Review of the Medical Follow-Up Agency

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OTA REVIEW

THE MEDICAL FOLLOW-UP AGENCY

Background Paper

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OTA Review of the Medical Follow-Up Agency

SUMMARY

The Medical Follow-Up Agency (MFUA), a division of the Institute of Medicine. specializes in biomedical and epidemiologic studies that rely on records of the Departments of Defense and Veterans Affairs. The agency' has operated continuously since it was created at the end of the Second World War. MFUA researchers conduct some research entirely within the agency, but for the most part, they collaborate with biomedical researchers from government (in particular the National Institutes of Health and the Departments of Defense (DoD) and Veterans Affairs (VA)) and universities. Several large studies currently under way by MFUA staff were mandated by law.

OTA was asked by the Chairmen of the House and Senate Committees on Veterans' Affairs to convene a workshop (similar to one held by OTA in 1988 also at the request of these committees) to address three main questions regarding MFUA:

1. What progress has been made in addressing the findings and recommendations made in OTA's 1988 review?

2. What level (if any) of core finding is required to keep MFUA operational?

3. How can the MFUA database be made more useful, including efforts to analyze data and disseminate research results?

The workshop was held on August 2, 1994, attended by MFUA staff (including the Director). other IOM officials (including the IOM president). officials and researchers from the Departments of Defense and Veterans Affairs, researchers from the National Institutes of Health. university-based researchers. and one member of a veterans' service organization (see Appendix 2).

This Background Paper summarizes OTA's findings with regard to the three questions asked. based on the workshop discussion as well as background information and discussions with various individuals before and after the workshop. A complete transcript of the workshop proceedings is also available.

Two things set MFUA apart among research agencies: first is its collective expertise m finding and interpreting military and veteran records and second, its medical records on more than 100,000 subjects belonging to about 700 defined groups of veterans ("cohorts" or "rosters"), These study cohorts allow for long-term follow-up studies on a wide range of medical topics which otherwise would be difficult at best, and in many cases impossible to do in the United States, While service personnel and veterans are the populations studied by MFUA. the findings of most of the studies are of general medical importance and apply to the population at large. not just veterans or the military'.

In 1988, when OTA was first asked to examine the issue of core finding, MFUA was at a transition point. It was without a permanent director and had experienced a relatively large staff turnover (especially for such a small **agency), its research agenda** appeared to be dwindling, and it had just been made part of the Institute of Medicine, moving from the National Research Council's Commission on Life Sciences. It was still operating in a largely mainframe computer and paper-based environment; the need to move to microcomputers and to computerize its various paper data files was clear, but funds to do so were not available. OTA at that time recommended core funding of $500,000 per year for a five-year period to allow the agency to address the pressing problems. Despite a recommendation from Congress that MFUA be **given the full $500,000** per year, they have never received more than a compromise level of $200,000 (and that much only in one year), and the payment schedule has been erratic. **Even with this minimal core funding, significant improvements have been wrought since 1988 (with plans for further progress awaiting adequate core funding), placing MFUA on much stronger footing.**

MFUA occupies a small but unique niche in U.S. biomedical research; should it cease to function, important research opportunities would be lost irremediably. The key core functions of maintaining the existing cohorts (including updating and documenting morbidity and mortality, and not just storing records) and carrying out pilot projects (but not general administrative overhead), which are central to the continued functioning of MFUA. cannot, given the realities of research grant budgets, be supported by project-specific finds or by any other IOM or NAS institutional finds. **Core funds should be part of government spending on biomedical research, and should not fall below the modest level of $500,000 per year for the foreseeable future (see table 1).** Within the biomedical research community. separate core support is accepted as a necessary expenditure for the maintenance of other specific research cohorts and is built into program budgets. The issue of transferring funds from the government to the private sector for such core activities rarely arises because virtually' all epidemiologic research is supported directly' by government (NIH) programs. The case of MFUA, as part of a private institution that is funded on a study-by-study basis, is different in this regard, making the issue of core support a more explicit one than it is in most other circumstances. There are some other examples, however. For instance the National Cancer Institute supports core activities, currently at a level of about $140,000 per year each, of a Swedish and a Danish cancer registry. in addition to funding specific studies using these two registries.

MFUA rosters are used by researchers funded by DoD, VA, and NIH, so it would be logical to turn to one or more of these agencies for permanent core funding (all three contribute in the current short-term core funding arrangement). The most appropriate mechanism for achieving a stable core finding situation is not obvious, however, and was not addressed by OTA. **The current situation, in which MFUA has not received the full amount promised it in most years, and receipt of at least a portion of those funds has been unpredictable, is unacceptable.**

TABLE 1: MFUA Minimum Core Funding Needs

Activity	Cost per year ($)
Maintenance of cohorts	
Twins	150,000
All other cohorts	10,000
Pilot and feasibility studies (4-5 per year)	160,000
Board meetings (2 per year	20,000
Portion of salary, benefits, overhead, etc.	130,000
Software unique to MFUA	5,000
Hardware unique to MFUA	25,000
TOTAL	**$500,000**

MFUA'S NICHE IN U.S. BIOMEDICAL RESEARCH

The feature that has distinguished MFUA since its inception after the end of the Second World War is its access to a variety of records from DoD and VA, for which it depends on both Washington-based personnel and MFUA staff based at the National Personnel Records Center in St. Louis. MFUA has served as a repository for records of military and veteran populations that are of special interest, either because they share a common condition (e.g., prisoners of war, battle wounds, vaccines) or because of their unique value to medical researchers (e.g.. twins). Longitudinal research on defined populations is difficult in the population at large in the United States because of our relatively poor ability to track and link different kinds of administrative and medical records. Being military veterans means that members of MFUA cohorts are easier to find later on and many records related to their military service and veteran experience can be linked together to provide a longitudinal picture of significant health events.

Over the years, MFUA also has taken on large-scale epidemiologic studies in veterans at the behest of Congress (through contracts with executive branch agencies). The main examples of this currently are two studies of mortality among atomic veterans. While these studies might be done by other groups (e.g., consulting firms or university researchers), few if any research groups have the necessary staff expertise in military and veteran matters to undertake them without long startup times and learning curves. In addition, there continues to be political benefit of having MFUA, which is, by its own reputation as well as by its position within the Institute of Medicine. widely trusted to undertake them in an unbiased manner, The same can be said of the current Persian Gulf project, also the result of a congressional mandate. which is providing guidance to Congress on the work of DoD and VA in their studies of Persian Gulf veterans' health problems,

The atomic veteran and Persian Gulf projects are funded entirely through contracts with DoD and VA and are not affected directly by the lack of core finding. Core funds are needed not for these and other specific studies, but rather to organize and update the approximately 700 study rosters that are MFUA'S unique resource. MFUA'S director estimates that ultimately about 150 study populations will emerge from the 700 (by some being discarded as not useful and other small rosters with similar characteristics being coalesced) that will be fully described and maintained in a "Catalog of Cohorts" (Appendix 1 gives some sample entries). Some examples of cohorts include soldiers admitted for treatment for special conditions while in the military *2,819* who had rubella in 1944; 1,141 who had schistosomiasis (a parasitic disease of tropical countries) in 1944-45: *465* who had scrub typhus in 1944; and a total of 1,321,862 hospital admissions for a variety of conditions of army personnel over the period 1950-54. Each of these groups offers potential for studying the long-term effects of their conditions, even if the medical importance is not immediately obvious.

An example of the sometimes unpredictable value of these cohorts is a Korean War cohort in MFUA'S files that has just recently become of potential interest to researchers. The background is that two epidemiologic studies published since 1993 have suggested that having blood transfusions might place people at an increased risk of developing non-Hodgkins lymphoma (one of the few cancers not related to smoking that appears to be increasing in incidence in the United States and in other countries), but the conclusions that can be drawn from the existing studies are far from definite. The relevant MFUA cohort is a group of men who had transfusions for war-

related injuries during the Korean conflict. Follow-up of this group and their controls to determine the incidence of non-Hodgkins lymphoma could provide a valuable piece of evidence toward answering this open epidemiologic question.

The NAS-NRC twin registry (see box A) is perhaps the best example of MFUA'S unique research resources. While a number of countries maintain national twin registries, the United States does not (although some other twin registries do exist in this country), and because of the difficulty of linking various types of records here, it is unlikely that we will start one.

At the OTA workshop, participants wrestled with the issue of how to measure objectively the value of an agency like MFUA. While it is easy to enumerate the costs of the agency, there is no obvious scale for measuring the benefits in common units. Taking the example of a research group within one of the NIH institutes, it was suggested that regular reviews of the MFUA'S research program might be conducted periodically by outside peer reviewers. Even with an exercise like that, however, there is no scale that can be used to rank groups. particularly' when the groups are substantially different in the types of research they do. It should be noted that the desirability of having an objective measure did not arise from doubts about MFUA'S value. but more from the desire to document in a more formal way the acknowledged value of their work and to help assure that quality of the work remains high.

PROGRESS SINCE 1988

At the time of OTA's 1988 review of MFUA, the agency had a number of acute problems. It was without a permanent director and its uncertain future made recruiting a new one difficult. There were no core funds at all, so little or no maintenance of the cohorts was going on. computer resources were in need of upgrading but no finds were available for this, and the agency was relatively poorly known within the epidemiologic and biomedical research community. It appeared that the research going on at that time would wind down within a few years, and the future was uncertain. On the positive side, MFUA had just been moved from the Council on Life Sciences of the National Research Council into the IOM, bringing it in closer touch with the medical research community than it had been before.

OTA reported in 1988 that MFUA should not be allowed to slip into nonexistence. Its research record over the years, both in studies conducted by MFUA staff and research by others relying on MFUA cohorts, is distinguished and its value unquestioned. The growing importance and interest in studying chronic disease and the distant sequelae of remote events made preserving the MFUA cohorts even more attractive. OTA, based on the consensus of workshop participants at that time, recommended a five-year period of core finding at $500.000 per year to allow MFUA to begin to deal with the most serious problems.

MFUA began receiving core funding in FY1991 at $200,000 or less each year Even with this rather modest amount (plus small amounts from the National Academy of Sciences), MFUA has undergone major changes addressing, m some fashion, all of the issues raised by OTA in 1988,

Overall, the agency weathered the transition period well and has emerged with much greater stability and resiliency. Some specific changes are listed below.

1. A capable physician-epidemiologist was hired as director and the professional staff has been augmented so that the current studies are fully staffed.

2. The MFUA Oversight Board, now a 10-member body, was expanded and reinvigorated to provide scientific guidance to the agency.

3. Steps have been taken to increase the visibility of the agency within the research community, including the 1990 Conference on Epidemiology} in Military Veteran Populations, and an ongoing series of outreach visits and seminars to professional societies and government research groups by the director.

4. MFUA also has become more receptive to commentary from veterans' groups. which have presented invited testimony on several occasions at atomic veteran and Persian Gulf Health Effects committee meetings.

5. In terms of moving the agency forward substantively, perhaps the most important development has been to begin developing the "cohort catalog." discussed earlier (and see appendix 1).

During the period since 1988, ongoing research continued as well. MFUA staff published 21 scientific papers of their own and collaborated with outside researchers on an additional 29 Key findings from some recent studies include the following:

1 A study of former prisoners of war (POWs) found an association between ischemic heart disease (IHD) and a history of lower limb edema (evidence of "wet beriberi") while in prison camp. POWs who had experienced lower limb edema were three times more likely to die of IHD than those who had not, Based on this finding. VA is planning to compensate former POWs with IHD.

2. In 1942, Army recruits were vaccinated against yellow fever with vaccine unknowingly contaminated with the hepatitis B virus. An epidemic of hepatitis B ensued. Long-turn follow-up of these recruits has established that there has been no long-term increase in liver-related mortality. This series of studies has established clearly that adult onset hepatitis B, at least in Westerners, has an entirely different natural history than does hepatitis B in Japan, China, and other parts of the world, where the virus is transmitted from mother to child shortly after birth. The studies have changed thinking about the relative importance of hepatitis B and hepatitis C as causes of liver cirrhosis and primary liver cancer in the United States.

3. Long-term follow-up of a World War 11 cohort for the development of multiple sclerosis has yielded insights into ancestry and ethnicity as previously unknown or undocumented risk factors for the disease,

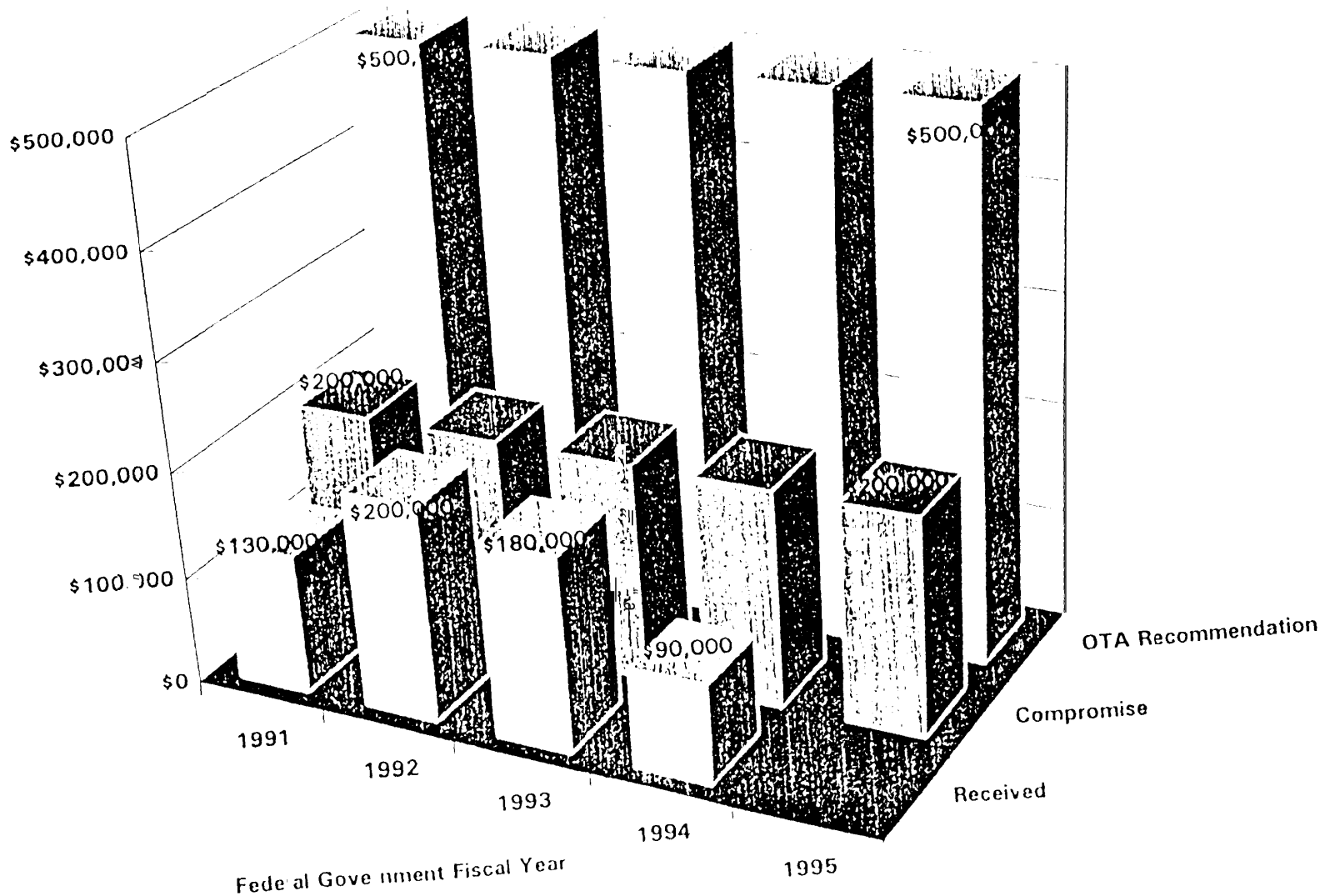
NEED FOR CORE FUNDING

In 1988 part of the rationale for recommending a period of core finding was to provide a temporary boost to MFUA so that the agency could address some of its short-term problems. The future at that time was somewhat uncertain. OTA recommended in 1988 a level of $500,000 per year of core finding for a period of five years. Acting on that recommendation, Senator Alan Cranston, then Chairman of the Senate Committee on Veterans' Affairs, wrote to VA's Chief Medical Director, the Assistant Secretary of DoD for Health Affairs, and the NIH Director. requesting that VA and DoD each contribute 40 percent ($200,000 each) and that NIH contribute 20 percent ($100,000) per year to make up the necessary core funding. The agencies did not agree to contribute at those levels, however, and a compromise level of $200,000 per year was negotiated ($65,000 each from DoD and VA and $70,000 from NIH), beginning in Fiscal Year 1991. MFUA first received funds in 1991, at a level of $130,000 (see figure 1). In the following two years they received $200,000 and $180,000, and in FY 1994, as of August, they had received $90.000 and were expecting to receive an equal amount by the end of the fiscal year (September 30). FY 1995 is the last year that the $200,000 annual core funding stemming from the earlier legislation and compromise is due. The contributors have been reluctant to provide even the compromise amount (and have not met that obligation in at least two years) and are unlikely to continue without additional direction from the Congress beginning in FY 1996.

MFUA'S situation in 1994 is much clearer than it was in 1988: reliable core finding is an absolute necessity to maintain and extend MFUA'S unique study cohorts, and to earn out small pilot studies. The need for money to maintain research resources is by no means unique to MFUA, but the placement of MFUA in the Institute of Medicine, which operates on project-by-project finding rather than an annual budget allocation exposes this need, where it is not obvious in government research organizations such as NIH and the research arms of the VA. All the various registries and data maintenance functions of NIH (e.g., the Surveillance, Epidemiology}', and End Results Program, which tracks cancer incidence in a portion of the U.S. population) receive substantial operating funds, some of which is spent on "core" activities. though they are not necessarily identified as such. The maintenance of existing cohorts and the ability to assemble new ones when opportunities present themselves cannot be accomplished with project-specific finding alone.

The second main use of core funds is for conducting small pilot and feasibility studies to demonstrate the potential for studies to researchers and finders. Researchers are unlikely to apply for research funding (and unlikely to get it if they do apply) without some concrete demonstration that cohort members can be found and that they will participate in studies. MFUA has developed a list of feasibility studies on important medical topics that they could carry out relatively soon, given small amounts of core funds. These include work on the "healthy soldier" effect, a continuation of their work on mortality of former POWs and atomic veterans, studies of female veterans, and a follow-up study on Korean hemorrhagic fever.

FIGURE 1: MFUA Core Funding 1991-95



OTHER FUNDING ISSUES

The National Academy of Sciences charter prohibits its research units from competing with other institutions for grant and contract finding, and this includes MFUA. In 1988. OTA was asked to consider whether it would be advantageous if a mechanism could be found to make it possible for MFUA to compete for funds. At the time, we reported that it might well be advantageous given all the uncertainties then surrounding MFUA. No change occurred. however, and, according to the current president of IOM, it will not. This situation was considered by the 1994 OTA workshop group and was seen in a somewhat different light. It was felt that MFUA should not try to become one among many research groups competing for finds, but should continue to capitalize on the resources that are unique to it (the staff expertise in military and veteran records and the research cohorts). This question should. therefore. be considered closed at the present time.

LEVEL OF CORE FUNDING REQUIRED AND CONTRIBUTORS

The core finding since 1991 has allowed a minimum of maintenance on the rosters. and only the beginning of putting together the cohort catalog. It has been sufficient to keep the work going and to hint at the potential for progress, but not to take things very far. Table 1 provides a breakdown for how $500,000 in core finding could be profitably spent. **This full amount should be provided to MFUA annually--$500,000 should not be a starting point for negotiating downward.** In addition, the mechanism of allocation should be made more secure than **in** the recent period, during which funds were often supplied irregularly and unpredictably.

OTA considered the question of where MFUA'S core fund should come from The agencies currently providing support (DoD. VA, and NIH) are still the obvious candidates. but Congress might also consider arbitrarily assigning the role of core finder to a single agency. The actual mechanism to assure that the chosen funder or finders allocate those funds is beyond the scope of this review.

IMPROVING THE USEFULNESS OF MFUA'S RESEARCH RESOURCES

MFUA has taken a number of initiatives to improve the usefulness of its cohorts, as discussed earlier. The OTA workshop participants generally agreed with the directions taken and made a number of additional suggestions for increasing MFUA'S visibility}' and interactions with the research community. At this time, it appears that MFUA is on an appropriate and productive upward course. With adequate core funding, the next few years should see significant progress. The agency has good scientific guidance and OTA has not identified any major opportunities that have been overlooked by MFUA.

BOX A: THE NAS-NRC TWIN REGISTRY

The best known and among the most important of the cohorts is the NAS-NRC Twin Registry, a group of about 16,000 pairs of male twins, **all** of whom served in the military during the Second World War. MFUA has granted access to and coordinated studies of these twin pairs for **30** years, resulting in a wealth of knowledge including important findings on the genetic influences on many conditions, including. atopic dermatitis, schizophrenia, manic-depressive illness, headache, multiple sclerosis, cancer mortality, alcoholic cirrhosis, Parkinson's disease, and stroke.

Twins have been a focus of epidemiologic research since the late 19th century because they provide a unique opportunity to help sort out the roles of heredity and environment in the etiology of disease. Methods in twin epidemiology have become more sophisticated and diverse during this century, and twin registries are sought after and extensively used as a resource for addressing the role of genetic versus environmental influences,

The NAS-NRC Twin Registry contains nearly all the white male twin pairs who served in the military during World War II. The fact that they are veterans means that extensive records, both from the military and from their experience as veterans, are available for study and long-term follow-up A number of epidemiologic questionnaires have been administered to the twins over the years, and researchers carrying out specific projects have added to the knowledge base about these men. Although it is limited to white males, this twin registry IS among the most valuable of longitudinal cohorts of aging men available anywhere in the world

MFUA has conducted a very small pilot study toward assembling a new veteran twin registry, as a joint endeavor with the Department of Defense, of people who have served from 1986 forward, Including men and women of all racial and ethnic groups. Additional core funds are needed to move this pilot testing far enough along to allow MFUA to seek the funding to actually put the registry together No other group in the United States is in a position to assemble such a registry.

Examples of Studies Using the Twin Registry

Genetic Influences on Smoking

The twins were surveyed in 1967-69 (when they were 40 to 50 years old) and again in 1983-85 (when they were 56 to 66) about their smoking habits. The study established moderate, but real, genetic Influences on lifetime smoking practices and IS consistent with current thinking about nicotine addiction

Suicide

Suicide tends to cluster in families, suggesting genetic or shared environmental Influences Results of a study of the NAS-NRC suggested a significant genetic Contribution to the likelihood of an individual committing suicide.

Alzheimer's Disease

A telephone interview was conducted to identify individuals in the registry who might have been suffering from dementia, and those so identified were followed up by clinical interview. These individuals and their twins as controls) have been followed over time to track the development of true dementia, which has turned out to be less common than had been expected. The studies also suggest that many cases of Alzheimer's disease with very early onset lack a genetic predisposition, which is common in older victims The comparison of genetically identical twins provides an ideal way to examine the environmental factors that may trigger the disease

Appendix 1

Sample Entries for MFUA "Cohort Catalog"

Cohort 290: Korean Hemorrhagic Fever

Summary: A cohort of 1554 veterans who survived an acute episode of Korean Hemorrahagic Fever (KHF), the prototype hantavirus infection, acquired while serving with the Army in Korea in 1950- 1952, suitable for natural history study of long term sequelae of infection. A control population, cohort 291, consisting of 831 individuals was selected from comparable military units in which no case of KHF occurred because of concern at that time about asyptomatic infections.

References: 1. Rubini ME, Jablon S, and McDowell ME. Renal residuals of acute epidemic hemorrhagic fever. Arch Int Med 1960; 106: 378-87.

2. Glass GE, Watson AJ, LeDuc JW, et al. Infection with a ratborne hantavirus in US residents is consistently associated with hypertensive renal disease. J infect Dis 1993; **167: 614-20**

Fields:

Name (1OO% complete)
Service # (99% complete, 1% missing)
Sex (IOO% Male, O% Female, O% Unknown, 2% Missing)
Race (91% White, 3% Black, 470 Other, 0% Unknown, 2% Missing)
Age (86% complete, 1470 missing) •
Rank (98% complete, 2% missing)
Unit (1 OO% complete)

Keywords: Korean Hemorrhagic Fever, KHF, Epidemic Hemorrhagic Fever, Hemorrhagic Fever with Renal Syndrome, Nephropathia Epidemica, Hemorrhagic Nephrosonephritis, Hantavirus, Korea, Korean veterans, Korean Conflict

Cohort 291: Korean Hemorrhagic Fever Study Controls

Summary: A cohort of **831** individuals selected from combat units serving in the Korean theater in 1950- 1952 in which no case of KHF occurred. Used as control population for study referenced (1) below.

References: **1.** Rubini ME, Jablon S, and McDowell ME. Renal residuals of acute epidemic hemorrhagic fever. Arch Int Med 1960; 106: 378-87.

2. Glass GE, Watson AJ, LeDuc JW, et al. Infection with a ratborne hantavirus in US residents is consistently associated with hypertensive renal disease. J infect Dis 1993; 167: 614-20

Fields:

Name (100% complete)
Service Number (99% complete, 1% missing)
Sex (100% Male, 0% Female, 0% Unknown, O% Missing)
Race (100% White, 0% Black, 0% Other, 0% Unknown, 0% Missing)
Age **(89%** complete, 11% missing)
Rank **(98%** complete, 2% missing)
Unit (100% complete)

Keywords: Korean Hemorrhagic Fever, KHF, Epidemic Hemorrhagic Fever, Hemorrhagic Fever with Renal Syndrome, Nephropathia Epidemica, Hemorrhagic Nephrosonephritis, Hantavirus, controls, Korea.

Cohort 621: Navy Aircraft Electronics Technicians and Aircraft Electricians Mates

summary: A cohort of 5,404 Navy veterans who served on bored carrier vessels during the 1950-1954 period and were part of a larger cohort (see cohort 622) occupationally exposed to microwave radiation.

References: Robinette CD, Silverman C, Jablon S. Effects upon health of occupational exposure to microwave radiation (radar). Am J Epidemiol 1980; 112:39-53

Fields:

Name (100% complete)
Service # (99% complete, 1% missing)
Sex (100% Male, O% Female, 0% Unknown, 2% Missing)
Race (80% White, 3% Black, 9% Other, 6% Unknown, 2% Missing)
Age (98% complete, 270 missing)
Rank (99% complete, 1% missing)
Military Occupational Specialty (100% complete)
Unit (100% complete)
Exposure level estimate (100% complete)

Keywords: Microwave, Radar, Radiation, Non-ionizing Radiation, Navy, Ships, Carriers, Electronics, Korea, Korean veterans, Korean Conflict

Cohort 622: **Navy Electronic Technicians Radar operators, etc.**

Summary: A cohort of 37,348 Navy veterans who served on board carrier vessels during the 1950-1954 period and were part of a `larger Cohort (see cohort 621)` occupationally exposed to microwave radiation.

References: Robinette CD, Silverman C, Jablon S. Effects upon health of occupational exposure to microwave radiation (radar). Am J Epidemiol 1980; 112:39-53

Fields:

Name (100% complete)
Service # (99% complete, 1% missing)
Sex (100% Male, 0% Female, 0% Unknown, 2% Missing)
Race (80% White, 3% Black, 9% Other, 6% Unknown, 2% Missing)
Age (98% complete, 2% missing)
Rank (99% complete, 1 % missing)
Military Occupational Specialty (1000/0 complete)
Unit (100% complete)
Exposure level estimate (100% complete)

Keywords: Microwave, Radar, Radiation, Non-ionizing Radiation, Navy, Ships, Carriers, Electronics, Korea, Korean veterans, Korean Conflict

Influenza	101, 127, 128, 129,423
Kala Azar	**484**
Kawasaki Syndrome	**567**
KIA/MIA	**453**
Knee Injuries	**037,645,657**
Knee, menisectomies	**037**
Korea	112,290,291,423,542, 621,622
Korean Conflict	112,290,291,423, 542,621,622
Korean Hemorrhagic Fever	290,291
Korean Veterans	112,290,291,423, 542,621,622

Meningococcal Disease	**504**
Menisectomies	**037**
Microwave radiation (radar)	**621,622**
Multiple Sclerosis	**282,288,324,328-351**

Appendix 2

Participants at OTA Workshop

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Richard Miller. MD
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