

INSTITUTE OF MEDICINE



Exploring the Untapped Potential of the “Ranch Hand” Research Assets

- Presentation at APHA Annual Meeting November 5, 2007
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-
- Institute of Medicine

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Intent of this talk

- Introduce the National Academies, Institute of Medicine, and Board on Military and Veterans Health
- Summarize
 - the intent and structure of the Air Force Health Study (Ranch Hand study).
 - the characteristics of the biologic samples and data collected in the course of the study.
 - the major findings of the 2006 IOM report *Disposition of the Air Force Health Study*.
- Describe the current status of the Ranch Hand research assets and plans for the future.

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The National Academies

- Chartered by the U.S. Congress in 1863 as an independent non-governmental institution.
- “[T]he Academy shall, whenever called upon by any department of the Government, investigate, examine, experiment, and report upon any subject of science or art”

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The Institute of Medicine

- Component of the National Academies.
- Chartered in 1970 “to enlist distinguished members of the medical and other professions in the study of problems that affect the public’s health.”

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The Board on Military and Veterans Health

- Established in 2006 to focus on issues of health and health care related to military service within the IOM.
- Includes the Medical Follow-up Agency, which ...
 - has over 60 years of experience in researching the health of active-duty military personnel and veterans.
 - is the home of the MFUA Cohort Catalog, a collection of study populations of former military personnel assembled as part of proposed or completed research dating back to the 1940's.

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The National Academies study process

- Committee of volunteer experts formed.
- Reports written on the basis of
 - systematic literature reviews
 - public hearings and workshops
 - written testimony and other information
- Final report subjected to external peer review.

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The Air Force Health Study (AFHS)

- Study instigated by US Air Force (USAF) in June 1979.
- Protocol subjected to ten rounds of review and revision; final version (11) published in January 1982.
- Protocol called for a 20-year morbidity study with up to six physical examination cycles in years 1, 3, 5, 10, 15, and 20, plus companion mortality and reproductive studies.
- Total study cost (through FY 2006): ~\$143M

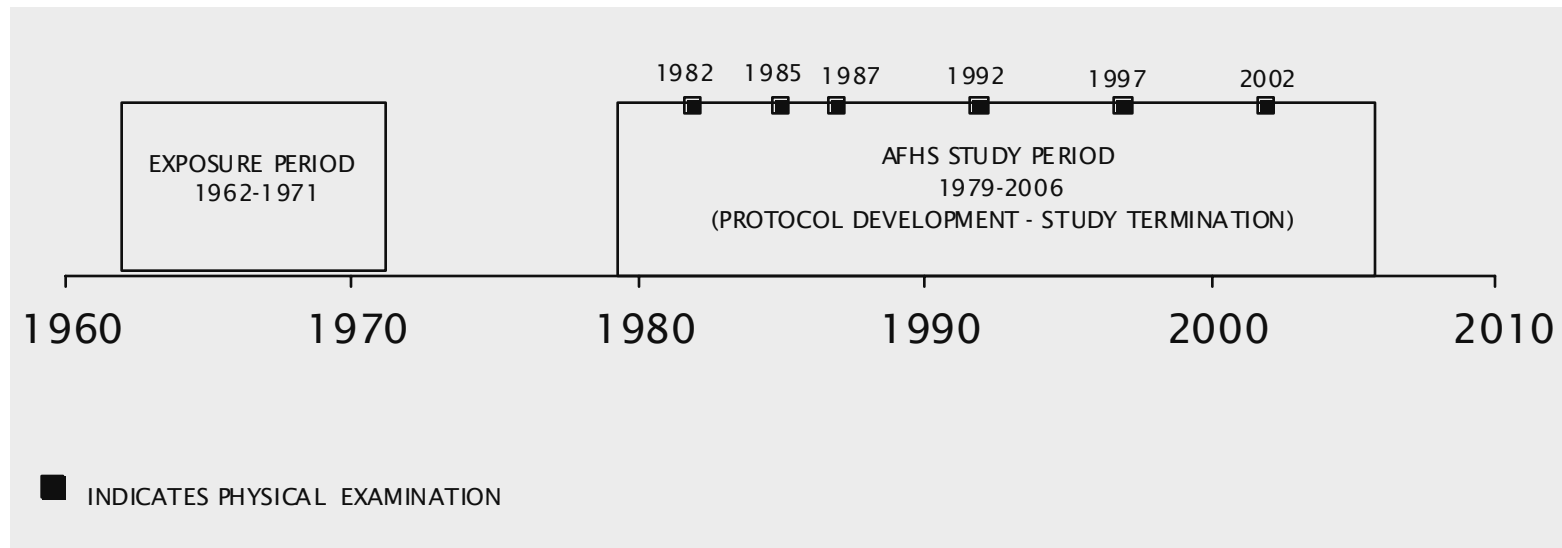
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AFHS timeline



Source: *Disposition of the Air Force Health Study*, Figure 2-1, p. 33 (IOM, 2006)

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AFHS morbidity study clinical examination health endpoints

- general health
- endocrine
- pulmonary
- immunologic
- neurologic
- renal
- gastrointestinal
- hepatic
- hematologic
- dermatologic
- psychiatric
- neoplasia (cancer)
- cardiovascular
- reproductive

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AFHS morbidity study clinical examination data gathering

- blood draws
- urine and semen collection
- skin and fat biopsies
- stool smears
- spirometry
- chest X rays
- electrocardiograms (ECGs)
- dermatology examinations
- peripheral vascular exams
- neurological assessments
- psychological testing
- many other clinical endpoints

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AFHS morbidity study questionnaire data gathering

- education
- employment
- income
- marital and fertility history
- spirometry
- child and family health
- health habits
- physical activities
- toxic substances exposure
- neurologic health
- military experience
- wartime herbicide exposure

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AFHS morbidity study data assets

- Detailed physical, mental, laboratory, and demographic data from 2,758 subjects who participated in at least one exam, including
 - ~15,000 chest X-rays
 - ~51,000 serum samples
(~2,000 serum dioxin assays)
 - ~20,000 whole blood samples
 - ~7,000 urine samples
 - ~9,000 semen samples
 - ~300 adipose tissue samples

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AFHS reproductive outcomes study

- Comprehensive reproductive histories ascertained through interviews of current and former wives or partners.
- Medical records data gathered from partner and offspring health providers.
- Offspring followed through age 18.
- Medical data collected and verified for 9,921 conceptions and 8,100 live births.

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AFHS mortality study

- Mortality data collected through periodic status queries to major databases: Social Security Administration, DVA, IRS, USAF, National Death Index.
- Date of death and reported primary and secondary underlying cause of death coded.
- Data collected and analyzed on ~20,000 subjects.

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AFHS contributions to the scientific literature

- Papers on
 - pharmacokinetics of TCCD and its half-life in humans.
 - Vietnam veterans health status.
- Papers and reports have influenced determinations of the association between herbicide exposure and health effects in Vietnam veterans.
 - Type 2 diabetes (diabetes mellitus)
 - spina bifida in the children of veterans

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The National Academies and the Ranch Hand study

- National Academies *Panel on the Proposed Air Force Study of Herbicide Orange* reviewed version 6 of the AFHS protocol, issuing their final report in 1980.
- Ranch Hand study results reviewed as part of IOM's *Veterans and Agent Orange* -series of reports from 1994 through the present.
- The Veterans Benefits Act of 2003—enacted as Pub. L. 108-183 §602(c)—directed IOM to offer advice on the AFHS research assets.

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The charge to the IOM committee in Pub. L. 108-183 §602(c) [excerpt]

[Evaluate the] “scientific merit of retaining and maintaining the medical records, other study data, and laboratory specimens collected in the course of the Air Force Health Study after the currently scheduled termination date of the study in 2006”.

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IOM's response to the congressional charge

- *Committee on the Disposition of the Air Force Health Study* formed in 2004.
- Committee meetings, a workshop, and information gathering and analysis—including a site visit to the AFRL research facility and biorepository in San Antonio, TX—conducted in 2005.
- Interim letter report released in November, 2005; final report in February, 2006.

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Committee on the Disposition of the Air Force Health Study

David J. Tollerud, MD, MPH (Chair)
University of Louisville

Dan G. Blazer, MD, PhD
Duke University

Susan E. Hankinson, ScD
Harvard University

Ellen Wright Clayton, MD, JD
Vanderbilt University

David A Kalman, PhD
University of Washington

Manning Feinleib, MD, DrPH
The Johns Hopkins University

DeJuran Richardson, PhD
Lake Forest College

Mark S. Goldberg, PhD
McGill University (Canada)

Regina M. Santella, PhD
Columbia University

Consultants to the committee

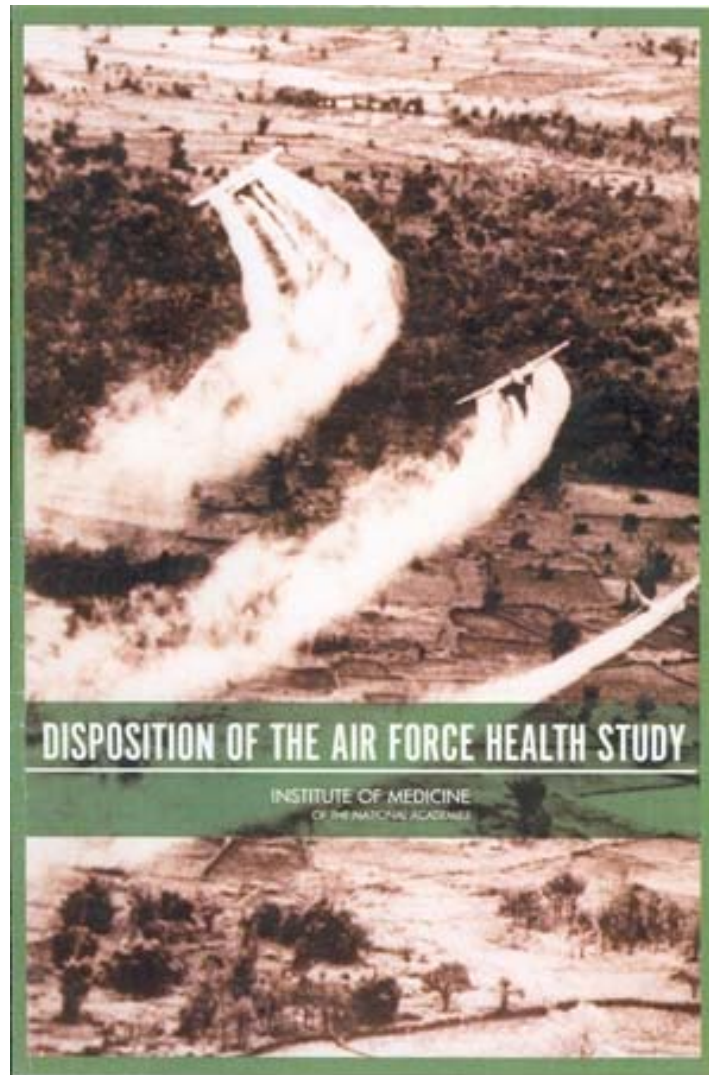
James G. Hodge, Jr., JD, LL.M.
The Johns Hopkins University

Victor Pontes, MS
Channing Lab. (Harvard University)

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2006 IOM report content

Conclusions and recommendations were offered on several topics including ...

- the value of the AFHS research assets,
- alternatives for the future of the assets,
- characteristics of a good custodian of the assets,
- establishing the assets as a resource for researchers, and
- future review of support for the assets.

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Value of the research assets – conclusions –

- The AFHS data assets are unique: no other epidemiologic dataset on Vietnam veterans contains as detailed information over as long a time period.
- The data collected by the AFHS appear to be of high quality and the specimens appear to be well preserved.
- Analysis of the AFHS data assets has contributed to the literature addressing the health of Vietnam veterans.

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Value of the research assets – conclusions –

- It follows that there is scientific merit in retaining and maintaining these resources after the study's currently scheduled termination date.
- However, the AFHS dataset has weaknesses that limit its utility as a means of evaluating the health impacts of Agent Orange exposure.

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Weaknesses of the AFHS dataset

- Inherently small size of the cohort.
- Cohort is unrepresentative of in-theater veterans.
- Lack of biomarkers of herbicide exposure other than TCDD.
- Little information on subjects' wartime locations.
- Unavailability of detailed exposure histories.
- Possible herbicide exposures in the comparison population.

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Value of the research assets – conclusions –

These limitations are not an intrinsic obstacle to retaining and maintaining the assets after the currently scheduled termination date.

Further study of the AFHS medical records, other study data, and laboratory specimens is thus advisable.

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Value of the research assets

– conclusions –

The potential value and relevance of extending study of the data assets rest in taking full advantage of available information and in the application of the results of future research that could encompass:

- reanalysis of outcomes examined by the AFHS using different assumptions and approaches than have been applied to date,
- new analyses of the medical records and other study data that examine questions that were not addressed in the AFHS,

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Value of the research assets

– conclusions –

The potential value and relevance of extending study of the data assets rest in ... future research that could encompass:

- new studies of the collected biospecimens that take advantage of advances in technology and science to conduct analyses that were not contemplated in the AFHS protocol,
- expansion of the study's period of analysis through follow-up of the cohorts using publicly available information, and
- additional follow-up of health outcomes in AFHS participants.

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Alternatives for the future of the AFHS research assets – conclusions –

- It is advisable to extend the AFHS by making the database and associated biospecimen collection available for study via a custodian that should take an active role in fostering research on the assets.
- It is advisable to allow for the possibility of collecting additional data and specimens.

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Characteristics of a good custodian of the AFHS research assets

- Ability to satisfy operational requirements related to the supervision of and access to the data and biological materials.
- Commitment to address the complex ethical, legal, social, and related issues that arise when managing epidemiologic records and associated biospecimens.

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Options for future management of the AFHS research assets

- Use the National Archives data management and distribution mechanisms.
- Use the existing AFHS infrastructure within the USAF.
- Use Department of Defense epidemiologic data management and distribution mechanisms.
- Use Department of Veterans Affairs or VA-affiliated epidemiologic data management and distribution mechanisms.

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Options for future management of the AFHS research assets

- Use National Institutes of Health or Centers for Disease Control and Prevention epidemiologic data management and distribution mechanisms.
- Use the Institute of Medicine (IOM) Medical Follow-up Agency.
- Identify a new custodian through a competitive process.

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Options for future management of the AFHS research assets

- The committee did not offer a recommendation on the specific federal or nonfederal entity best suited to assume responsibility for the AFHS research assets.
- It concluded that all of the options it listed had advantages and disadvantages, and all could be made to work with the appropriate provision of funds, commitment on the part of the custodian, and implementation of the recommendations offered in the report.

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Characteristics of the good candidates

Prior experience in:

- conducting veterans' health studies,
- collecting and storing epidemiologic data, and disseminating it to independent researchers,
- fostering collaborations with independent researchers,
- maintaining quality control over the studies that use their datasets, and
- publishing results in the peer-reviewed literature.

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Characteristics of the good candidates

- All have military or veterans health issues as the central focus of their operations, but also conduct other types of studies with their data assets.
- To the committee's knowledge, none has experienced a breach in their system of protecting subjects' privacy and the security of their data.

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Options for future management of the AFHS data assets

The committee identified three good candidates for custodianship:

- The Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) of the VA.
- The Seattle Epidemiologic Research and Information Center (Seattle ERIC) of the VA.
- The Medical Follow-up Agency (MFUA) of the National Academies' Institute of Medicine.

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Establishing the AFHS assets as a resource for researchers

- The committee recommended that Congress allocate a minimum of \$250,000 per year for three years to cover the direct costs of small grants for secondary data analysis or pilot projects using the data assets of the AFHS. This allocation will provide seed money for one to three investigations each year.
- Research support beyond the seed money will be the responsibility of prospective researchers, who will need to obtain it from other funding sources.

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Future review of support for the AFHS assets

- A five-year commitment—that is, two years after the last small grants proposed above are made—should be sufficient to establish whether the AFHS resources have value and relevance as a resource.
- Therefore, five years after the chosen custodian assumes responsibility, a committee should be convened to evaluate the potential value and relevance of extending further support to the maintenance of access to the data or the biospecimens collected in the course of the AFHS.

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Events since the release of the 2006 IOM report

- Section 714 of the John Warner National Defense Authorization Act for Fiscal Year 2007 (Public Law 109-364) directed that MFUA assume custodianship of the AFHS's data and biospecimens at the conclusion of the Study.
- AFHS sought permission from the Study cohort to transfer its data assets to MFUA; 94% consented.
- AFHS transferred Study data to MFUA shortly before ceasing operations on 30 September, 2007.

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Events since the release of the 2006 IOM report

- Because MFUA does not have an in-house capability to maintain biospecimens, it sought an alternative location to securely store them; the Air Force Research Laboratory at Wright Patterson Air Force Base (Dayton, OH) agreed to assume this responsibility.
- AFHS biospecimens are being maintained at the San Antonio facility until renovation of an appropriate space at AFRL-WPAFB is complete.

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Events since the release of the 2006 IOM report

Bills currently under consideration in the US Congress would allocate funding to support maintenance of the AFHS assets and provide seed money for new research

- H.R. 2681 – *To provide for the maintenance, management, and availability for research of assets of Air Force Health Study*
- S. 1315 – *Disabled Veterans Insurance Improvement Act of 2007 (§ 805)*

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MFUA's plans for the Ranch Hand research assets

Once funding is provided, MFUA will seek to promote new and innovative research on the AFHS assets by ...

- soliciting proposals from qualified researchers,
- subjecting submissions to rigorous scientific and IRB review,
- seeking collaborative relationships with successful applicants,
- disseminating available support money to promising proposals, and
- promoting publication of research results.

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Learning more about MFUA's Ranch Hand research assets initiatives

- Full text of *Disposition of the Air Force Health Study*:
<http://www.nap.edu/catalog/11590.html>
- Home page of the Board on Military and Veterans Health:
<http://www.iom.edu/CMS/26761.aspx>
- Information on the MFUA Cohort Catalog:
<http://www.iom.edu/CMS/3795/4903.aspx>

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