFS and have received federal funding for their research projects. These Subcommittee members will most likely advocate for increased funding of CFS research utilizing the same or similar funding mechanisms as are currently used.

The current method of funding government-sponsored CFS research is to rely on investigator-initiated proposals. Proposals are submitted to a federally appointed review panel for grading as to merit and potential for funding. In theory, any "qualified" investigator can submit a proposal on any aspect of CFS. An individual proposal will be judged and ranked in relation to the other proposals received. This procedure is analogous to fishing. The reviewers of the proposals are the fishermen. The proposals (and their authors) are the fish. The reviewers hope to snag a few, good fish. They can reel them in, look at them carefully, and, if the proposals are not to the fishermen's individual likings, the proposals can be tossed back. Proposals which are appealing will be recommended for funding. While such a mechanism may be appropriate for leisure-time fishing, is it appropriate for eradicating and curing an illness that dramatically incapacitates nearly 1 million Americans?

This mechanism for deciding which research receives funding and, therefore, which research is performed, is known as peer review. The peer reviewers are the judges and they are as different from each other as one fisherman is from another. What constitutes an attractive fish (or grant proposal) to one or some may not be at all attractive to others. Nevertheless, they decide and, in deciding, they consider factors other than the proposal itself: Does the investigator have the facilities with which to perform the research? (If s/he does not, the proposal will probably be rejected.) Does the investigator have experience performing this kind of research? (If s/he does not, the proposal will probably be rejected.) Does the investigator have a "track record" of bringing to fruition the research promised on previous NIH grants? (If s/he does not, the proposal may not be funded.) What is perhaps most disturbing in this mechanism for funding research is that a proposal containing the best ideas can be rejected for reasons which have nothing to do with the quality or value of the proposed research.

Unfortunately, there are additional obstacles. A proposal may take 6 months or even a year to generate. Is it worth an investigator's time and energy to propose a research project that is such a gamble? Why risk writing a research proposal in a new area when there is less risk in writing a proposal in an area where the investigator has been previously funded? Even if the investigator receives funding for a CFS research project under a one-time announcement of CFS-emphasis grants, what will support the investigator when the CFS-emphasis funds are no longer available? Would it not be better, from

the point of view of the investigator, to write research proposals in areas that have been well funded in the past, are being well funded in the present and have every expectation of remaining well funded in the future? With all these obstacles to be overcome, what would motivate an investigator new to CFS research to submit a CFS research proposal?

Under these circumstances, the disappointing results of the federally funded CFS research programs to date are not difficult to understand. It is also not difficult to extrapolate how little progress will be made in CFS research if the CFSAC recommends that research be funded by the “as usual” mechanism of the point of view of the investigator, to write research proposals in areas that have been well funded in the past, are being well funded in the present and have every expectation of remaining well funded in the future? With all these obstacles to be overcome, what would motivate an investigator new to CFS research to submit a CFS research proposal?

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The Future

A serious commitment to CFS research requires a well-organized, strategic plan. The plan needs to be analogous to a military campaign, analogous to fighting a war. Funding CFS research by one or several variations of the current NIH peer review system is not waging war on CFS. Since 1988, the current funding mechanisms have not found the cause of CFS, have not found a cure for CFS, nor have they resulted in an adequate treatment of CFS. Why pin our hopes on those mechanisms now? Therefore, the questions to be asked are: How do we wage war against a disease? Can we identify a pre-existing mechanism or model for aggressively funding CFS research? Are their existing research-funding mechanisms that can be employed or modified to meet the needs of CFS research? Do we need to create research funding mechanisms de novo?

The World Health Organization's Tropical Disease Research Program (TDRP) and the European Union's Framework Program (FP) offer elements which promote disease-related research more aggressively than current CFS research programs in the United States. Some, if not all, of the elements present in these programs could and possibly should be incorporated into an aggressive campaign against CFS

The World Health Organization's TDRP (<http://www.who.int/tdr/about/strategy/default.htm>, 6/4/04), contains procedures more appropriate for waging a war on illness than the procedures employed by the NIH. For example, rather than lump all proposals together and fund only “the best,” the TDRP divides disease-related, research effort into areas. By so doing, they wage war on a disease on multiple fronts without waiting for an investigator to submit a proposal that might be relevant to a particular and needed area of research. To maintain the balance between areas, Disease Research Coordinators are used. One feature of the TDRP program that seems lacking in the US effort to combat CFS is Research Capability Strengthening (RCS). RCS functions to promote and fund research training and institutional development. It serves to increase participation in the development and use of new tools for diagnosis, treatment, prevention and control. More importantly, however, it functions to build a critical mass of human resources, institutional capacity and a conducive environment for research. In the past, the NIH supported CFS centers which built human resources, institutional capacity and provided a conducive environment for CFS research. Funding for these centers has been withdrawn. While it may be argued that the TDRP'S RCS effort is meant to build resources in less developed countries, we must ask ourselves: what is our current capacity of these resources in the United States and should they be increased?

The European Union's method of funding research (http://europa.eu.int/comm/research/fp6/index_en.html, 6/4/04), their Framework Program (FP), utilizes procedures and policies which would appear to stimulate CFS research more than the methods used in the United States.

The FP supports Centers of Excellence whose purpose is to provide instruments and resources, and coordination of research programs. The FP also encourages “mobile” research scientists. A mobile health scientist can work on health-related projects without fear of loss of employment. A cadre of such scientists could and perhaps should be developed in the U.S. The FP’s application process for research funds is less arduous than the process we employ and, therefore, encourages more applications. The FP application process is initiated by a letter of intent, 3 – 5 pages in length. The authors of “promising” letters are invited to submit full proposals. Such an application process provides less risk to investigators than the method currently employed by NIH. Finally, the FP offers Partner Services. One of these services, CORDIS, the Commission’s Research and Development Information Service, is a free service which allows investigators to find partners for their projects amongst companies, research institutions and universities.

If incorporating aggressive research strategies used by agencies outside of the United States is not acceptable, then the CFSAC should appreciate that there are several existing NIH programs that are not currently used in the campaign against CFS. A laboratory devoted to CFS research could be developed within the NIH. Currently, the NIH contains laboratories, and in fact institutes, devoted to specific diseases. Why not establish a laboratory devoted to CFS? Clearly, the number of individuals affected by this illness warrants such an effort. This laboratory should be led by a leading CFS researcher capable of attracting other researchers with interests in CFS. The current NIH model of trying to generate interest in CFS research by forming a working committee of individuals who have a peripheral interest in CFS from any and all NIH Institutes is not sufficient. Participants do not necessarily represent all the disciplines necessary to investigate CFS in a logical and thorough manner, nor is the commitment of these researchers to CFS research 100 percent.

For other diseases, the NIH funds extramural centers of excellence. According to Institute of Medicine information (http://epscorfoundation.org/cdi/NIH/NIH_Centers.htm, June 9, 2004) the NIH reported funding 1,144 research centers for fiscal year 2003 at a cost of \$2.2 billion. It requested an increase of \$339 million for 1,211 center grants in FY 2003. The NIDDK (National Institute of Diabetes & Digestive & Kidney Diseases) currently funds 75 research centers which include 3 centers for cystic fibrosis, and 16 centers for diabetes. Seven NIH research institutes co-fund 21 Centers for AIDS Research (<http://www.niaid.nih.gov/research/cfar/>, June 9, 2004). Recently, the NIH has awarded \$19 million for two autism centers (<http://www.mental-health-matters.com/events/release.p...>, June 9, 2004). Currently, the NIH is soliciting proposals for Research Centers for Alzheimer’s Disease (<http://www.fedgrants.gov/Applicants/HHS/NIH/NIH/R...>, June 9, 2004) and Muscular Dystrophy. The NIH intends to fund 2 -3 Muscular Dystrophy centers for 5 years with direct costs not to exceed \$1 million per year per center.

In deliberating the issue as to whether the establishment of Research Centers for CFS is warranted, the CFSAC should consider that the NIH has established two Research Centers for Dietary Supplements at an approximate cost of \$1.5 million per year for 5 years. The Centers for dietary supplements will provide both health practitioners and consumers with adequate knowledge to evaluate the health effects of botanical products in the market place (<http://www.applesforhealth.com/dietsuppcent1.html>, June 9, 2004). The National Institutes of Health also awarded \$10 million in 1999 to fund five centers that focus on mind-body research. The mission of these centers is to determine how beliefs, attitudes, values and stress affect both physical and mental health.

When considered in the contexts of the numbers of individuals affected by CFS, the magnitude of the disability endured by the victims of CFS, the magnitude of other illnesses within the United States, and the numbers and reasons for establishing disease-related and other research centers, the CFSAC should consider recommending the re-institution of CFS research centers. These research centers should be similar to the proposed Senator Paul D. Wellstone Muscular Dystrophy Research Centers (<http://grants.nih.gov/grants/guide/rfa-files/FRA-AR-04...>, June 9, 2004) whose purposes are, “to increase basic and clinical research on all forms... promote side-by-side basic, translational, and clinical research; provide resources that can be used by the...research communities, and provide training and

advice...for researchers and physicians who provide initial diagnosis and treatment, including rehabilitation, care for cognitive and behavioral concerns, and therapy for other system complications. Taken together, the centers will constitute a cohesive program...operating under guidelines for NIH cooperative agreements.” In view of the large numbers of individuals with CFS, which knows no geographic or socio-economic borders, it would be appropriate to consider establishing a minimum of 4 centers, one in each quadrant of the continental United States. Funding should not be less than that of other research centers: \$1.5 million in direct costs/center for a period of not less than 5 years.

SUMMARY

In summary, the expected advocacy of experienced, well-respected, CFSAC members for the use of traditional, extramural, NIH funding mechanisms for funding future, CFS research must be weighed against the disappointing progress made in CFS research by the federal government with its reliance on these traditional NIH funding mechanisms and CDC sponsored research. The current funding mechanisms have been criticized publicly in scientific journals and contain shortcomings that are difficult to address and have not been corrected despite changes in grant reviewing processes within the NIH. Research funding mechanisms utilized by the World Health Organization and the European Union contain elements which can reasonably be incorporated into a more aggressive CFS research funding mechanism within the United States. In addition, there are more aggressive intramural and extramural NIH programs which could be invoked. The extent to which the above-cited, more aggressive funding elements should be incorporated into the United States' future funding of CFS research is a discussion that the CFSAC should entertain. If the CFSAC recommends no change from current funding mechanisms, it will be recommending a research program analogous to fishing. Alternatively, if the CFSAC recommends the incorporation of more aggressive elements into the research selection and research support processes, it will be recommending mechanisms more akin to waging war on CFS.

Fish or war? The CFSAC must decide.

About the Author:

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