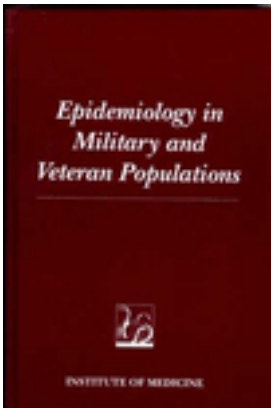

Epidemiology in Military and Veteran Populations: Proceedings of the Second Biennial Conference, March 7, 1990

William F. Page, Editor; Medical Follow-Up Agency, Institute of Medicine

ISBN: 0-309-57239-8, 112 pages, 6 x 9, (1991)

Epidemiology in Military and Veteran Populations

Proceedings of the Second Biennial Conference
March 7, 1990

William F. Page, Editor

Medical Follow-up Agency
Institute of Medicine

National Academy Press
Washington, D.C.1991

National Academy Press 2101 Constitution Avenue, N.W. Washington, D.C. 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for this report were chosen for their special competencies and with regard for appropriate balance.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an advisor to the federal government and its own initiative in identifying issues of medical care, research, and education.

This project was supported by funds from the Institute of Medicine and the Andrew W. Mellon Foundation.

Library of Congress Catalog Card No. 91-62332
International Standard Book Number 0-309-04548-7
Additional copies of this report are available from: National Academy Press2101 Constitution Avenue, NW Washington, DC 20418

S411
Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

Preface

In June 1988, the first Conference on Epidemiology in Military and Veteran Populations was held in Washington, D.C. at the National Academy of Sciences. That conference brought together a number of speakers on a variety of topics and produced, as a byproduct, several ideas for epidemiologic studies. The success of that first conference led to a second.

It was suggested that the proceedings of the second conference, when held, might be published. With the generous sponsorship of the Institute of Medicine and the Andrew W. Mellon Foundation, the second conference was held; with their continued help these proceedings are now being brought to print. In the interest of simplicity, the papers from these proceedings are being reproduced as submitted, without further copy-editing.

The obvious reason for publishing such proceedings is to bring the presentations at the conference to the attention of a wider audience, but here there are, in fact, two such audiences. A great deal of epidemiologic work in military and veteran populations is dispersed among a large number of independent organizations. One purpose of the proceedings is to make these organizations more aware of the relevant work of their colleagues in other settings; this is the first audience.

The second, even wider, audience is the community of all epidemiologists. Although there are some research issues and specific methodologies of primary interest only to those who study military and veteran populations, to a considerable degree the interests and practices of those who study such populations are the same as those of other epidemiologists. It is important that the wider community of epidemiologists is informed of and, in turn, informs the work of the smaller community doing epidemiologic research in military and veteran populations. The publication of these proceedings may assist in serving that end.

In closing this preface, let me offer my thanks to Dr. William Page, editor of these proceedings and planner of the conference. Let me also thank my colleagues, the members of the Medical Follow-up Agency's oversight committee, the Committee on Epidemiology and Veterans Follow-up Studies (list follows), for their assistance and support, as well as Dr. Samuel Thier, President of the Institute of Medicine, and Dr. Enriqueta Bond, its Executive Director, for their support and sponsorship. Thanks are, in addition, due to a number of persons on the Agency's staff who helped arrange travel, type letters and memos, and so forth--it is they who made the conference run smoothly. Finally, let me thank the presenters for their talks at the conference and their subsequent papers.

RICHARD D. REMINGTON, CHAIRMAN

COMMITTEE ON EPIDEMIOLOGY AND VETERANS FOLLOW-UP STUDIES

COMMITTEE ON EPIDEMIOLOGY AND VETERANS FOLLOW-UP STUDIES

Richard D. Remington, Ph.D. University of Iowa
Dan G. Blazer, M.D., Ph.D. Duke University Medical Center
Ethel S. Gilbert, Ph.D. Battelle Memorial Institute
Michel A. Ibrahim, M.D. University of North Carolina at Chapel Hill
Lawrence F. McMahon, Jr., M.D., M.P.H. University of Michigan Medical Center
Paul D. Stolley, M.D. University of Pennsylvania
H. Eldon Sutton, Ph.D. University of Texas at Austin
Myrna M. Weissman, Ph.D. Columbia University

Contents

Means and Ends

The papers of these proceedings largely are examinations of some of the varied ways in which epidemiologic data may be collected from military and veteran populations and used in their study. Because these papers are about the means used to gather and analyze data, a word is in order about the ends that such activities serve. These papers have a wide applicability in that they are not only a part of military medicine but of clinical and scientific medicine generally. The study of military and veteran populations should be regarded as part of the study of the general population. The purpose of this introduction is to illustrate that the apparently specialized means employed in these studies are meant to serve the most general of ends: an understanding of the workings of disease in order to realize health.

The general applicability of results from studies of military and veteran cohorts is easily observed in the cases where such cohorts resemble other well-defined, usually occupational, cohorts. This is the case in the presentation by Brundage and the papers of Carmelli et al., and, to some extent, Jablon. Being infected by the human immunodeficiency virus (HIV), being a twin, or being exposed to low-level ionizing radiation are things that may befall members of the general population. Having made this obvious statement, one may ask the obvious question: Why study a military cohort?

There are at least two good, practical answers. First, the study of a military cohort can provide opportunities to gather information in a particularly efficient way. Second, military cohorts by their constitution often differ in small, yet important, ways from the nonmilitary cohorts available for study.

The first advantage in studies of military and veteran cohorts, efficiency of data gathering, comes about from things like the ready availability of material from which to assemble study cohorts and the possibility of attaining a very high degree of completeness of follow-up without great expense. For example, in the talk by Col. John Brundage,

which is not included in these proceedings, the fact that all active-duty Army personnel were required to be screened periodically for HIV infection makes available a large cohort of HIV-positive individuals. In addition, the annual examination of these individuals is already part of an ongoing Army program, so that follow-up information is obtained at low cost to the researcher, although the degree of completeness of this information is an issue that remains to be studied.

The second potential advantage of a military cohort is also illustrated by that study. The Army cohort is almost surely more representative of the U.S. general population than are, for example, the special cohorts, such as male homosexuals or hemophiliacs, whose study has provided most of the information available on the natural history of HIV infection to date. If nothing else, the Army's national data are not limited to a local geographic area. However, it should be pointed out that representativeness is a complicated matter, and that the active-duty military population is not strictly representative of the general population. In particular, the military induction examination screens from military service certain persons with selected medical conditions, no doubt with varying rates of success; hemophiliacs, for example, are almost certainly screened out. In addition, the military's proscription of homosexual activity and illicit drug use should, at least in the long run, tend to remove from military service many individuals engaging in these activities, which are associated with a high risk of acquiring HIV infection. Notwithstanding such reservations about the strict representativeness of the active-duty Army population, it is clear that much that is new will be learned by studying it and by comparing results derived from it with those obtained from other, even less representative, cohorts.

Moving from those studies in which a military cohort more closely resembles a nonmilitary cohort, we come to those studies in which a military cohort is defined by an event that would likely not be experienced outside the armed services. Such is the case for military captivity (Engdahl and Page), large-scale exposure of Americans to epidemic hemorrhagic fever (LeDuc et al.), or to herbicides such as Agent Orange (Kang et al.). A case for the general applicability of results from studHP LaserJet II DHPLAIID.PRSzed as relatively rare. Although some events might reasonably never be seen outside the military, others could occur in some fashion among civilian populations, although often the full range and intensity of the military experience is unmatchable. The study of cohorts defined by events and exposures that might reasonably occur outside the military is more easily recognized as being capable of producing results of general applicability. Yet even studies of cohorts whose experiences are truly unusual, and whose infrequency may at first suggest that their study will not produce any information relevant to general populations, may

nevertheless provide such information. Take, for example, perhaps the most singular case, the study of prisoners of war reported by Engdahl and Page.

As reported by these authors, the treatment of military personnel during captivity—as evidenced, for example, by an average body weight loss during captivity of almost 40 percent among prisoners of the Japanese—seems unparalleled in its brutality; thus, it might be expected to produce correspondingly singular psychological after-effects. However, it turns out that the psychological after-effects of military captivity are similar to the more general after-effects of other serious trauma, such as being the victim of a natural disaster. This similarity of after-effects was not immediately apparent and took a while to be discovered; thus, for a time, the psychological sequelae of military captivity were studied only in relative isolation. Now, however, it appears that the differences between the psychological sequelae of military captivity and other traumatic experiences may be differences of degree, not of kind, and that in studying adaptations to combat stress, one may learn much about psychological adaptation in general.

In conclusion, whether the military cohort is defined on the basis of a unique event or exposure, or on the basis of something largely ordinary, its study is meant to yield insights of a more general nature. This point needs to be kept in mind as one reads the papers in these proceedings, for while they possess something of a specialized nature, they have as their end the provision of information of general applicability. They demonstrate how the epidemiology of military and veteran populations is so rich an area of study.

WFP

Synopses of Papers

In the paper by Seeff, we learn about a study whose purpose was to examine whether hepatitis B infection in an area of low endemicity conveys the same risk of subsequent liver cancer as it does in endemic areas. The opportunity for this study was an outbreak of hepatitis among World War II (WW II) Army servicemen involving some 50,000 cases; it is now known, because of this study, that this outbreak was the largest point-source outbreak of hepatitis B ever recorded. Seeff reports limited case-control mortality data as well as serologic data on three groups: those servicemen who received hepatitis-contaminated yellow fever vaccine and were hospitalized, those who received the vaccine and who were asymptomatic, and a third group who did not receive the contaminated vaccine. In the serologic study, a large proportion of subjects in the first two groups had markers for the hepatitis B virus—97.7 percent and 77 percent, respectively, versus 13 percent for the control group. Of greater interest was the fact that hepatitis B surface antigen was found for only one person in the first two groups, yielding an overall carrier rate of less than 0.5 percent, unexpectedly low given the prevailing view that 5 to 10 percent of acutely hepatitis B virus-infected persons are supposed to become carriers. It is not surprising that this striking result has begun to overturn conventional thinking in hepatitis research.

In the Carmelli et al. paper, heritability estimates for tobacco, alcohol, and coffee use are produced using data from the Medical Follow-up Agency's (MFUA) large panel of WW II twins. The heritability estimates produced are very much in line with similar, previous estimates, yet they have the additional feature that they are derived using multivariate statistical models as well as the usual univariate ones. It is the size of the twin panel as well as the availability of longitudinal covariate data (which are used to adjust the heritability estimates) that permits these more powerful analyses, illustrating the fact that even when veteran status, per se, is relatively unimportant, veteran cohorts can nevertheless provide significant opportunities for research. But it should be noted that in at least one regard the veteran twins in the MFUA panel are not so typical:

their reported history of tobacco use ("ever smoked") was a very striking 82 percent. This high rate is attributed to the distribution of free cigarettes to WW II soldiers.

In the paper by LeDuc et al., we learn of a "very interesting set of sera" collected by the Hemorrhagic Fever Commission, formed by the Army during the Korean conflict to deal with the "new" disease encountered by U.S. troops in Korea. In the subsequent decades, the cause of this new disease was identified and named ("hantaan virus," after the Hantaan River in the endemic area of Korea), and a serologic test for the agent was developed. Thus did these sera become very interesting: it was now possible to test them with the new assays and determine whether the Korean conflict epidemic was actually due to the newly identified hantaan virus. LeDuc et al. report that it was--some 94 percent of the time the original clinical diagnoses were accurate. Having verified the clinical diagnosis, it is now possible to follow up the men who provided these sera and study the long-term sequelae of hantaan virus infection.

Moreover, not only is all of this fascinating from a medical point of view, but there are also potential public health ramifications. Specifically, studies of Korean patients residing in urban centers and diagnosed as having hemorrhagic fever with renal syndrome led to the identification of a new virus, now named the Seoul virus, related to but distinct from the hantaan virus. Of special interest was the fact that this new virus had been found in domestic rats rather than in its usual vector, the striped fieldmouse. Studies of the rat population in the inner city of Baltimore have shown that these Seoul-like viruses are also common there, and studies of inner-city Baltimore residents done at Johns Hopkins Hospital found that they had a five-fold higher prevalence rate of seropositivity for this virus; the most common diagnosis among seropositives in the group was hypertensive renal disease. If past hantaan viral infection is associated with subsequent development of chronic renal disease, as the evidence in this paper suggests, then such illnesses represent a multi-million-dollar public health problem.

The paper of Engdahl and Page reports data from one of the unique cohorts discussed earlier. Data are presented on depressive symptoms showing that former prisoners of war (POWs) still have notable psychiatric sequelae nearly forty years after their release from captivity, a three-to five-times-higher prevalence of depressive symptoms than expected. More important, this higher rate of depressive symptomatology is statistically linked with severity of treatment during captivity and with demographic factors such as years of education and age at capture. Such results not only have relevance to the current medical treatment of POWs but also

provide valuable insights into post-traumatic adaptation in the more general sense.

The paper by Kang et al. (which appeared in the January 1991 issue of the Journal of the American Public Health Association) makes innovative use of general population data to study the health effects of dioxin on Vietnam veterans. In contrast to the kinds of studies discussed earlier, wherein data from military or veteran populations are important because of their applicability to the general population, in this study the general population data are important because they pertain to a certain subset of military veterans. Notwithstanding the irony of this particular situation, the use of routinely gathered samples from the general population to study the effects of environmental exposures in a special subpopulation is commendable.

The data themselves come from a bank of adipose tissue samples assembled under the auspices of the U.S. Environmental Protection Agency. Although the target population for the samples was meant to be all non-institutionalized persons in the United States, the invasive nature of adipose tissue collecting limited the actual sampled population to decedents who died from external causes (90 percent) and surgical patients (10 percent). The samples were then analyzed to determine the presence of 2,3,7,8-TCDD (tetrachlorodibenzo-p-dioxin), one of the toxic contaminants of Agent Orange, a defoliant sprayed on parts of Vietnam during the Vietnam conflict. The records of the Agent Orange spraying missions (the so-called HERBS tape) were used to derive an Agent Orange exposure index. The study found that mean dioxin levels did not differ among Vietnam veterans, non-Vietnam veterans, and civilian controls, with or without adjustment for confounding factors. In addition, none of the surrogate measures of Agent Orange exposure was associated with adipose tissue dioxin levels.

The last paper presented at the conference was Jablon's paper on radiation risk studies in military populations. In this insightful paper, Jablon divides studies of radiation risk in humans into two classes: "scientific studies" and, for lack of a better term, "population studies." This classification is central to the paper, for the two kinds of studies yield very different kinds of information—in the first case, quantitative information concerning the risk of radiation carcinogenesis, and in the second, evidence (or lack of it) that some given radiation exposure was likely to have caused excess cancer. Studies of veterans, Jablon asserts, generally fall into the second class, due to the fact that accurate exposure data are seldom available. Notwithstanding the difficulty, if not impossibility, of deriving quantitative radiation risk data from studies of military veterans, Jablon goes on to identify some of the advantages of studying military veterans, pointing out the now familiar themes of (1) the

availability of large, well-identified cohorts and (2) the potential for large-scale, relatively quick-and-easy mortality follow-up. He further concludes that studies of radiation carcinogenesis in veterans are of strategic importance because very large populations must be studied over very long time intervals, and because the federal government has undertaken responsibility to compensate individuals for injuries from military service.

Finally, although a panel discussion was held on opportunities for research in military and veteran populations, formal written presentations by the panel members were not submitted. In lieu of a transcript of the panel's remarks, these proceedings include a paper kindly provided by Dr. Kang on the data sources he uses in his studies of veterans. This paper describes three automated information systems, the Beneficiary Identification and Records Locator Subsystem (BIRLS), the Patient Treatment File (PTF), and the Agent Orange Registry, and discusses not only the information these data bases provide but also their strengths and weaknesses.

The BIRLS file is a huge file of VA beneficiaries that may be used to ascertain the vital status of war veterans and to obtain copies of their death certificates; the completeness of its mortality ascertainment, however, is still under study. The PTF file is likewise a large file, but it contains only computerized VA hospital discharge information (VA hospitalization is not a "benefit," so BIRLS and PTF are independent files). PTF has served as the source of a number of clinical studies, but the quality of its diagnostic information requires that studies include independent diagnostic verification: only about one-half of putative cancer diagnoses were verified during hard-copy record review in the examples Dr. Kang cites. The Agent Orange Registry is a different kind of file altogether, being a record of a special health examination of some 200,000 Vietnam veterans who presented themselves to a VA medical center. Each of these resources can be used either as a sampling frame for studies or a source of morbidity or mortality follow-up information.

WFP

Yellow Fever Vaccine-Associated Hepatitis Epidemic During World War II:Follow-up More Than 40 Years Later

Leonard B. Seeff*

INTRODUCTION

A well-recognized sequel to acute hepatitis B virus (HBV) infection is the development in some infected individuals of the viral carrier state, associated with progression to chronic hepatitis (1, 2). This sequence is best described in the Far East and Sub-Saharan Africa where HBV infection is endemic. In these geographic areas, most instances of transmission of this virus take place at birth through an infected carrier mother. The majority of newborns to such mothers are themselves infected, virtually all become and remain carriers for life, and many of them develop progressive liver disease, advancing from chronic hepatitis to cirrhosis and, ultimately, to primary hepatocellular carcinoma (HCC) (2–4). Indeed, HCC is the most common malignant tumor in these areas of the world.

In contrast, in areas of the world nonendemic for HBV, such as the United States, HBV infection occurs predominantly in late adolescence or early adulthood, the carrier state is low, and HCC is an uncommon form of cancer (1). Limited data from such areas have suggested that advancement from acute to chronic hepatitis occurs in 5–10% of acutely infected persons (5, 6). Although it is presumed that such carriers also are at risk of developing HCC, it has been difficult to prove this relationship in low endemicity areas because of the low infection rate and hence of a

* Leonard B. Seeff, M.D., is Chief of Gastroenterology and Hepatology at the Department of Veteran Affairs Medical Center, Washington, D.C., and Professor of Medicine at the Georgetown University School of Medicine.

sufficiently large population among whom to conduct natural history studies.

An opportunity to undertake just such a study, however, seemed provided by the knowledge of an extensive outbreak of hepatitis that had affected United States Army servicemen during World War II (7–9). This outbreak was first noted in March 1942, prompting an intensive investigation soon after its recognition of the surrounding circumstances. A careful questionnaire survey led to the conclusion that the epidemic appeared attributable to the receipt of presumed hepatitis-contaminated yellow fever vaccine. Accordingly, the Surgeon General ordered on April 14 that the implicated vaccine lots be withdrawn and replaced with vaccine that was serum free. The epidemic reached a peak in June 1942, after which the number of reported cases of "jaundice" slowly returned to the baseline level. It was estimated that there were approximately 50,000 cases of hepatitis involved in this outbreak. Thus, if this epidemic could be shown to be of HBV origin, and if the infected patients could be traced now more than 40 years later, it was believed that the link known to exist in the Far East between chronic HBV infection and HCC might be demonstrable in the United States also.

An essential requirement for such a study would be to have access not only to those who had been overtly infected and developed jaundice in 1942, but also to those who had received the vaccine at that time and had developed inapparent disease, since chronic hepatitis has been believed to evolve more frequently following anicteric than icteric hepatitis (10). Moreover, it would be necessary to evaluate individuals who, during that time, had received non-contaminated vaccine, in order to determine the background prevalence of cirrhosis and HCC in this "control" group. Because it indeed appeared possible to assemble the necessary groups, the present investigation was undertaken with two goals in mind: first, to determine whether HBV was responsible for the epidemic and, second, to establish whether the epidemic, assuming it to be of HBV origin, had increased the rate of development of cirrhosis and/or HCC.

METHODS

A three-pronged approach was planned (11). The first consideration was to define the responsible virus by serologic means; the second was to establish a link between receipt of the contaminated vaccine and the occurrence of cirrhosis and HCC by means of a cohort mortality study, comparing the rates of these endpoints among the selected cohorts; and the third was to conduct a case-control study, comparing the frequency of receipt of the implicated vaccines among World War II veterans who had died from HCC with the frequency of their receipt among those who had

died from other pre-defined forms of cancer. Presented here are only the serologic and limited case-control mortality data.

The following three cohorts were chosen for serologic and mortality study: Group I were patients who had received the plasma-containing yellow fever vaccine and had been hospitalized with jaundice in 1942; this "symptomatic" group were derived from the microfilmed file of 31,500 military personnel who had been questioned during 1942–1943 in regard to their hospitalization for jaundice. Group II individuals had been vaccinated with one of the seven most "infectious" lots, but had not developed jaundice or been hospitalized, thus being acceptably referred to as the "asymptomatic" group; their names came from the payroll rosters of enlisted men in units who had received the contaminated vaccine matched against the file of patients from those units hospitalized for jaundice. The use of the lot number as a basis for inclusion was precluded because a fire in 1973 in St. Louis, where personnel folders had been stored, had destroyed the vast majority of them. Group III were men who had entered the Army after July 1942 and hence had received only serum-free vaccine; their names were derived from a 2% file of men who had taken out National Service Life Insurance after August 1942. The selection of persons for serologic evaluation was confined in all three groups to white males alive on January 1, 1946, while Groups II and III were further restricted to men whose names did not appear in the 1942 file of persons hospitalized for jaundice. The total numbers of persons in each group from which the selections were made were 21,415, 19,114, and 25,262, respectively.

For the serologic analysis segment of the study, a sample of men from each of the three groups was selected, the numbers being based on sound statistical principles; approximately 200 persons in each group were believed to be necessary to distinguish a statistically significant difference in the HBV carrier rate among the three groups. A further guiding principle was that the subjects had to live within a 50-mile radius of the six Veterans Administration Medical Centers that had been asked to participate in the study (Boston, Massachussetts; Hines, Illinois; Dallas, Texas; Los Angeles, California; Miami, Florida; and Washington, D.C.) (11). The addresses of the study subjects were acquired with the help of the Internal Revenue Service, the Social Security Administration, and the Health Care Financing Administration. Once located, they were asked to come to one of the six study centers where they were subjected to an historical interview and a brief physical examination, and had a sample of blood drawn for the following hepatitis serologic assays: hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to the hepatitis B core antigen (anti-HBc), antibody to the hepatitis A virus (anti-HAV), and antibody to the hepatitis delta virus

(anti-HDV); testing for the hepatitis B e antigen (HBeAg) and for the presence of hepatitis B virus DNA (HBV DNA) was to be conducted in all HBsAg-positive samples and among a limited number of randomly selected HBsAg-negative samples; in all instances, commercial radio-immunoassays, from Abbott Laboratories, N. Chicago, were used. In addition, samples were tested by enzyme-linked immunoassay for the presence and concentration of alpha-fetoprotein (AFP) levels as a marker of incipient HCC.

For the cohort mortality segment of the study, mortality status was established by examining the Veterans Administration Beneficiary Identification and Records Locator System, which has recorded over 90% of deaths of World War II veterans. Cause of death was derived from a review of the death certificates, seeking the classification code number 155 (malignant neoplasm of liver and biliary passages) in the 7th revision of the International Classification of Diseases (ICD) of the World Health Organization. Where possible, confirmation of diagnosis was sought from a review of clinical and pathologic information relating to cause of death.

RESULTS

Serologic Assay Results

Hepatitis B Viral Antibody Markers:

Blood samples were obtained from 221 Group I, 171 Group II, and 205 Group III subjects. Among the Group I individuals, HBV markers were detected in a total of 216 (97.7%). This consisted of a single person with HBsAg and anti-HBc (0.5%), 199 (90%) who were positive for both anti-HBs and anti-HBc, and 16 (7%) who were positive for anti-HBC alone. The Group II individuals had detectable HBV markers in 131 (77%); this consisted of both anti-HBs and anti-HBc in 120 (70%), anti-HBs alone in 10 (6%), and anti-HBc alone in 1 (1%). In marked contrast was the finding of HBV markers in only 27 (13%) of the Group III subjects—both anti-HBs and anti-HBc in 13 (6%) and anti-HBs alone in 14 (7%). With respect to anti-HBc, this marker was detected in all of those in Group I with positive HBV markers, in 92% of those in Group II with markers, and in 48% of the Group III subjects with markers. A striking statistically significant difference in detected anti-HBs and anti-HBc together was noted between the individuals of both Groups I and II and those of Group III ($p<0.0001$) and also between the subjects of Group I and those of Group II ($p<0.0001$).

Hepatitis A Viral Antibody Markers:

Anti-HAV was found in 165 (75%) of the individuals in Group I, in 124 (73%) of those in Group II, and in 129 (63%) of Group III. Although a similar prevalence of anti-HAV was detected in all three groups, the figure was significantly lower in Group III.

HBsAg, HBV Subtyping, Anti-HDV, and AFP:

HBsAg was found in only 1 subject (from Group I), representing an overall positivity rate of 1 in 392 (0.26%) exposed persons (Groups I and II combined). This person was positive also for hepatitis B e antigen (HBeAg) and hepatitis B virus DNA (HBV DNA).

The single HBsAg-positive individual was subtyped as adw2. Sixty-four anti-HBs-positive specimens from Groups I and II were also subtyped, 62 with anti-a, 24 with anti-d, 10 with anti-w, and 7 with anti-w2.

None of the subjects had detectable anti-HDV.

AFP levels ranged from 0.05 to 31.4 ng/ml (median, 2.2). The slightly elevated levels (>10.0 ng/ml) did not differ among the three groups or correlate with serologic findings.

"Concentration" of HBV Antibodies:

The "concentrations" of anti-HBs and anti-HBc, as judged by the median positive:negative ratios of the radioimmunoassay tests, showed the following: anti-HBs was significantly higher in Group II as compared to the other two groups, while anti-HBc was significantly higher in Group I in comparison to the other two.

Case-Control Mortality Data

Standardized mortality ratios showed that death from all causes did not differ significantly among the three groups. The numbers of deaths attributed to liver and gall bladder cancer were not unexpectedly high (30, 33, and 20 in the three groups, respectively). Standardized mortality ratios for cancer of the liver and gall bladder also did not differ significantly as a set, although there was a significantly higher ratio for Group II than for Group III. Deaths from liver diseases of other types, in particular viral hepatitis and nonalcoholic chronic liver disease, showed no significant differences.

DISCUSSION

These data indicate that the yellow fever vaccine-related hepatitis outbreak was clearly a result of HBV infection, that the epidemic was associated with an unexpectedly low HBsAg carrier rate, and that the epidemic appears not to have increased the rate of development of the two feared consequences of chronic HBV infection, namely cirrhosis and HCC. The evidence in support of the implication of HBV is the strikingly high prevalence of HBV antibody markers among both those who had received the vaccine and developed jaundice (97%) and those who had received the implicated vaccine but did not develop overt disease (77%). In contrast, the prevalence of these markers in the "control" group (Group III) was comparable to the prevalence in the general adult U.S. population (12). Although the prevalence of antibody to hepatitis A also was high, it was present in similar frequency in all three groups and also similar to that of the general adult U.S. population of an equivalent age (13).

It can be estimated, based on the knowledge that 427,000 doses were administered from the known icterogenic vaccine lots, on the knowledge that 50,000 overt vaccine-related hepatitis cases occurred, and on the anti-HBc results among Group II of the present study, that 78% of all recipients of the known icterogenic lots were probably infected with HBV. Extending the calculations further, it appears that about 330,000 men who received these vaccines developed HBV infection, the ratio of icteric:anicteric hepatitis being 1:7. This epidemic thus is the largest point-source hepatitis B outbreak ever recorded.

Several of the serologic findings are worthy of special mention. First is the evidence that this dramatic hepatitis B epidemic did not appear to be associated with the expected HBV carrier rate. It had been anticipated that approximately 10% of acutely infected persons would become carriers, especially if they had had subclinical infection (5, 6). Instead, the rate as based on the single carrier, whose subtype characteristics conformed to the findings among those with anti-HBs, was less than 0.5%. A second item of importance is the evidence that HBV antibodies that derive from an overt infection appear to persist for life, as indicated by their high "concentration" detected more than 40 years after the original infection. This contrasts with the shorter life span of antibodies induced by hepatitis B vaccination (14).

The reason for the unexpectedly low carrier rate is not apparent from this study. Conceivably, it could be accounted for by the loss to follow-up of carriers who had died from cirrhosis or cancer. The fact that the mortality study failed to detect excess mortality from cirrhosis and/or HCC, however, tends to disprove this view. On the other hand, it could be low because of certain host-related or virus-related factors. Host-related

factors that are known to be of importance in regard to the rate of chronicity are age at which the initial infection occurs, the immune status of the infected person, gender, and race. The first two items appear to be the most compelling correlative factors (15, 16). Data from highly endemic areas where perinatal transmission is the predominant mode of virus propagation indicate that there is a strong inverse relationship between the age of the primary infection and the likelihood of becoming a carrier, the rate declining dramatically with advancing age (17–19). The outbreak under discussion involved young, generally healthy white males, permitting the conclusion that this population group uncommonly become carriers following acute HBV infection. How then to reconcile this information with the prevailing view that 5–10% of acutely HBV-infected persons in the United State become carriers?

A critical analysis of the extant literature indicates that the figure of 5–10% derives from studies of markedly heterogeneous populations (5, 6). Such studies have involved groups that have included multiply exposed homosexual men, intravenous drug abusers, and persons of Asian descent among whom a subclinical HBsAg carrier state is relatively common. Many of these individuals may present for the first time with a bout of apparent acute hepatitis B, HBsAg persisting after the acute illness has subsided, leading to the mistaken conclusion that chronic hepatitis has just evolved. In actual fact, they may actually be unrecognized pre-existing carriers who are given a diagnosis of acute hepatitis when spontaneous or induced viral reactivation or superimposed infection with another undetected virus (A, non-A/non-B, or D) occurs (1, 20, 21). Because acute hepatitis B in young, healthy, immunocompetent, singly exposed persons is relatively uncommon, it has been difficult to develop accurate data on the frequency of development of the carrier state in this population group.

Virus-related factors conceivably also could account for the lower-than-anticipated carrier rate, factors such as the size of the inoculum, viral subtype or strain differences, or other factors that might interfere with viral replication. There is little to support the former two items with respect to altering the frequency of chronicity, but there is evidence that viral interference can occur and change the natural history. For example, it is apparent that a reduction in viral replication results when the HBsAg carrier is superinfected with other known hepatitis viruses, such as those of hepatitis A, non-A/non-B hepatitis, and hepatitis D (1). It is possible, therefore, that the virus of yellow fever in the vaccine could have altered the outcome. Similarly, anti-HBs that almost certainly was present in the original pooled plasma could have affected both the incubation period and the carrier state. The opportunity to study these potential interfering factors is, unfortunately, thwarted by the inability to trace the original contaminated yellow fever vaccine lots.

It is perhaps not surprising that this dramatic and extensive epidemic of hepatitis B was not associated with a correspondingly high rate of cirrhosis and HCC. The data seem indisputable that HBsAg carriers are at unusually high risk of developing these serious sequelae (22). However, since this epidemic did not culminate in a recognizably high carrier rate, these sequelae did not emerge. Further information in this regard is anticipated from the case-control study.

REFERENCES

1. Seeff LB, Koff RS: Evolving concepts of the clinical and serologic consequences of hepatitis B virus infection. Sem Liv Dis 1986;6:11–22.
2. Popper H, Shafritz DA, Hoofnagle JH: Relation of the hepatitis B virus carrier state to hepatocellular carcinoma. Hepatology 1987;7:764–772.
3. Szmuness W: Hepatocellular carcinoma and the hepatitis B virus: evidence for a causal association. Prog Med Virol 1978;24:40–69.
4. Kew MC: The possible etiologic role of hepatitis-B in hepatocellular carcinoma: evidence from Southern Africa. In: Chisari FV, ed. Advances in Hepatic Research. New York: Masson Publishing USA, Inc., 1984:203–215.
5. Redeker AG: Viral hepatitis, clinical aspects. Am J Med Sci 1975;270:9–16.
6. Hoofnagle JH, Seeff LB, Bales ZB, Gerety RJ, Tabor E. Serologic responses in HB. In: Vyas GN, Cohen SN, Schmid R, eds. Viral Hepatitis: A Contemporary Assessment of Etiology, Epidemiology, Pathogenesis and Prevention. Franklin Institute Press, 1978:219–242.
7. Sawyer WA, Meyer KF, Eaton MD, Bauer JH, Putnam P, Schwentker FF: Jaundice in Army personnel in the western region of the United States and its relation to vaccination against yellow fever. Am J Hyg 1944;39:337–430.
8. Idem. Jaundice in Army personnel in the western region of the United States and its relation to vaccination against yellow fever. Am J Hyg 1944;40:35–107.
9. Walker DW: Some epidemiological aspects of infectious hepatitis in the U.S. Army. Am J Trop Med 1945;25:75–82.
10. Alward WLM, McMahon BJ, Hall DB, e al: The long-term serologic course of asymptomatic hepatitis B virus carriers and the development of primary hepatocellular carcinoma. J Infect Dis 1985;151:604–609.
11. Seeff LB, Beebe GW, Hoofnagle JH, et al: A serologic follow-up of the 1942 epidemic of post-vaccination hepatitis in the United States Army. New Engl J Med 1987;316:965–970.
12. McQuillan GM, Townsend TR, Fields HA, Carroll M, Leahy M, Polk BF: Seroepidemiology of hepatitis B virus infection in the United States: 1976 to 1980. Amer J Med 1989;87(suppl 3A):5S–10S.
13. Szmuness W, Dienstag JL, Purcell RH, Harley EJ, Stevens CE, Wong DC: Distribution of antibody to hepatitis A antigen in urban adult populations. N Engl J Med 1976;295:755–759.
14. Hadler SC: Are booster doses of hepatitis B vaccine necessary? Ann Intern Med 1988;109:657–458.
15. McMahon BJ, Alward WLM, Hall DB, et al: Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985;151:599–603.
16. Szmuness W, Prince AM, Grady GF, et al: Hepatitis B infection: a point-prevalence study in 15 US hemodialysis centers. JAMA 1974;227:901–906.

17. Beasley RP, Hwang L-Y, Lin C-C, et al: Hepatitis B immune globulin (HBIG) efficacy in the interruption of perinatal transmission of hepatitis B virus carrier state. Lancet 1981;2:388–393.
18. Beasley RP, Hwang L-Y, Lin C-C, et al: Incidence of hepatitis B virus infections in preschool children in Taiwan. J Infect Dis 1982;146:198–204.
19. Beasley RP, Hwang L-Y, Lin C-C, Ko Y-C, Twu S-J: Incidence of hepatitis among students at a University in Taiwan. Am J Epidemiol 1983;117:213–222.
20. Davis GL, Hoofnagle JH: Reactivation of chronic type B hepatitis presenting as acute viral hepatitis. Ann Intern Med 1985;102:762–765.
21. Rizzetto M, Verme G: Delta hepatitis-present status. J Hepatol 1985;1:187–193.
22. Beasley RP, Hwang L-Y, Lin C-C, Chien C-S: Hepatocellular carcinoma and hepatitis B virus: a prospective study od 22,707 men in Taiwan. Lancet 1981;2:1129–1133.

ACKNOWLEDGMENTS

I am indebted to Drs. Gilbert W. Beebe (National Cancer Institute), James E. Norman (National Heart, Lung, and Blood Institute), and Jay H. Hoofnagle (Division of Digestive Diseases and Nutrition, NIH), without whom this study would not have been initiated or conducted. I would also like to thank the following study participants: Zelma Buskell-Bales, B.S., Jeanne G. Waggoner, B.A., Neil Kaplowitz, M.D., Raymond S. Koff, M.D., John L. Petrini, Jr., M.D., Eugene R. Schiff, M.D., James Shorey, M.D., and Malcolm M. Stanley, M.D.

Substance Use in World War II Veteran Twins: A Genetic Analysis

Dorit Carmelli, Gary E. Swan, and Dennis Robinette*

BACKGROUND

Significant contributions of genetic factors to variation in alcohol and tobacco consumption have been demonstrated repeatedly using a variety of study designs including monozygotic (MZ) and dizygotic (DZ) twin pairs, extended family studies, and adoption-based studies. Hughes[1] recently summarized a number of twin studies in which heritability estimates (the proportion of variance attributed to genetic factors) for tobacco use ranged from 0.28 to 0.84, with a mean of 0.53; heritability estimates for alcohol use ranged from 0.28 to 0.51, with a mean of 0.42. Other studies have reported heritability for coffee drinking in male twins in the range of 0.46[2,3] to 0.88.[4] Results from these studies, including our own analysis of a relatively small subset of the National Academy of Sciences-National Research Council (NAS-NRC) World War II Twin Registry, known as the NHLBI Twin Study, are summarized in Table 1. We note from examination of Table 1 the relatively wide range of heritability estimates, which may have resulted from both the wide range in sample sizes that the studies were based on and the use of different measures of smoking, alcohol use, or coffee consumption.

* Dorit Carmelli, Ph.D., and Gary E. Swan, Ph.D., are with the Health Sciences Program, SRI International, Menlo Park, California. Dennis Robinette, Ph.D., is with the Medical Follow-up Agency, National Academy of Sciences, Washington, D.C. Correspondence to Dr. D. Carmelli, SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025, USA. This research was supported by Contracts N01-HC-55029 and N01-HC-85078 from the National Heart, Lung, and Blood Institute.

Despite the findings suggestive of a significant role for genetic factors, behavioral scientists seem generally reluctant to acknowledge the contribution of these factors to appetitive behaviors that fall within the "normal" range of consumption. For example, neither the 1988 nor the 1989 Surgeon General's Report[5,6] mentions any of the studies cited above that show small but significant heritable components to smoking behavior. The reluctance to acknowledge the results from these studies may be related to the belief that genetic determinants imply a lack of modifiability. However, if genetic effects do play a role in smoking behavior, further studies that sort out these effects could lead to an increased understanding of why there continues to be a relapse problem among smokers who have recently quit, despite the most ardent and forceful efforts of public health specialists to change these behaviors.

In the present paper, we hope to demonstrate the potential value of studying twins in general and, more specifically, of the NAS-NRC World War II Twin Registry, for examining issues related to the genetics of substance use. It is our belief that twin studies actually provide valuable opportunities for investigating the contribution of environmental influences on substance use behavior. For example, by comparing the life-long smoking behavior of genetically identical MZ twin pairs, it is possible to eliminate genetic variability, thereby creating a pure culture of nongenetic determinants—determinants that can be identified as being "environmental exposures" and "personal behaviors." Once we have established that such environmental exposures during adult life are responsible for a behavior in question, appropriate changes in the environment could be recommended as an effective means of intervention.

Apart from the power of the twin method to assess the roles of genetic and environmental factors of health behaviors during late adulthood, the NAS-NRC Twin Registry is noteworthy for several specific features. First, the cohort is sufficiently large to support powerful analyses; second, excellent longitudinal data are available on these subjects from military induction (ages 17 to 28 years) and during middle age; and, third, repeated information on an array of cardiovascular disease risk factors and health behaviors was collected on these subjects when they were 42 to 55 years old and repeated 10 years later by the administration of standardized epidemiological questionnaires. It is our intent in this report to present some preliminary results from a genetic analysis of smoking, alcohol use, and coffee consumption in the NAS-NRC Twin Registry. Our results support the conclusion that genetic factors contribute to the variation in substance use behaviors in late adulthood and that these behaviors are minimally influenced by shared environmental factors and the simultaneous occurrences of combinations of these behaviors.

THE NAS-NRC TWIN REGISTRY

Figure 1 presents an overview of the sample on which the analyses presented in this chapter were performed. The NAS-NRC Twin Registry was developed originally on approximately 16,000 pairs of twins who were inducted into World War II and for whom medical records were available. All twins were born between 1917 and 1927. The original and current intent of the registry was the follow-up of the twins for eventual mortality so that genetic contributions to coronary heart disease and cancer could be determined.[7] The method by which zygosity was determined in the registry relied on twin self-report, which was confirmed in a subset through the use of fingerprint and blood analysis.[7] During 1969–72, approximately 5,000 twin pairs (MZ pairs = 2,390, DZ pairs = 2,571) completed a mailed questionnaire that was standardized to be similar to questionnaires used by the Swedish and Finnish Twin Studies.[8] The questionnaire requested information on a variety of variables, including substance use, diet, work history, and various illnesses. At the time of completion of the questionnaire, the mean age of the respondents was 49 years.

SUBSTANCE USE IN THE NAS-NRC TWIN REGISTRY

Substance use in the NAS-NRC Twin Registry and, for comparison purposes, that for the younger Finnish Twin Registry[9] are presented in Table 2. The extremely high prevalence of ever smoking (81%) in the NAS-NRC Registry, compared with the Finnish Registry (62%) and with the general U.S. population, is noteworthy. The most probable explanation for this high prevalence is the twins' participation in World War II, during which cigarettes were dispensed routinely, free of charge, to all servicemen. It should also be noted that the NAS-NRC Registry consists of individuals drinking alcohol at levels equivalent to those found in the Finnish Registry and, with regard to coffee drinking, at levels somewhat lower than those of the twins from Finland.

SUBSTANCE USE: ENVIRONMENTAL CORRELATES AND CO-OCCURENCE

The computation of heritability estimates of appetitive behaviors, based on twin studies, is complicated by the fact that multiple nongenetic sources of variance underlie twin similarity or dissimilarity. Among these are age, sex, socioeconomic and marital status, and frequency of twin contact.[10,11,12] Another source of confounding variance lies in the fact that smoking, alcohol use, and caffeine consumption are correlated.

Evidence for the bivariate associations between these substance use behaviors, as reviewed by Istvan and Matarazzo,[13] reveals a consistent pattern for smoking, as opposed to nonsmoking, to be related to greater consumption of alcohol and, within smokers, for higher amounts of tobacco consumption to be related to more drinking.[14,15,16,17] Other large population-based studies[14,18,19,20] show moderate to strong associations between caffeine consumption and cigarette smoking in males. There is no evidence for an association between caffeine and tobacco consumption, but, as pointed out by Istvan and Matarazzo,[13] this finding is based on relatively few studies and the relationship warrants further investigation.

The conclusion that use of these three substances is often related has led some to speculate that a common pathophysiological process may underlie their use.[18,21] However, as Istvan and Matarazzo[13] point out, with one recent exception,[22] no study exists that has investigated the use of these three substances simultaneously.

From the perspective of behavioral genetics, these known relationships among the various substance use behaviors and their relationships to environmental factors present interesting problems for interpreting broad heritabilities derived for each behavior separately. Although recent studies do indicate the presence of significant heritability estimates for smoking and alcohol use[1,4] and caffeine consumption,[3,4,21] these analyses did not account for shared covariance. Only one study that we are aware of has attempted to investigate the genetics of combined heavy use of alcohol and tobacco. While finding no genetic effect for combined heavy use, the authors point out that this result may have been due to the small sample size of heavy users.[15] This represents another area in which the comparatively large sample size of a narrow age group of adults in the NAS-NRC Registry may eventually prove valuable.

A first attempt to deal with the complexity of heritability analyses of appetitive behaviors is presented in the following analysis. Our primary objective was to control for the effects of environmental factors and covariance among appetitive behaviors while examining the heritability of each appetitive behavior individually. To our knowledge, this approach is new and has been reported only recently in a series of studies of the NHLBI Twin Study subsample.[23,24]

STATISTICAL METHODS

Analyses were directed at estimating the heritable components of smoking, alcohol use, and coffee consumption, both before and after taking into account the effects of other substance use, age, socioeconomic status, and a measure of occupational adjustment. Unadjusted and adjusted heritability estimates were calculated and compared to evaluate the

contributions of these variables to the confounding of genetic variance when each of the appetitive behaviors is examined separately. In this approach, the adjustment of smoking for the consumption of alcohol and/or coffee was accounted for at the individual level, whereas the heritability analysis was conducted on twins as pairs following these adjustments. Using this approach, individual differences in the joint behavior of smoking, alcohol use, and coffee consumption were reflected in the heritability estimates of the adjusted variables.

Smoking status was based on the self-reported number of cigarettes ever smoked per day; ascertaining only current cigarette smoking consumption, as has been done in several earlier studies, is unsatisfactory in intrapair comparisons if the smoking durations are different within the pairs. For the smoking variable we therefore selected the daily average cigarette consumption for all the subjects who had been smoking, past and present. Alcohol consumption was determined from self-reported total number of drinks per week in a typical week at the time of assessment and included beer, wine, and cocktails. For each type of beverage, the reported consumption in glasses or bottles per month was converted into grams of absolute alcohol and summed to give an individual average consumption per month. Mean consumption of cups of coffee per day was used as a caffeine dose variable. A socioeconomic score was constructed using education and military rank. The occupational adjustment score included items related to changes in employment, occupation, the type of employment (subordinate vs. supervisory position), and the frequency of overtime work or additional employment.

To determine the extent to which covariates were related to smoking and alcohol use, both univariate and multivariate analyses were performed. A linear regression was developed using each appetitive behavior as the dependent variable and related characteristics such as other substance use, age, and socioeconomic status as independent variables. Separate models for MZ and DZ twins were developed under the assumption that these covariates contribute differentially to twin similarity in the two zygosities.

The derived multivariate models had two purposes: first, to determine the amount of variance explained by associated variables in the two groups of twins, and, second, to use the derived models to adjust the raw values for the contribution of these variables to the between-pair variability. The actual adjustments were carried out on twins as individuals. For example, amount ever smoked was regressed on use of alcohol and coffee, age, and occupational adjustment (see Table 3). Intraclass correlations and heritability estimates were calculated for the residual values and compared with the corresponding estimates calculated for the unadjusted raw values.[23,24]

We used both intraclass correlation heritability estimates[25] and a path model approach[26] to estimate parameters representing the effects of genes and the environment. The models used were $r_{MZ} = H + C$ and $r_{DZ} = 0.5H + C$, where r_{MZ} and r_{DZ} refer to MZ and DZ intraclass correlations, H refers to the effect of shared genes (i.e., heritability), and C refers to the effect of shared environment. It should be emphasized that the simplest classical twin design assumptions are made in these models: purely additive genetic effects, random mating, the absence of gene-environment correlations or interactions, and the same degree of environmental similarity for MZ and DZ pairs. Moderate failure to meet these assumptions may result in estimated parameters that do not have the simple interpretations intended. Nevertheless, provided the departures are not drastic and the data fit the model tested, meaningful conclusions may still be drawn from broad comparisons among different genetic and environmental models. The NAS-NRC data permit testing such models with H, C, or both constrained to be the same for each appetitive behavior against models that allow differences in H and C for the different appetitive behaviors.

BIVARIATE ASSOCIATIONS BETWEEN SMOKING, ALCOHOL USE, COFFEE CONSUMPTION, AND COVARIATES

Table 4 presents the correlation matrix of the bivariate associations between smoking, alcohol use, coffee consumption, and demographic variables treating twins as individuals. As expected from previous research, we observe that alcohol use and coffee consumption were positively related to cigarette smoking. Daily coffee consumption was unrelated to the amount of alcohol consumed monthly. Age was negatively related to the number of cigarettes ever smoked per day but not to total amount of alcohol consumed monthly or to number of cups of coffee consumed daily. Socioeconomic status was positively associated with alcohol consumption and negatively related to the number of cigarettes ever smoked per day. Occupational adjustment was negatively associated with the number of cigarettes per day and the number of cups of coffee per day. Given these relationships, we developed separate models for adjustment for each of the appetitive behaviors. Table 3 presents these models in detail.

GENETIC ANALYSES

Raw measures of smoking, alcohol use, and coffee consumption showed significant differences in total variances; in some cases, we also observed differences in means as well as deviations from normality. When

a log transformation of the observed raw values was employed, the majority of these differences were eliminated.

Smoking

Estimates of genetic variance for the log-transformed amount of cigarettes smoked daily (unadjusted and adjusted) are presented in Table 5. Heritability estimates for unadjusted cigarette smoking are moderate, with the additive genetic component accounting for 52% of the total variance. After adjustment for covariates, this genetic component of variance was reduced to 42% of the total variance. Estimates of heritability were highly significant both before and after adjustment, and shared environmental effects among twins did not contribute to twin similarities.

Alcohol

The heritability estimate of the log-transformed alcohol variable was moderate and significant, with 36% of the total variance attributable to an additive genetic effect. The estimate of an effect of shared environment was 15% of the variation in alcohol consumption. Adjusting the amount of alcohol consumed for smoking and related covariates lowered the heritability estimate of alcohol consumption to 30% and removed the effect of shared environment.

Coffee

Although average coffee consumption was significantly higher in DZ than MZ twins, this difference was eliminated by the log transformation and the adjustment for covariates. The heritability estimate for coffee consumption was 44% and highly significant. Adjusting coffee for smoking had no effect on this estimate, and the shared environmental component was not significant.

DISCUSSION

In this analysis we have demonstrated an epidemiological approach to the investigation of twin similarity in smoking, alcohol use, and coffee consumption. Our approach takes into account confounding and shared covariance between appetitive behaviors, as well as selected demographic variables and their differential impact on MZ and DZ similarity. Because this approach treats the heritability analysis of substance use as essentially a multivariate problem (as opposed to its traditional treatment as a univariate problem), it provides a method to account for the confounding of estimates of heritability of smoking, alcohol use, and coffee use when analyzed separately.

Our results showed unadjusted heritability estimates for smoking and alcohol to be consistent with previously published research. For smoking, the estimate obtained in the present study was 0.52, which is identical to the average cited by Hughes.[1] For alcohol use, the unadjusted heritability estimate was 0.36, somewhat lower than the mean value of 0.42 reported by Hughes.

Although the adjustment process resulted in heritability estimates that were somewhat lower than the unadjusted estimates, all estimates remained significant. The apparent robustness of the genetic component in smoking, alcohol use, and coffee consumption, even after the adjustment for covariates, supports the general conclusion that each of the substance use behaviors is, in part, genetically determined. Genetic analyses of cardiovascular risk factors have shown a similar robustness under conditions of adjustment for environmental covariates for HDL and LDL cholesterol, triglycerides, relative weight, and some measures of Type A behavior[24] but not for systolic and diastolic blood pressure.[27]

Our results also suggest that the most important source of nongenetic variation for each of the appetitive behaviors in late adulthood is nonshared environmental effects. When computed as the variance remaining after genetic and shared environmental effects are taken into account, these estimates range from 0.57 to 0.63. Even though these estimates include measurement error, they account for a substantial proportion of the total variation. Moreover, in all cases the adjustment for shared covariance among these behaviors resulted in an increase of the nonshared variance component unique to the individual. For alcohol consumption, the 15% of shared variation observed before adjustment was reduced to zero after adjustment. This means that being reared in the same family and sharing the same home environment do not contribute to similarity in alcohol use later in life. Moreover, the magnitude of such individual nonshared environmental variance components was similar for each of the smoking, alcohol use, or coffee consumption behaviors.

Other investigators[28] have argued for a multivariate genetic path model approach that allows the estimation of the separate and joint effects of genes and environment that underlie the covariation of symptoms or behaviors in twin pairs. This approach, which we believe may further contribute to the understanding of substance use behaviors, is different from that used in the present analysis. We strongly believe that it is important to explore the effects of confounding variables before fitting causal models based on assumptions that these effects have no influence on how genes and environment interact.

Because of the high prevalence of smoking and the comparatively high levels of heavy alcohol consumption, the NAS-NRC Twin Registry provides a unique opportunity to examine issues surrounding substance use

at various levels and frequencies. More recently, results from a 1981 survey of alcohol consumption patterns in the Australian Twin Register[11,12] revealed that adult alcohol consumption patterns are determined by separate Abstinence, Quantity, and Frequency dimensions. Moreover, for the latter two dimensions there were substantial genetic effects, whereas twin correlations for Abstinence were consistent with nongenetic determination of this dimension. What has yet to be ascertained is whether there exist low levels of alcohol or tobacco use that are the equivalent of total abstinence, and that are environmentally determined. To address such questions, large cohorts of twins with normal ranges of consumption are needed. The NAS-NRC Twin Registry has these unique features.

Finally, this study has several limitations that the reader should bear in mind. First, this is a heritability analysis of substance use, not of addiction. Second, our analysis included only male twins who were somewhat older than samples on which previous heritability analyses have been conducted. It would be interesting to see whether the effects of adjustment generalize to younger males and to females. Most important, it is, at this point, equally plausible to suggest that differences in smoking, alcohol use, or coffee consumption behavior cause or result from twin similarity or dissimilarity on the variables used in this analysis. Several aspects of the data also limit inferences regarding the differential impact of contact between the twins on twin similarities of appetitive behaviors. For example, although we may have superficial knowledge of the extent of the interaction between twins, we have no knowledge of the type and quality of the interaction. Moreover, we do not know whether any early environmental differences existed between MZ and DZ twins, or whether there were differences in parental behavior that could account for present differences. We hope to address these issues in future analyses.

REFERENCES

1. Hughes JR. Genetics of smoking: A brief review. Behavior Therapy , 17:335–345, 1986.
2. Kaprio J, Koskenvuo M, Sarna S. Cigarette smoking, use of alcohol, and leisure-time physical activity among same-sexed adult male twins. In: Gedda L, et al. (Eds.), Twin Research 3: Epidemiological and Clinical Studies. New York: Alan R. Liss, pp. 37–46, 1981.
3. Partanen J, Brunn K, Markkanen T. Inheritance of Drinking Behavior: A Study of Intelligence, Personality and Use of alcohol of Adult Twins. Oslo: The Finnish Foundation for Alcohol Studies, 1966.
4. Pedersen N. Twin similarity for usage of common drugs. In: Gedda L, Parisi P, Nance WE (Eds.), Twin Research 3: Part C, Epidemiological and Clinical Studies. New York: Alan R. Liss, pp. 53–59, 1981.

5. Department of Health and Human Services. The health consequences of smoking: Nicotine addiction. Rockville, Maryland: U.S. Public Health Service. DHHS (CDC) 88–8406, 1988.
6. Department of Health and Human Services. Reducing the health consequences of smoking: 25 years of progress. Rockville, Maryland: U.S. Public Health Service, DHHS (CDC) 89–8411. 1989.
7. Jablon S, Neel JV, Gershowitz H, Atkinson GF. The NAS-NRC twin panel: Methods of construction of the panel, zygosity diagnosis, and proposed use. American Journal of Human Genetics, 19:133–161, 1967.
8. Cederlof R, Epstein FH, Friberg L, Hrubec Z, Radford EP. Twin registries in the study of chronic disease. Acta Medica Scandinavica , Supp. 523, 1971.
9. Kaprio J, Koskenvuo M, Artimo M, Sarna S, Rantasalo I. Baseline Characteristics of the Finnish Twin Registry. Section I: Materials , Methods, Representativeness and Results for Variables Special to Twin Studies. Helsinki, Finland: Department of Public Health Science M47, 1979.
10. Kaprio J, Koskenvuo J, Langinvainio H, Romanov K, Sarna S, Rose RJ. Genetic influences on use and abuse of alcohol: A study of 5,638 adult Finnish twin brothers. Alcoholism: Clinical and Experimental Research, 11:349–356, 1987.
11. Jardine R, Martin NG. Causes of variation in drinking habits in a large twin sample. Acta Geneticae Medicae et Gemellologiae, 33:435–450, 1984.
12. Heath AC, Jardine R, Martin NG. Interactive effects of genotype and social environment on alcohol consumption in female twins. Journal of Studies on Alcoholism, 50(1):38–48, 1989.
13. Istvan J, Matarazzo JD. Tobacco, alcohol, and caffeine use: A review of their interrelationships. Psychological Bulletin, 95:301–326, 1984.
14. Friedman GD, Klatsky AL, Siegelaub AB, McCarthy NM. Kaiser-Permanente epidemiological study of myocardial infarction: Study design and results for standard risk factors. American Journal of Epidemiology , 99:101–116, 1974.
15. Kaprio J, Hammar N, Koskenvuo M, Floderus-Myrhed B, Langinvainio H, Sarna S. Cigarette smoking and alcohol use in Finland and Sweden: A cross-national twin study. International Journal of Epidemiology , 11:378–386, 1982.
16. Reynolds I, Harnas J, Gallagher H, Bryden D. Drinking and drug-taking patterns of 8,516 adults in Sydney. Medical Journal of Australia, 2:782–785, 1976.
17. Cummins RO, Shaper AG, Walker M, Wale CJ. Smoking and drinking by middle-aged British men: Effects of class and town of residence. British Medical Journal, 283:1497–1502, 1981.
18. Dawber TR, Kannel WB, Gordon T. Coffee and cardiovascular disease: Observations from the Framingham study. New England Journal of Medicine , 291:871–874, 1974.
19. Prineas RJ, Jacobs DR, Crow RS, Blackburn H. Coffee, tea, and VPB. Journal of Chronic Diseases, 33:67–72, 1980.
20. Hrubec Z. Coffee drinking and ischemic heart disease. Lancet, 1:583, 1973.
21. Kaprio J, Koskenvuo M. A prospective study of psychological and socioeconomic characteristics, health behavior and morbidity in cigarette smokers prior to quitting compared to persistent smokers and non-smokers. Journal of Clinical Epidemiology, 41(2):139–150, 1988.
22. Carmody TP, Brischetto CS, Matarazzo JD, O'Connell RP, Connor WE. Co-occurrent use of cigarettes, alcohol, and coffee in healthy, community-living men and women. Health Psychology, 4(4):323–335, 1985.
23. Swan GE, Carmelli D, Rosenman RH, Fabsitz RR, Christian JC. Smoking and alcohol consumption in adult male twins: Genetic heritability and shared environmental influences. Journal of Substance Use, 2:39–50, 1990.

24. Carmelli D, Rosenman RH, Chesney MA, Fabsitz R, Borhani N. Genetic heritability and shared environmental influences of Type A measures in the NHLBI Twin Study. American Journal of Epidemiology, 127:1041–1052, 1988.
25. Falconer DS. The inheritance of liability to certain diseases estimated from the incidence among relatives . Annals of Human Genetics , 29:51–76, 1965.
26. Eaves LJ. The utility of twins. In: Anderson VE (Ed.), Genetic Basis of the Epilepsies. New York: Raven Press, 1982.
27. Austin MA, King MC, Bawol RD, Hulley SB, Friedman GD. Risk factors for coronary heart disease in adult female twins. Epidemiology, 125 :308–318.
28. Heath AC, Neale MC, Hewitt JK, Eaves LJ, Fulker DW. Testing structural equation models for twin data using LISREL. Behavior Genetics, 19:9–35, 1989.

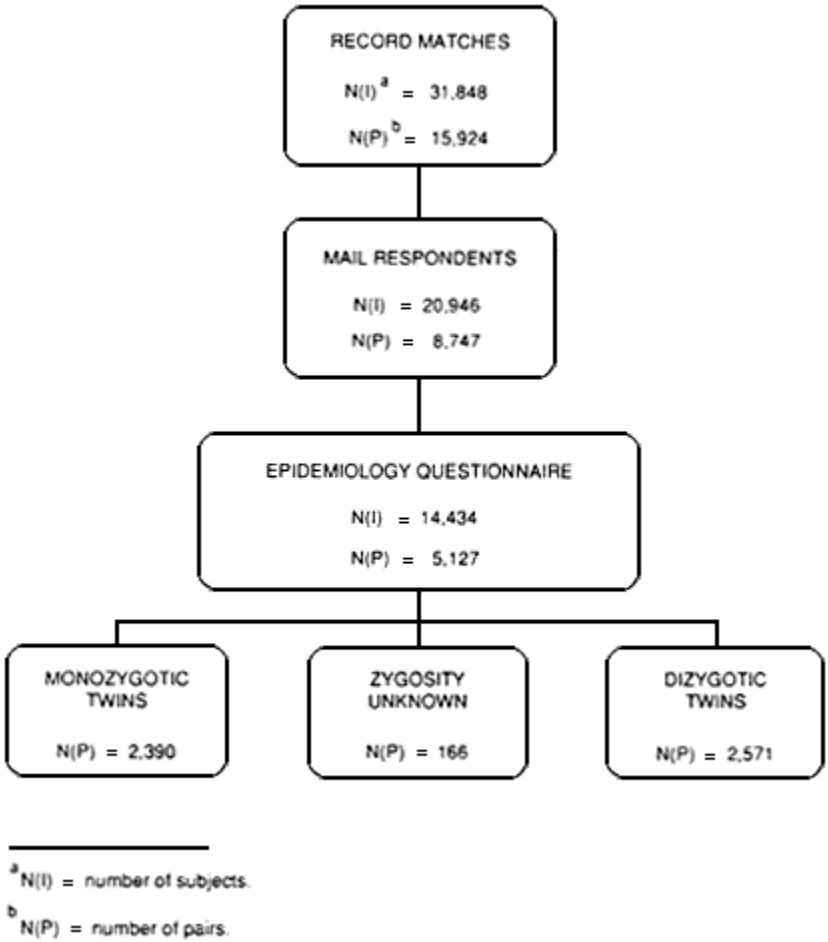

Figure 1 The NAS-NRC Twin Registry

TABLE 1 HERITABILITY ESTIMATES FOR THE USE OF VARIOUS SUBSTANCES IN TWIN STUDIES FROM FINLAND, SWEDEN, AND THE UNITED STATES

			Heritability[a]		
Study	Sample Size (Twin Pairs)	Country of Origin	Tobacco	Alcohol	Caffeine
Partanen et al.[3]	902	Finland	0.28	0.47	0.46
Pedersen[4]	137	Sweden	0.84	0.28	0.88
Kaprio et al.[2]	5,044	Finland	0.46	0.51	0.46
Swan, Carmelli, et al.[23] [NHLBI Twins]	360	USA	0.52	0.60	—

[a] Proportion of total variance attributed to additive genetic effects.
Note: Adapted from Hughes.[1]

TABLE 2 SUBSTANCE USE IN THE NAS-NRC AND FINNISH TWIN REGISTRIES

Substance Use	NAS-NRC Registry	Finnish Registry
Smoking		
Nonsmoker	19.1%	38.1%
Current smoker	58.7	42.5
Former smoker	22.2	19.4
Alcohol use (g/month)		
0 – 250	46.7	47.7
251 – 500	14.4	25.8
> 500	38.9	26.5
Coffee drinking (cups/day)		
0	11.0	6.1
1–5	66.1	51.0
> 6	22.9	43.9

TABLE 3 MODELS FOR ADJUSTMENT a,b

$$\text{CIGSDAY} = + \beta_1 \text{ ALCOHOL} + \beta_2 \text{ COFFEE} + \beta_3 \text{ AGE} + \beta_4 \text{ OCCADJ} \quad (1)$$

$$\text{ALCOHOL} = + \beta_1 \text{ CIGSDAY} + \beta_2 \text{ COFFEE} + \beta_3 \text{ AGE} + \beta_4 \text{ SOCEC} \quad (2)$$

$$\text{COFFEE} = + \beta_1 \text{ CIGSDAY} + \beta_2 \text{ ALCOHOL} + \beta_3 \text{ OCCADJ} \quad (3)$$

[a] Adjustment was done within zygosity group.
[b] Adjusted variables are Student-t residuals from equations (1) – (3).

TABLE 4 CORRELATIONS AMONG APPETITIVE BEHAVIORS AND SOCIODEMOGRAPHIC VARIABLES

	Smoking	Coffee	Age	Occupational Adjustment	Socioeconomic Status
Alcohol	0.224	(0.021)	(-0.018)	(0.013)	0.081
Smoking	———	0.332	-0.047	-0.048	-0.035
Coffee		———	(-0.015)	-0.036	(-0.015)
Age			———	(0.012)	(-0.034)
Occupational adjustment				———	0.049

Note: Values in parentheses are not significantly different from zero.

TABLE 5 GENETIC ANALYSES OF CIGARETTE SMOKING, ALCOHOL USE, AND COFFEE CONSUMPTION WITH AND WITHOUT ADJUSTMENT FOR COVARIATES

	Intraclass Correlations		Genetic Variance	Individual Environment	Shared Environment
Substance Use	MZ	DZ	H	E	C
Smoking					
Log (cig)	0.50	0.24	0.52	0.50	(-0.02)
Adjusted	0.38	0.17	0.42	0.62	(-0.04)
Alcohol					
Log (dose)	0.51	0.33	0.36	0.49	0.15
Adjusted	0.37	0.22	0.30	0.63	(0.07)
Coffee					
Log (dose)	0.42	0.21	0.44	0.54	(0.02)
Adjusted	0.43	0.22	0.42	0.57	(0.01)

Note: Values in parentheses are not significantly different from zero.

Hemorrhagic Fever with Renal Syndrome: Past Accomplishments and Future Challenges

James. W. LeDuc, James E. Childs, Greg E. Glass, and A. J. Watson*

Hemorrhagic fever with renal syndrome (HFRS) is a disease which has not gained widespread recognition among clinicians in the United States, but which is, in fact, of considerable significance in many parts of the world. This syndrome is caused by a newly recognized genus of viruses, the genus Hantavirus, of the family Bunyaviridae[1], and these viruses are of special interest, as they clearly cause acute renal failure, and there is growing evidence that they may predispose a person to subsequent development of chronic renal disease.

Human disease due to hantaviral infections first came to the attention of Western medicine during the Korean Conflict, when a mysterious "new" disease, Korean hemorrhagic fever, was seen among the United Nations forces. At that time, over 2,000 U.S. troops were infected, and many deaths occurred[2]. In spite of intense investigations by some of the most prominent medical scientists of the era, the causative agent was not identified, and it wasn't until 1976, just over a decade ago, that the etiologic agent was finally discovered[3].

* James W. LeDuc is with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Ft. Detrick, Frederick, Maryland; James E. Childs and Greg E. Glass are with the Department of Immunology and Infectious Diseases, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland; and A. J. Watson is with the Division of Nephrology, Johns Hopkins University, Baltimore, Maryland. Correspondence to James W. LeDuc, Disease Assessment Division, USAMRIID, Ft. Detrick, Frederick, MD 21701–5011. The views of the author(s) do not purport to reflect the positions of the Department of the Army or the Department of Defense, who have approved this report for public release with unlimited distribution.

Dr. Ho Wang Lee and collaborators, working in Seoul, Korea, were the first to isolate the virus that causes Korean hemorrhagic fever. They named it "Hantaan virus" in recognition of the Hantaan River, which transsects the endemic region of Korea near the demilitarized zone. The virus was isolated from lung tissues of the striped field mouse, Apodemus agrarius, and this species is now recognized as the major rodent host of the virus[3].

Within a year or two of its initial isolation, Hantaan virus was adapted to grow in cell culture, which allowed for development of a serologic test[4]. The availability of both the virus and a serologic test allowed experimental infection of natural rodent hosts to be undertaken, and through these studies, one of the key characteristics of the hantaviruses was discovered. A brief viremia follows experimental inoculation of seronegative Apodemus agrarius. Subsequently, hantaviral antigen is detectable for weeks to months in many major organs, but, most importantly, infectious virus is shed in saliva, feces, and especially urine, perhaps for the duration of the rodent's life. This virus shedding occurs in spite of the presence of both indirect immunofluorescent antibody (IFA) and neutralizing antibody in serum[5]. Thus, the infected rodent becomes a persistent source of infectious virus, and we suspect that it is through aerosolized virus that is excreted in infected rodent urine and feces that most human infections occur. This persistent shedding of infectious virus by chronically infected rodents appears to be a general characteristic of all the hantaviruses and their rodent hosts, and is a critical aspect in the epidemiology of this group of viruses[6].

Acute hantaviral infections cause a wide spectrum of illness, which typically includes abrupt onset, fever, renal dysfunction, and often hemorrhagic manifestations[7]. The name hemorrhagic fever with renal syndrome has been proposed by the World Health Organization to cover all human disease due to hantaviral infections[8]. In Asia and some parts of Europe where inadequate treatment facilities exist, mortality rates may exceed 10%, and, even with modern treatment, mortality rates of 5% or greater are not uncommon for some forms of HFRS.

A very interesting set of sera was collected by the Hemorrhagic Fever Commission during the Korean Conflict. This commission was formed by the Army to investigate the "new" hemorrhagic fever that was seen among the forces in Korea. While they were ultimately unable to isolate the causative agent, they did develop a considerable body of knowledge about both the clinical disease and its treatment. They also systematically collected acute and convalescent sera from patients studied. This collection remains intact, and we recently tested these sera for evidence of past hantaviral infection[9].

The sera were stored in three metal trunks over the years. The collection was very carefully packed, and surprisingly, almost none of the tubes was broken during their many years in storage. The collection contains three sizes of preserved sera, with each tube labeled with the patient's name and number, date of collection, volume, and a "DD" number, which we believe represents the day of disease. The information on the labels is the only patient data that we have located, so we used this to calculate days post-onset when presenting our results.

Each serum sample was tested by enzyme immunoassay for the presence of hantaviral antigen, and IgM and IgG antibodies. The last serum for each patient was also tested by plaque-reduction neutralization test to determine which strain of hantavirus was responsible for the infection.

We tested over 600 sera from 245 patients, and only 15 patients failed to develop anti-hantaviral antibodies over the course of their illnesses. A few of these sera were from patients where only one sample was obtained, and could perhaps represent patients who died early in disease; but most of the negative sera were from patients where more than one sample was obtained and appear to represent infections with other than hantaviruses. Using the worst-case figures, the Commission clinicians were then accurate in their clinical diagnosis at least 94% of the time.

These results demonstrate the utility of the IgM capture assay as the method of choice for diagnosis of acute HFRS. This was further enforced when we were unsuccessful in our attempts to detect hantaviral antigen in early sera. When we tested the last serum drawn from each patient by plaque-reduction neutralization tests, we found highest titers to prototype Hantaan virus, indicating that this virus was the likely infecting agent.

These results confirm that the disease seen among U.S. forces during the Korean Conflict was indeed due to Hantaan virus infection. This confirmation of the clinical diagnosis, and the availability of sera drawn during acute illness, will prove very useful in some follow-up studies that we will propose later.

Nephropathia epidemica is a less severe form of hemorrhagic fever with renal syndrome that is found in Scandinavia, the western Soviet Union, and much of Europe. This disease was first described in the medical literature during the 1930's[10,11,] and the similarities between it and the Asian forms of hemorrhagic fever with renal syndrome have been known for some time[12]. Like Hantaan virus in Asia, Puumala virus, the cause of nephropathia epidemica, is also associated with a rodent host, in this case the bank vole, Clethrionomys glareolus[13,14]. The clinical details of nephropathia epidemica are very similar to the Asian forms, with renal dysfunction as a prominent characteristic, but generally lacking the serious

hemorrhagic manifestations and marked mortality characteristic of hantaviral infections in Asia[15].

A severe form of hemorrhagic fever with renal syndrome occurs in the Balkan region of Europe, with documented mortality rates of around 15% in Greece[16]. The clinical disease more closely resembles that due to Hantaan virus, as seen in Asia, rather than the milder nephropathia epidemica of Scandinavia and Western Europe. A virus has been isolated from an acutely ill Greek patient, and it has been shown to be antigenically similar to prototype Hantaan virus, but sufficiently distinct to allow specific recognition; we have proposed the name Porogia virus for this apparently new hantavirus[17]. Investigations of the natural host of this virus indicate that the yellow-necked mouse, Apodemus flavicollis, is the most likely reservoir of Porogia virus[18].

To summarize briefly with regard to the hantaviruses discussed so far, three distinct hantaviruses are recognized that are regionally associated with hemorrhagic fever with renal syndrome. Hantaan virus is found in Asia and is responsible for a moderate to severe form of hemorrhagic fever with renal syndrome locally called Korean hemorrhagic fever or epidemic hemorrhagic fever. Puumala virus is found in Scandinavia, the western Soviet Union, and much of Europe, and causes a less severe form of HFRS called nephropathia epidemica. Porogia virus, and perhaps some other closely related strains, are found in the Balkan region and cause a severe form of HFRS.

Seoul virus is another distinct hantavirus that is associated with domestic rats. The story of Seoul virus begins in the early 1980's, and again, Ho Wang Lee and his Korean colleagues played a prominent role in its discovery[19]. With the aid of the serologic test developed for Hantaan virus, they diagnosed hemorrhagic fever with renal syndrome among patients who resided in the urban centers of Korea, far from the recognized endemic region of Korean hemorrhagic fever. The patients were city dwellers, people with no history of travel outside the city. When attempts were made to collect small rodents around patients' houses, no Apodemus could be found; however, domestic rats (Rattus rattus, R. norvegicus) were present, and both antigen and antibody to what appeared to be Hantaan virus were detected. Subsequent study with more specific techniques, however, found that the virus in domestic rats was a distinct agent, closely related to prototype Hantaan virus. It was named Seoul virus, after the Korean city where it was first isolated.

Soon thereafter we began a global serosurvey of domestic rats to determine the distribution of this newly recognized virus[20]. Antibody-positive rats were found in many parts of the world, suggesting that the virus itself was not new, but rather, our ability to detect it had changed.

We then focused our efforts locally to investigate the maintenance of this virus among domestic rats. We concentrated on the inner-city neighborhoods of Baltimore, Maryland, in areas where litter and trash abound, and rats are common. We have studied hantaviruses in the rat populations in these neighborhoods for several years, and we have found Seoul-like viruses especially common among rats in this environment[21].

We have isolated strains of Seoul-like virus from rats captured there, and we have monitored the hantaviral antibody prevalence rates in these populations[22]. We examined the percent seropositive by various body-mass groupings, which is a good estimator of age, and found that about a third of the animals in the lowest mass group, or youngest age group, had antibody to hantaviruses[22]. We suspect that this was maternal antibody, which was lost over the next several weeks, and is reflected in the dip in prevalence rates at about the 200-g mass group. As the rats aged, the prevalence rates increased, until virtually all were positive in the heaviest mass groups, representing the oldest segment of the population.

With such an abundance of infected rats coexisting with the resident human population, and recognition in Asia that Seoul virus is capable of causing overt human disease, we next attempted to document human infection among Baltimore residents.

We first sampled 2,470 persons visiting a venereal disease clinic located in a neighborhood where many infected rats were found (Table 1). The population sampled here was young, in their mid-20's, predominantly black males, of lower socioeconomic status[23]. Six persons from this sample clearly had been infected with the local rat-borne strain of hantavirus, yielding an antibody prevalence rate of 2.4 per thousand.

We next examined 1,250 patients seen at the Johns Hopkins Hospital who had proteinuria of greater than 250 mg/24 hr (Table 1). This population was also drawn from inner-city Baltimore locations where infected rats are common. Persons sampled in this group were typically older, in their mid-40's, predominantly black females, and again from lower socioeconomic neighborhoods. We found 15 persons antibody positive in this group, for a prevalence rate fivefold higher, at 12 per thousand.

None of the seropositive patients had evidence of acute HFRS, but all had some form of chronic disease[24]. When we attempted to match each seropositive by age and sex to five seronegative controls from this same population, we found that seropositive persons were significantly more likely to suffer from hypertension, chronic renal disease, or have a history of cerebrovascular accidents, although rates of diabetes were not significantly different (Table 2). A nephrologist from Johns Hopkins Hospital then reviewed the charts for the primary diagnosis underlying their renal disease, without knowledge of their serological status. Diagnosis was based on reported histories, examinations, laboratory tests

and radiography, and biopsies when available. Hypertensive renal disease was the most common diagnosis among the seropositives. These results differed significantly from those of the matched controls, where diabetes mellitus was the most common cause of renal disease; other factors such as drug abuse, polycystic disease, and glomerulonephritis were secondary (Table 3). The differences seen could not be explained on the basis of race alone.

Finally, a serological survey targeted 402 patients utilizing chronic renal dialysis units in Baltimore (Table 1). Individual identifiers and personal histories were not available for these sera, but the population age distribution and sex ratio were similar to those of the Johns Hopkins Hospital population. The confirmed seroprevalence rate in this group was 20/1,000, the highest of any group sampled.

While these serological results are drawn from differing segments of the Baltimore population, they do share several common characteristics, and suggest that strains of Seoul-like virus found in the United States may predispose individuals to later development of chronic renal disease, at least among lower socioeconomic segments of inner-city populations.

The possibility of long-term renal dysfunction after a hantaviral infection has not been well studied. One of the earliest studies was done by Rubini and his colleagues, including staff of the Medical Follow-up Agency[25]. They examined Korean War veterans who had suffered hantaviral infections, and a group of matched controls, in 1956, about 3 to 5 years after most cases would have been infected. This study was noteworthy in that they found a significant increase in the rate of genitourinary hospital admissions among the HFRS cases, at rates which increased with the severity of their original disease. Other findings included hyposthenuria, persistent mild albuminuria, and a suggestion of incipient hypertension among some examined. These early indications of chronic renal dysfunction are consistent with the hypothesis that the patients' conditions could evolve over time to conditions similar to those seen among the Baltimore residents.

Interestingly, the files from this study still exist at the Follow-up Agency. Clearly, another look at this population is desperately needed, and a collaborative study with the Follow-up Agency and USAMRIID is now being developed.

We also encouraged our colleagues in the Balkan region of Europe to examine their serologically confirmed HFRS patients for evidence of chronic renal insufficiency, and their results are shown in Table 4[26272829]. About 10% of those who survived acute disease were left with evidence of chronic renal insufficiency. These figures are based on renal function evaluations taken anytime between discharge from hospital to about 5 years post-onset. Five years represents about the longest period of time that

HFRS has been diagnosed accurately in this area, so we haven't known infected patients for longer follow-up. Nonetheless, there is a striking similarity in the results from several different medical centers, which suggests that chronic renal insufficiency is not an uncommon sequela among patients sick enough to be hospitalized during acute illness. We are continuing to examine these patients over time, and we are trying to determine if there is a correlation between seropositivity and chronic renal disease or hypertension among long-term residents of the area as seen in Baltimore.

To summarize, the past decade has yielded a wealth of new knowledge regarding hemorrhagic fever with renal syndrome. We now know that several different viruses are capable of causing clinically similar diseases, which are called collectively hemorrhagic fever with renal syndrome. These viruses are maintained in nature by chronically infected rodents, and they are distributed much more widely than once suspected. We are in a position to diagnose acute HFRS rapidly and accurately, and we have preliminary evidence to suggest that past hantaviral infection may be associated with subsequent development of chronic renal disease.

Providing the proof of this association represents an exceptional challenge, and the resources of the Follow-up Agency, the Department of Defense, and the Veterans Administration are especially well suited to answer this question definitively. Hantaviral infections can be acquired either overseas, including as part of military service, or right here in the United States, from local infected rats; but regardless of the source of infection, there is growing evidence that some patients will progress to chronic renal disease and perhaps end-stage kidney failure. It has been estimated that the United States spends more than $30 billion a year for medical care for kidney and urologic diseases, and about $3 billion is Medicare payments for dialysis and transplantation for people with end-stage kidney disease. If even a small portion of this burden is due to hantaviral infections, say, the 2% we found in our Baltimore dialysis units, then we, as a nation, are spending about $60 million a year on this disease. Clearly, we cannot afford to let this question remain unresolved.

REFERENCES

1. Schmaljohn, C.S., Hasty, S.E., Dalrymple, J.M., LeDuc, J.W., Lee, H.W. , von Bonsdorff, C.H., Brummer-Korvenkontio, M., Vaheri, A., Tsai, T.F., Regnery, H.L., Goldgaber, D., Lee, P.W. 1985. Antigenic and genetic properties of viruses linked to hemorrhagic fever with renal syndrome. Science 227:1041–1044.
2. Earle, D.P. 1954. Symposium on epidemic hemorrhagic fever. Am. J. Med. 16:617–709.
3. Lee, H.W., Lee, P.W., Johnson, K.M. 1978. Isolation of the etiologic agent of Korean hemorrhagic fever. J. Infect. Dis. 137:298–308.

4. French, G.R., Foulke, R.S., Brand, O.A. 1981. Korean hemorrhagic fever. Propagation of the etiologic agent in a cell line of human origin. Science 211:1046–1048.
5. Lee, H.W., Lee, P.W., Baek, L.J. 1981. Intraspecific transmission of Hantaan virus, etiologic agent of Korean hemorrhagic fever, in the rodent Apodemus agrarius. Am. J. Trop. Med. Hyg. 30:1106–1112.
6. LeDuc, J.W. 1987. Epidemiology of hantaan and related viruses. Lab. Anim. Sci. 37:413–418.
7. McKee, K.T., MacDonald, C., LeDuc, J.W., Peters, C.J. 1985. Hemorrhagic fever with renal syndrome. Mil. Med. 150:640–647.
8. World Health Organization. 1985. Haemorrhagic fever with renal syndrome: memorandum from a WHO meeting. Bull. WHO 61:269–275.
9. LeDuc, J.W., Ksiazek, T.G., Rossi, C.A., Dalrymple, J.M. 1990. A retrospective analysis of sera collected by the Hemorrhagic Fever Commission during the Korean Conflict. J. Infect. Dis. (submitted).
10. Zetterholm, S.G. 1934. Akata nefriter simulerande adata bukfall. Svenska Lakartidningen 31:425–429.
11. Myhrman G. 1934. En njursjukdom med egenartad symptombild. Nord. Med. Tidskr. 7:793–794.
12. Gajdusek, D.C. 1953. Acute infectious hemorrhagic fevers and mycotoxicoses in the Union of Soviet Socialist Republics. Medical Science Graduate School, Walter Reed Army Medical Center, Washington, D.C.
13. Brummer-Korvenkontio M, Vaheri, A., Hovi T., von Bonsdorff, C.H., Vuormies, J., Manni, T., Penttinen, K., Oker-Blom, N., Lahdevirta, J. 1980. Nephropathia epidemica: detection of antigen in bank voles and serologic diagnosis of human infection. J. Infect. Dis. 141:131–134.
14. Niklasson, B., LeDuc, J.W. 1987. Epidemiology of nephropathia epidemica in Sweden. J. Infect. Dis. 155:269–276.
15. Lahdevirta, J. 1971. Nephropathia epidemica in Finland. A clinical, histological, and epidemiological study. Ann. Clin. Res. 3:1–154.
16. Antoniadis, A., LeDuc, J.W., Acritidis, N., Alexiou-Daniel, A., Kyparissi, A., Saviolakis, G.A. 1989. Hemorrhagic fever with renal syndrome in Greece: clinical and laboratory characteristics of the disease . Rev. infect. Dia. 11:S891–S896.
17. Antoniadis, A., Grekas, D., Rossi, C.A., LeDuc, J.W. 1987. Isolation of a hantavirus from a severely ill patient with hemorrhagic fever with renal syndrome in Greece. J. Infect. Dis. 156:1010–1013.
18. LeDuc, J.W., Antoniadis, A., Siamopoulus, K. 1986. Epidemiological investigations following an outbreak of hemorrhagic fever with renal syndrome in Greece. Am. J. Trop. Med. Hyg. 35:654–659.
19. Lee, H.W., Baek, L.J., Johnson, K.M. 1982. Isolation of Hantaan virus, the etiologic agent of Korean hemorrhagic fever, from wild urban rats. J. Infect. Dis. 146:638–644.
20. LeDuc, J.W., Smith, G.A., Childs, J.E., Pinheiro, F.P., Maiztegui, J.I., Niklasson, B., Antoniadis, A., Robinson, D.M., Khin, M., Shortridge, K.F., Wooster, M.T., Elwell, M.R., Ilbery, P.L.T., Koech, D., Rosa, E., Salbe, T., Rosen, L. 1986. Global survey of antibody to Hantaan related viruses among peridomestic rodents. Bull. WHO 64:139–144.
21. Childs, J.E., Korch, G.W., Smith, G.A., Terry, A.D., LeDuc, J.W. 1985. Geographic distribution and age related prevalence of antibody to Hantaan-like virus in rat populations of Baltimore. Am. J. Trop. Med. Hyg. 34:385–387.
22. Childs, J.E., Korch, G.W., Glass, G.E., LeDuc, J.W., Shah, K.V. 1987. Epizootiology of Hantavirus infections in Baltimore: isolation of a virus from Norway rats and characteristics of infected rat populations. Am. J. Epidemiol. 126:55–68.
23. Childs, J.E., Glass, G.E., Korch, G.W., Arthur, R.R., Shah, K.V., Glasser, D., Rossi, C., LeDuc, J.W. 1988. Evidence of human infection with a rat-associated Hantavirus in Baltimore, Maryland. Am. J. Epidemiol. 127:875–878.

24. Glass, G.E., Childs, J.E., Watson, A.J., LeDuc, J.W. 1990. Association of chronic renal disease, hypertension and infection with a rat-borne Hantavirus. Arch. Virol. (in press).
25. Rubini, M.E., Jablon, S., McDowell, M.E. 1960. Renal residuals of acute epidemic hemorrhagic fever. Arch. Int. Med. 106:378–387.
26. Cizman, B., Ferluga, D., Avsic, T., Kaplan-Pavlovcic, S., Licina, A., Furlan, P., Gradecki, I., Drinovec, J. 1989. Clinico-laboratory evaluation of patients with HFRS4 years of investigation. 2nd Symposium on Arboviruses in the Mediterranean Countries, 24–29 September 1989, Dubrovnik, Yugoslavia, Abstract S19.
27. Dmitrovic, R., Djordjevic, D., Djerkovic, V., Obradovic, M., Dimkovic, N., Dimitrijevic, Z., Ostric, V., Gligic, A. 1989. Epidemiological and clinical aspects of chronic renal insufficiency in patients who have had HFRS. 2nd Symposium on Arboviruses in the Mediterranean Countries, 24–29 September 1989, Dubrovnik, Yugoslavia, Abstract S30.
28. Ahmetic, S., Kufllovci, M., Baljosevic, S., Avdiu, S. 1989. Clinical and epidemiological characteristics of haemorrhagic fever with renal syndrome (HFRS) induring epidemic 1986 in SAP Kosora (sic). 2nd Symposium on Arboviruses in the Mediterranean Countries, 24–29 September 1989, Dubrovnik, Yugoslavia, Abstract S34.
29. Siamopoulus, K.C., Elisaf, M., Antoniadis, A. 1989. Initial and long term evaluation of renal function in hemorrhagic fever with renal syndrome. 2nd Symposium on Arboviruses in the Mediterranean Countries, 24–29 September 1989, Dubrovnik, Yugoslavia, Abstract S16.

TABLE 1 PREVALENCE OF ANTIBODIES TO HANTAVIRUSES AMONG SELECTED POPULATIONS OF BALTIMORE, MARYLAND

Population	Prevalence
Young (mid-20's), predominantly black males seen at a sexual disease clinic	2.4/1000
Older (mid-40's), predominantly black patients seen at Johns Hopkins Hospital	12/1000
Patients using chronic renal dialysis units	20/1000

TABLE 2 COMPARISON OF HANTAVIRUS-SEROPOSITIVE AND HANTAVIRUS-SERONEGATIVE PERSONS FOR PREVALENCE OF CHRONIC DISEASES IN BALTIMORE, MARYLAND, CASE-CONTROL STUDY, 1986–88

Disease	Seropositive	Seronegative	P value*
Chronic renal disease	12 (80%)	32 (44%)	<0.025
Hypertension	14 (93%)	47 (64%)	<0.05
Cerebrovascular accident	4 (27%)	5 (7%)	<0.025
Diabetes mellitus	6 (40%)	35 (48%)	ns
Total	15	73	

* Chi square analysis.

TABLE 3 SPECIFIC CAUSES OF CHRONIC RENAL DISEASE IN BALTIMORE, MARYLAND, CASE-CONTROL STUDY, 1986–88

Condition	Seropositive	Seronegative	P value
Chronic renal disease	12 (80%)	32 (44%)	<0.025
Hypertension	7 (47%)	3 (4%)	<0.005*
Diabetes mellitus	2 (13%)+	16 (22%)	
Drug induced	1 (7%)+	6 (8%)	
Obstructive	0	3 (4%)	
Autoimmune	0	4 (5%)	
Unknown	1 (7%)	0	
None	3 (20%)	41 (56%)	

* Chi square analysis with 3 df.
+ Drug induced also with diabetes.

TABLE 4 CHRONIC RENAL INSUFFICIENCY AS A SEQUELA OF HFRS AMONG SEROLOGICALLY CONFIRMED PATIENTS DIAGNOSED IN YUGOSLAVIA AND GREECE

	No. Pos/No. Tested	%
Yugoslavia		
Ljubljana	2/20	10
Belgrade	3/19	16
Kosova	4/39	10
Greece	2/19	10
Total	11/97	11

Psychological Effects of Military Captivity

Brian E. Engdahl, William F. Page*

ABSTRACT

Studies of former prisoners of war (POWs) provide valuable insights into post-traumatic adaptation because they gather information from a large population that survived the traumatic experiences of military captivity. Previous studies of POWs have shown elevated rates of psychiatric symptoms and disorders. This report presents evidence from a longitudinal study of three large, representative national samples of former POWs. The study finds that depressive symptomatology, as measured by the Center for Epidemiologic Studies depression scale, is elevated in World War II POWs from the Pacific and European theaters and in Korean conflict POWs. Decades later, depressive symptomatology is found to be strongly associated with prior treatment in captivity. Differences in depressive symptomatology among the three POW groups can be attributed to captivity-related factors and to buffering factors such as age at capture and education.

INTRODUCTION

Studies of former prisoners of war, a large population that survived the traumatic experiences of military captivity, are important in their own right, have relevance to survivors of other captivity maltreatment (Engdahl and Eberly, 1990), and provide insights into the phenomenology of general

* Brian E. Engdahl, Ph.D., is with the U.S. Department of Veterans Affairs medical center in Minneapolis, Minnesota, and William F. Page, Ph.D., is with the Medical Follow-up Agency, Institute of Medicine in Washington, DC.

post-traumatic adaptation. Although a few studies find little long-term negative effect and even psychological growth among POWs (Ursano, 1981; Sledge, Boydstun, and Rabe, 1980), most studies report elevated incidence of psychiatric symptoms and disorders. Cohen and Cooper (1954) found a four-to five-fold excess of hospitalizations for psychoneurosis but not psychosis among World War II Pacific theater POWs and European theater POWs compared with their controls. Beebe (1975) extended this follow-up study and found significantly more hospitalizations of POWs for a variety of psychiatric illnesses, including schizophrenic disorders, anxiety reactions without somatization, alcoholism, "nervousness and debility," and other psychoneurotic reactions. Psychoneuroses (particularly anxiety reactions and somatization) and psychoses (e.g., schizophrenia) were especially frequent among Pacific World War II and Korean conflict POWs when compared with their non-POW controls. Kluznik et al. (1986) retrospectively diagnosed psychiatric disorders among 188 World War II and Korean conflict POWs. Within one year of their release, 67% fulfilled DSM-III criteria for post-traumatic stress disorder, and more than half of those continued to have symptoms over 40 years later. Generalized anxiety disorders and depressive disorders also were frequent.

Psychiatric symptoms, particularly depressive symptoms, were elevated among Australian World War II POWs in a recent series of studies (Tennant et al., 1986a,b; Dent et al., 1987). Examination of 170 POWs and comparable controls revealed that POWs were significantly more depressed than non-POW controls some 40 years after repatriation. No differences were found in state anxiety, trait anxiety, neuroticism, psychoticism, and hostility. To explain the persistence of depressive symptoms for 40 years after release from captivity, the investigators linked these findings, suggesting that over the long follow-up period anxiety might diminish but depression might increase as a reaction to chronic post-traumatic impairment. Dent et al. (1987) reported separate regression analyses for the Australian POWs and controls showing the following variables to be predictive of present-day depressive symptoms: experiencing a nervous illness during World War II or a depressive illness after World War II, having a lower level of education or socioeconomic status, and being unmarried, unemployed, or retired.

The present study collected data on the prevalence, severity, and correlates of depressive symptoms in a large national representative sample of American POWs. Other recent reports of POWs' adaptation have been based on smaller samples drawn from a single region of the country (such as Goldstein et al., 1987, at the Pittsburgh Veterans Administration Medical Center (VAMC); and Speed et al., 1989, at the Minneapolis VAMC). The size of the samples in the present study enables more detailed analyses within the three POW eras (POWs of the Pacific and

European theaters, plus POWs of the Korean conflict) as well as comparisons among these eras. Also, the representative nature of the national samples strengthens generalizations made from them to the population of all POWs. We present descriptive data first, followed by data on the correlations between individual predictor variables and depressive symptoms. Finally, we use multiple regression to examine the combined effects of predictors on depressive symptoms.

METHODS

Subjects

The Medical Follow-up Agency of the Institute of Medicine, National Academy of Sciences, has studied the health of former POWs since the early 1950s. Cohen and Cooper (1955) assembled representative rosters of former World War II POWs and non-POW controls and characterized their mortality, morbidity, and disability after liberation. Nefzger (1970) added Korean conflict prisoners and controls and studied their mortality. Beebe (1975) conducted a 20-year morbidity follow-up, collecting data from military and Veterans Administration (now Department of Veterans Affairs) records and from questionnaires. Keehn (1980) continued the mortality follow-up through 1976. We report data collected from a questionnaire follow-up of these earlier-defined cohorts.

Cohen and Cooper (1955) used the Army's official roster of all known World War II POWs to select random, independent samples of white Army servicemen who were captured in the Pacific and European theaters. Nefzger (1970) subsequently doubled the number of Pacific prisoners and controls in the study cohort and added a group of Korean conflict POWs and nonprisoner controls.

The follow-up reported here began with a review of VA mortality records, which ascertained that 1,319 men from the earlier studies were alive as of mid-1984 and thus eligible for the questionnaire study. Addresses were obtained from the Internal Revenue Service (under an arrangement with the National Institute for Occupational Safety and Health) and from two commercial tracing firms. IRS provided addresses for roughly 90% of the total sample, and tracing firms provided addresses for an additional 3% of subjects. Next, up to three mailings per person were made to each address, with a mailgram preceding the third mailing to alert the addressee to the forthcoming questionnaire. The mailings contained a cover letter from the study director at the time, Robert Keehn, and the questionnaire. Also included in the third mailing was a letter from the National Commander of the American Ex-POWs encouraging participation in the study. The actual mailing of questionnaires began late in 1984, and replies were accepted through December 1985. The

questionnaire included the 20-item Center for Epidemiologic Studies-Depression scale (CES-D; Radloff, 1977), the Lie and Hysteria scales of the Minnesota Multiphasic Personality Inventory (MMPI; Hathaway and McKinley, 1951), questions on smoking and drinking, history of hospitalizations since 1965, medical conditions under treatment, and medical conditions not being treated.

Measures

The CES-D, a standardized self-administered rating instrument (see Table I), was chosen as the measure of depressive symptoms, which are known to be elevated among POWs (Tennant et al., 1986a). The CES-D is well suited to estimate the severity and prevalence of depressive symptoms among the general population of POWs, as it is widely used in epidemiologic studies of the prevalence and correlates of depression in non-clinical populations (e.g., Murrell et al., 1983; Weissman et al., 1977). The use of the CES-D allowed a large number of subjects to be surveyed and permitted comparisons with previous CES-D-based general and special population surveys. Although CES-D scores correlate modestly with clinical diagnoses of depression (Myers and Weissman, 1980; Boyd et al., 1982), the CES-D does not yield a diagnosis. Its primary utility is in the estimation of symptom prevalence and in clinical or research efforts as a first-stage screening test. Breslau (1985) and Roberts, Vernon, and Rhoades (1989) conclude that the CES-D detects generalized anxiety about as well as it detects major depression. Roberts et al. (1989) hypothesize that its content indicates a single dimension that they label "demoralization." Alternatively, Golding and Aneshensel (1989), in reviewing the CES-D's factor structure, conclude that four factors best represent its content: Negative Affect, Positive Affect, Somatic Symptoms, and Interpersonal Problems. We view the CES-D as a measure of general psychological impairment, primarily indexing depression. Each of the 20 CES-D items was assigned a score of 0 to 3, and all the responses were summed. Scores may range from 0 to 60; the standard indication of significant depressive symptoms is a score of 16 or above. Missing item responses were assigned a weight of 0, and 5 or more missing responses on a single questionnaire resulted in the assignment of a missing total score for that person.

The MMPI Lie scale, which detects tendencies to place oneself in an unusually favorable light, was included to check for response bias. Concern that POWs might misreport their psychological symptoms led to inclusion of the MMPI Hysteria scale which focuses on symptoms and includes both over-reporting (Admit) and under-reporting (Deny) subscales (Little and Fisher, 1958).

For most subjects in the three POW groups studied here, earlier data collected by Beebe were available from medical and personnel records as well as from the 1965 questionnaire on medical problems suffered during captivity. Table 2 outlines these captivity medical problems and symptoms collected via self-report from earlier surveys. A total captivity symptom index score was calculated by adding the number of "yes" responses for each condition on the symptom list. Percent of body weight lost was calculated as the difference between self-reported weight at induction and self-reported lowest weight during captivity, divided by self-reported weight at induction.

The total number of responses received from the POWs was 989. After excluding deceased subjects discovered by the survey, the final response rates were 74.5% for the Pacific, 75.3% for the European, and 68.8% for the Korean POWs.

RESULTS

Military Captivity Data

Pacific and Korean POWs reported more captivity symptoms and greater weight loss than European POWs. We note that these self-reported data were collected some 20 years ago, and the accuracy of recall should be greater than that for data collected in the late 1980s. These data probably also are less susceptible to any recall biases introduced by age-associated declines in health. When exposed to comparable trauma, individuals who currently are more ill tend to recall (and report) greater severity of stress than those who are less ill.

Demographic Data

Table 3 reveals notable demographic differences among the three POW groups. Relative to the Korean group, both World War II groups were older and included a higher proportion of high school graduates and college-educated men; further, they only include whites. There also was a lower proportion of infantry in both World War II groups with a correspondingly higher proportion of Army Air Corps personnel and a higher proportion of officers, warrant officers, and sergeants in the Pacific POW group.

In addition to these differences in age, rank, and education, there were differences between the two World War II groups. On average the Pacific POWs were slightly older than European POWs at capture, had higher rank and education, and had a lower percentage of draftees. These differences primarily reflect underlying differences in military theaters and eras. As detailed in another report (Page, 1988), differences between

questionnaire respondents and nonrespondents were small but uniform, and limited primarily to rank and education; nonrespondents tended to have lower rank and less education.

MMPI

Using standard conversion formulas for the MMPI, we converted raw scores to standardized T scores with means of 50 and standard deviations of 10. The MMPI Lie scale and the Deny subscale detected very little response bias, with mean T scores close to the expected value of 50. For both scales across the three groups, mean scores ranged from 48.1 to 52.6. For the three groups, Hysteria scale scores and its Admit subscale scores were elevated, ranging from 66.4 to 74.7. The European POW group means were lower than the Pacific and Korean groups, as discussed in more detail below.

CES-D Scale

Community studies find the proportion of older males with high CES-D scores to range from 3% to 18%, with an average of roughly 10% (Comstock and Helsing, 1976; Frerichs, Aneshensel, and Clark, 1981; Murrell, Himmelfarb, and Wright, 1983; Eaton and Kessler, 1981). The proportions of CES-D scores at or above the cut-off point of 16 ranged from 54% in the Korean group and 50% for the Pacific group to 37% for the European group. The Pacific POW proportion above the cut-off was greater than the European proportion (chi-square = 12.0, df = 1, p = .00068), and the Korean proportion was greater than the European proportion (chi-square = 20.5, df = 1, p = .00002). The ranking of mean CES-D scores was identical to the ranking of proportions above the cutoff, and the means for the Pacific group (17.9) and the Korean group (18.8) were both above the cut-off. The European group mean CES-D score (13.4), which is significantly lower than those of the Pacific and Korean groups, is low only in comparison to them. Compared with figures for the general population (where normal groups average 5 to 8; National Center for Health Statistics, 1980), the European group mean CES-D rate is markedly high. Psychiatric populations have shown mean scores ranging from 37 for male acute depressives to 19 for male recovered depressives (Weissman et al., 1977).

Correlates of Depressive Symptoms

To understand further this basic finding of elevated depressive symptoms among POWs, we conducted additional analyses of the depressive symptoms' relationships to captivity intensity and individual factors. This approach assumes both the existence of a dose-response

relationship between severity of trauma and the post-traumatic depressive symptoms, plus the presence of individual factors that may moderate the dose-response relationship.

Bivariate Relationships of Antecedent Variables and the CES-D

In Table 4, the proportions of CES-D scores at or above the cut-off point are shown for the various demographic characteristics described earlier. Also shown are the results of chi-square tests comparing the proportions of men with elevated CES-D scores across the various levels of demographic characteristics, by POW group. The differences in the proportion of elevated CES-D scores among categories for race, age, and type of service (e.g., infantry) were somewhat smaller than the corresponding differences for rank/component of service, marital status at entry into service, years of education, and rank at separation. To illustrate, the marked decrease in the proportion of high CES-D scores as the number of years of education increases is evidence of a strong association. Similarly, rank at separation has a strong, graded association with the proportion of high CES-D scores. The consistent CES-D differences by education and rank suggest that a more general (though unmeasured) underlying factor, such as socioeconomic status, may moderate the prevalence and severity of depressive symptoms.

Self-reported number of drinks per day showed an association with CES-D score, in which both non-drinkers and heavy drinkers reported a higher prevalence of depressive symptoms than moderate drinkers. The non-linear nature of this relationship (a U-shaped distribution) argues against the inclusion of self-reported alcohol consumption in the current linear regression models; future analyses will focus on this variable.

Other crosstabulation analyses (not shown) revealed roughly the same proportion of men with high CES-D scores across the three POW groups when comparing men who reported the same range of weight loss or captivity symptom score. This suggests that more severe treatment, as reflected both by greater weight loss and greater number of captivity symptoms, is linked to a higher level of subsequent depressive symptoms, and that differences in severity of treatment at least partially will explain the differences in those symptoms across these POW groups. This observation, like the earlier observations, may be subject to confounding effects—therefore the need for the following multivariate analyses.

Multivariate Relationships of Antecedent Variables and the CES-D

We estimated the joint effect of multiple potential causal factors on CES-D scores through multiple regression analyses, treating the CES-D

total score as a continuous dependent variable. The rationale for variable selection was based on previous research, particularly the studies of Australian POWs. We examined the roles of several demographic and captivity-related factors: age at time of capture, marital status at entry into active duty, years of education, weight loss in captivity, captivity symptom score, and, for Korean POWs only, Army General Classification Test (AGCT) score, rank at capture, and race. We treated all but marital status, rank at capture, and race as continuous measures, with rank at capture assigned three ordinal categories (highest to lowest): commissioned officers, sergeants and corporals, and privates. We divided marital status into two categories: married and unmarried (single, separated, or divorced); and coded race into two categories: white and nonwhite.

Rank at capture and AGCT score data had too many missing observations for the Pacific and European POWs, and race was white only in these two groups. Thus rank at capture, AGCT score, and race were included only in a preliminary regression for the Korean POWs which showed that none of these factors was significant; therefore they were omitted from further analyses. Similarly, weeks of captivity had too many missing observations to be included in any of the regressions. We note, however, that weeks of captivity varied little within a POW group and thus would have explained little of the within-group variance in CES-D scores. Notably high among variable intercorrelations for the combined samples were rank at capture with years of education ($r = .436$) and weight loss with captivity symptom score ($r = .457$).

The final models for all three groups are statistically significant, suggesting that both captivity severity factors and demographic factors are directly predictive of later depressive symptoms. As Table 5 shows, the strongest predictors of subsequent depressive symptoms are the captivity symptom score and the number of years of education; age at capture is a significant predictor in both Pacific and Korean groups, and percent of body weight lost is a significant predictor only for Pacific POWs. As might be expected, subsequent depressive symptoms are positively associated with more captivity symptoms and greater weight loss, and inversely related to years of education, age at capture, and marital status. That is to say, POWs who had more education or were married at entry into active duty, or were older at capture, had less subsequent depression.

A regression equation based on the combined Pacific and Korean samples is presented in the last column of Table 5, including a dummy variable for POW status (in effect, Pacific POW status = 1 and Korean POW status = 2). The combined regression shows that both captivity factors and all demographic factors but one, marital status, are significant predictors of subsequent depressive symptoms. The strongest captivity-related predictive factor is captivity symptom score, and the strongest

demographic predictive factors are number of years of education and age at capture, each with roughly equal importance. It is interesting that the dummy variable for POW status has a small and insignificant predictive weight. All other things being equal, predicted Pacific and Korean POWs' depressive symptoms are essentially the same; the captivity and demographic factors shown here account statistically for the differences in subsequent depressive symptoms.

The European group was not combined with the others for several reasons. Because European POWs' captivity treatment was less harsh than that of Pacific or Korean POWs, it may be related differently to subsequent depressive symptoms. Also, because all three nonsignificant terms in the European group regression had opposite signs from those in the other groups, the regression estimates for the European group may be unstable, perhaps in part because this group is the smallest of the three.

Although weight loss is viewed as a strong indicator of harsh treatment (Beebe, 1975) and as a robust predictor of psychiatric sequelae (Speed et al., 1989), it is a significant predictive factor only for the Pacific group. In the European group it is possible that the lack of variability in weight loss accounted for its lack of statistical significance, but in the Korean group this explanation is not applicable. Overall, the captivity symptom score appears to be the better predictor of depressive symptoms.

Discussion

The data in this report differ from those in other studies in two important ways. First, they are drawn from the largest and most representative longitudinal samples of American POWs available. The size of the samples allows the kind of multivariate analyses presented here, and their representativeness ensures that generalizations to the population of all POWs will be sound. The second feature of the data, the inclusion of independent, nationwide samples from three different war theaters, allows separate group analyses and intergroup comparisons and contrasts.

Validity of the Data

The results from the MMPI Lie and Deny scales reflect no tendency to deny symptoms in these samples, but the elevated Hysteria and Admit scales raise the possibility of over-reporting of current symptoms. Keeping in mind that the Admit items are a subset of the Hysteria items, it is logical that Little and Fisher (1958) noted their high intercorrelation and recommend viewing them as interchangeable. In the present sample their correlation was .77. Also, systematic increases in Hysteria scores over time have been reported in normal samples (Leon et al. 1979). These increases

point to the presence of physical complaints and bodily concerns that might be quite realistic among older men, lowered energy levels, and depressive symptoms. Hysteria scores frequently are elevated in valid POW MMPI profiles (Klonoff et al., 1976; Goldstein et al., 1987). Although item-level analyses are required to resolve this question, we believe the elevated Hysteria and Admit scores reflect normal somatic symptoms and concerns plus depressive symptoms, not a response bias of symptom over-reporting.

Because internal consistency is an important component of validity, we again note that the high rates of depressive symptoms were associated with treatment in captivity, and the predicted effects of the majority of the buffering demographic variables were in the expected directions. When similar factors operate in similar ways in differing groups, we have evidence for the validity of results. In addition, unpublished comparisons with a control group of non-POW Korean combat veterans showed that they have significantly lower rates of depressive symptoms than Korean POWs. Finally, we note that Beebe's earlier regression analysis found a statistically significant relation between captivity factors and total score on the Cornell Medical Index (Beebe, 1975), producing results similar to the regression results presented here.

External consistency with other studies provides additional evidence of validity. Most important is the consistency of our findings with independent evidence from the studies of World War II Pacific theater Australian POWs (Tennant et al., 1986a,b) mentioned earlier. These independent findings not only parallel the results in this report but, significantly, are based on data collected using a different psychological instrument, the Zung depression scale (1965). Because the Australian studies measured different variables by different means, their significant regression analyses variables could not be duplicated by those found in this study. Nevertheless, there are clear parallels between the two sets of significant variables (education in both models and the related measure of socioeconomic status in the Australian model) and more tenuous parallels (nervous illness during World War II in the Australian model and captivity symptoms in the American). In all, the kinds of factors associated with the depressive symptoms found among American POWs some 40 years after capture are quite similar to those found among Australian POWs.

Symptoms and Diagnoses Contributing to the CES-D Scores

As mentioned earlier, there are several possible interpretations of elevated CES-D scores, any one of which may hold for a particular individual. Elevated CES-D scores in non-clinical samples may be part of a larger constellation of problems, particularly those associated with

medical illnesses (Murrell, Himmelfarb, and Wright, 1983) or lack of social support or economic resources (O'Harah, Kohout, and Wallace, 1985). Higher scores also may reflect "demoralization" (Roberts et al., 1989). CES-D symptoms may appear not only as a manifestation of depressive illness as such, (i.e., dysthymia or major depression), but as a manifestation of another psychiatric disorder. Two in particular are known to occur with elevated frequencies among POWs: post-traumatic stress disorder (PTSD) and generalized anxiety disorder (Kluznik et al., 1986). Depressive symptoms are an associated feature of PTSD, and major depression actually shares three diagnostic criteria with PTSD—loss of interest in activities, sleep disturbance, and impaired concentration. The ongoing study of these cohorts includes measurement of both PTSD and depression by questionnaire and by direct examination. This should help obtain a clearer understanding of POWs' adjustment.

CONCLUSIONS

In comparison with CES-D general population studies, the depressive symptom rates in this study are high. These groups of former POWs differ significantly from the general population and, in fact, they most resemble a clinical population of recovering depressives.

The statistical evidence from the regression analyses supports two conclusions: (1) the treatment of POWs during military captivity, at least as measured by self-reported medical symptoms (in all three groups) and weight loss (in Pacific POWs), is statistically linked with subsequent depressive symptoms; and (2) differences in depressive symptoms can be attributed to differences in these captivity-related factors, even when moderating factors such as age and education are considered. The events of military captivity suffered decades ago are predictive of current, chronic post-traumatic depressive symptomatology.

REFERENCES

Beebe GW (1975) Follow-up studies of World War II and Korean War prisoners, II: Morbidity, disability, and maladjustments . Am J Epidemiol 101:400–422.

Boyd JH, Weissman MM, Thompson WD, et al (1982) Screening for depression in a community sample. Arch Gen Psychiatry 39:1195–1200.

Breslau N (1985) Depressive symptoms, major depression, and generalized anxiety: A comparison of self-reports of CES-D and results from diagnostic interviews. Psychiatry Res 15:219–229.

Cohen BM, Cooper MZ (1954) A follow-up study of World War II prisoners of war. Veterans Administration Medical Monograph. Washington, DC: US Government Printing Office.

Comstock GW, Helsing KJ (1976) Symptoms of depression in two communities. Psychol Med 6:551–563.

Dent OF, Tennant CC, Goulston KJ (1987) Precursors of depression in World War II veterans forty years after the war. J Nerv Ment Dis 175:486–490.

Eaton WM, Kessler LG (1981) Rates of symptoms of depression in a national sample. Am J Epidemiol 114:528–538.

Engdahl BE, Eberly RE (1990) The effects of maltreatment. In P Suedfeld (Ed), Psychology and Torture. Washington, DC: Hemisphere Press.

Frerichs RR, Aneshensel CS, Clark VA (1981) Prevalence of depression in Los Angeles county. Am J Epidemiol 113:691–699.

Golding JM, Aneshensel CS (1989) Factor structure of the Center for Epidemiologic Studies Depression Scale among Mexican-Americans and non-Hispanic whites. Psychol Assess 1:163–168.

Goldstein G, van Kammen W, Shelly C, et al (1987) Survivors of imprisonment in the Pacific theater during World War II. Am J Psychiatry 144:1210–1213.

Hathaway SR, McKinley JC (1951) The Minnesota Multiphasic Personality Inventory Manual-Revised. New York: The Psychological Corporation.

Keehn RJ (1980) Follow-up studies of World War II and Korean Conflict prisoners: III. Mortality to 1 January 1976. Am J Epidemiol 111:194–211.

Klonoff H, Clark G, Horgan J, et al (1976) The MMPI profile of prisoners of war. J Clin Psychol 32:623–627.

Kluznik JC, Speed N, Van Valkenburg C, et al (1986) Forty-year follow-up of United States prisoners of war. Am J Psychiatry 143:1443–1446.

Leon GR, Gillum B, Gillum R, Gouze M (1979) Personality stability and change over a 30-year period-Middle to old age. J Consult Clin Psychol 47:517–524.

Little KB, Fisher J (1958) Two new experimental scales of the MMPI. J Consult psychol 22:305–306.

Murrell SA, Himmelfarb S, Wright K (1983) Prevalence of depression and its correlates in older adults. Am J Epidemiol 117:173–185.

Myers JK, Weissman MM (1980) Use of a self-report symptom scale to detect the depressive syndrome. Am J Psychiatry 197: 1081–1084.

National Center for Health Statistics (1980) Basic data on depressive symptomatology. DHEW Pub. No. 80-1666. Hyattsville, MD.

Nefzger MD (1970) Follow-up studies of World War II and Korean War Prisoners: I. Study plan and mortality findings. Am J Epidemiol 91:123–138.

O'Hara MW, Kohout FJ, Wallace RB (1985) Depression among the rural elderly: A study of prevalence and correlates. J Nerv Ment Dis 173:582–589.

Page WF (1988) A report of the longitudinal follow-up of former prisoners of war of World War II and the Korean conflict: data on depressive symptoms from the 1984–1985 questionnaire. Final report to the Veterans Administration under contract V101(93)P-1088. Washington, DC.

Radloff LS (1977) The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1:385–401.

Roberts RE, Vernon SW, Rhoades HM (1989) Effects of language and ethnic status on reliability and validity of the Center for Epidemiologic Studies-Depression Scale with psychiatric patients. J Nerv Ment Dis 177:581–592.

Rundell JR, Ursano RJ, Holloway HC, Silberman EK (1989) Psychiatric responses to trauma. Hosp Comm Psychiat 40:68–74.

Sledge WH, Boydstun JA, Rabe AJ (1980) Self-concept changes related to war captivity. Arch Gen Psychiatry 37:430–443.

Speed N, Engdahl BE, Schwartz J, Eberly RE (1989) Post-traumatic stress disorder as a consequence of the prisoner of war experience. J Nerv Ment Dis 177:147–153.

Tennant CC, Goulston KJ, Dent OF (1986a) The psychological effect of being a prisoner of war: Forty years after release. Am J Psychiatry 143:618–621.

Tennant CC, Goulston KJ, Dent OF (1986b) Clinical psychiatric illness in prisoners of war of the Japanese: Forty years after release. Psychol Med 16:833–839.

Ursano RJ (1981) The Vietnam era prisoner of war: Precaptivity personality and the development of psychiatric illness. Am J Psychiatry 138:315–318.

Weissman MM, Sholomskas D, Pottenger M, et al (1977) Assessing depressive symptoms in five psychiatric populations: A validation study . Am J Epidemiol 106:203–214.

Zung WWK (1965) A self-rating depression scale. Arch Gen Psychiatry 12:63–70.

ACKNOWLEDGMENTS

This paper is based in part on the final report to the Veterans Administration under Contract V101(93)P-1088. Special acknowledgment for help in that earlier report is made to Mr. Robert J. Keehn and Dr. Gilbert W. Beebe; thanks also to Dr. Richard D. Remington, Dr. Gerald L. Klerman and Dr. Raina E. Eberly for their review of it. The staff of the Medical Follow-up Agency also deserve credit for the careful and tireless work in collecting and organizing the data upon which this report is based. Above all, the cooperation of the former prisoners of war themselves made this research possible.

TABLE I CENTER FOR EPIDEMIOLOGIC STUDIES-DEPRESSION SCALE ITEMS

During the past week,

1. You were bothered by things that don't usually bother you.

2. You did not feel like eating; your appetite was poor.

3.You felt you could not shake off the blues even with help from your family or friends.

4. You felt that you were just as good as other people.

5. You had trouble keeping your mind on what you were doing.

6. You felt depressed.

7. You felt that everything you did was an effort.

8. You felt hopeful about the future.

9. You thought your life had been a failure.

10. You felt fearful.

11. Your sleep was restless.

12. You were happy.

13. You talked less than usual.

14. You felt lonely.

15. People were unfriendly.

16. You enjoyed life.

17. You had crying spells.

18. You felt sad.

19. You felt that people disliked you.

20. You could not get "going."

Weighting of item responses:

0 = Rarely or none of the time (less than 1 day).

1 = Some or a little of the time (1–2 days).

2 = Occasionally or a moderate amount of the time (3–4 days).

3 = Most or all of the time (5–7 days).

TABLE 2 CAPTIVITY MEDICAL PROBLEMS-SYMPTOMS AND SYMPTOM INDEX (PERCENT WHO EXPERIENCED THE PROBLEM), BY POW GROUP

	POW Group		
Captivity Problem and Symptoms	**Pacific**	**Europe**	**Korea**
Malaria	73.2	2.0	26.6
Diarrhea lasting I week or more	79.6	38.2	76.1
Blood or mucous in stool	89.7	50.0	88.8
Physician-diagnosed dysentery	61.3	14.7	28.0
Swelling of lower limbs	84.7	23.1	56.3
Swelling in feet or ankles	60.3	30.2	57.2
Persistent night vision problems	28.5	6.5	45.5
Continuous pain or burning in eyes	31.7	10.5	19.9
Blurred vision	47.8	14.4	36.3
Eye pain in bright light	41.7	13.4	31.6
Loss of vision, one or both eyes	18.0	1.0	12.7
Red, raw scrotum	44.2	5.0	12.2
Deep cracks, corner of mouth	51.4	10.0	32.3
Persistent severe, sunburn	14.9	1.5	1.7
Red, swollen, bleeding gums	40.9	15.9	35.6
Tongue pain inhibiting eating	47.0	6.5	35.1
Painful feet	72.4	37.8	60.7
Pain in leg muscles when squeezed	46.1	17.4	33.3
Cramps in feet & legs	59.9	31.8	51.0
Breasts enlarged	14.1	0.5	5.0
Symptom Index mean	9.45	2.55	6.76
Distribution of weight loss			
> 45%	27.9%	3.1%	22.8%
36–45%	37.4	13.4	32.5
26–35%	23.8	28.4	24.4
16–25%	9.6	36.1	11.9
`15%	1.4	19.1	8.4
Mean percent weight loss	38.8%	24.3%	35.1%

Numbers of subjects = 371 (Pacific); 209 (Europe), & 409 (Korea) except for weight loss data where N = 366 (Pacific), 194 (Europe), & 394 (Korea).

TABLE 3 PRISONER OF WAR GROUP DEMOGRAPHICS

Demographic Category	Pacific	Europe	Korea
Rank/Component			
Regular Army or Officer	74.3	24.8	68.5
Draft or Natn'l Guard	25.0	75.2	31.5
Marital Status *			
Single	92.0	79.7	85.0
All other	8.0	20.3	15.0
Years of Education *			
Less than high school	46.2	43.2	77.4
High school graduate	33.8	37.3	17.5
College	20.0	19.6	5.1
Race			
White	100.0	100.0	89.3
Black	-	-	6.8
Other	-	-	3.9
Year of Birth			
1919 or earlier	64.1	42.8	5.8
1920–1929	35.9	57.2	47.4
1930+	-	-	46.8
Type of Service			
Infantry	10.9	42.1	71.9
Artillery	8.6	5.5	17.1
Other ground	29.6	35.6	-
Air Corps/Army Air Force	32.6	42.8	-
Other	18.3	9.2	11.0
Rank at Separation			
Officer	11.1	22.1	6.3
Warrant officer/Sgt	34.2	14.0	14.5
T4 or corporal	52.3	37.6	52.3
Private/PFC	1.5	26.2	23.4

* At enlistment on active duty.
N = 476 (Pacific), 271 (Europe), & 572 (Korea); numbers include nonrespondents. Missing or unknown categories not displayed explicitly.

TABLE 4 PERCENTAGE OF CES-D+ SCORES 16 OR ABOVE AND CHI-SQUARE TESTS++, BY STUDY GROUP AND DEMOGRAPHIC CHARACTERISTICS

Demographic Characteristics	Pacific	Europe	Korea
Race	-	-	NS
White	50.3	37.1	54.6
Black or other	-	-	51.8
Rank/Component	***	NS	**
Draft or Natn'l Gd	42.3	37.2	51.9
Regular Army or Officer	52.0	46.3	58.7
Marital Status +++	**	NS	**
Single, Div'd, Sep	52.1	36.3	56.4
Married	25.9	38.8	37.3
Years Education	***	**	***
Less than HS grad	62.2	52.3	58.1
HS grad	44.5	34.3	42.3
College	33.7	19.6	31.0
Year of birth	NS	NS	*
1910			29.4
1910–1919	48.7	35.9	37.9
1920–1929	54.7	37.2	50.4
1930+	-	-	59.2
Type of Service	*	NS	NS
Infantry	55.1	43.4	55.6
Artillery/Armor	64.1	42.9	51.1
Other	48.8	39.1	47.6
Rank at Separation	***	***	***
Officer	21.2	27.6	25.7
Warrant Officer	46.5	36.1	46.9
Sgt/Corporal	59.0	28.6	61.4
Private	-	58.5	52.3

+ Center for Epidemiologic Studies-Depression scale.
++ Chi-square tests are within demographic variable within study group.
+++ At entry on active duty.
- Too few cases.
* $p < .05$;
** $p < .01$;
*** $p < .001$.

TABLE 5 MULTIPLE REGRESSION PREDICTION+ OF CES-D SCORES++, BY POW GROUP, USING CAPTIVITY SEVERITY FACTORS AND DEMOGRAPHIC FACTORS

Factor	Pacific	Europe	Korea	Pacific + Korea
Captivity severity				
Symptom Index	3.18***	3.49***	3.35***	3.39***
Weight loss	1.83**	-0.10	0.68	1.22*
Korean captivity	#	#	#	0.20
Demographic factor				
Years of education	-1.91**	-3.28***	-1.86**	-2.05***
Marital status+++	-0.64	0.08	-0.67	-0.57
Age at capture	-3.26***	0.31	-1.57*	-2.25***
R	.460	.470	.385	.416
R^2	.212	.221	.148	.173
Number of cases	364	193	394	758

+ Center for Epidemiologic Studies-Depression scale.
++ Standardized regression coefficients (beta weights) are shown.
+++ At time of entry into active duty; 1 = unmarried, 2 = married.
* $p < .05$;
** $p < .01$;
*** $p < .001$.
# Applicable only to combined Pacific + Korea regression.

Dioxins and Dibenzofurans in Adipose Tissue of U.S. Vietnam Veterans and Controls

Han K. Kang, Kevin K. Watanabe, Joseph Breen, Janet Remmers, Margaret G. Conomos, John Stanley, and Michele Flicker*

ABSTRACT

The primary reason for concern about the adverse effects of exposure to Agent Orange is attributable to its toxic contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), or dioxin. This study investigated whether 36 Vietnam veterans had significantly higher levels of dioxin in adipose tissue than a similar group of 79 non-Vietnam veterans or 80 civilians. The adipose tissue specimens for the study were selected from the 8,000 archived tissues that had been collected from the non-institutionalized general population by the U.S. Environmental Protection Agency for the National Human Adipose Tissue Survey. The geometric mean (± standard deviation) dioxin levels in adipose tissue for Vietnam veterans, non-Vietnam veterans and civilian controls were 11.7 (± 1.7), 10.9 (± 1.7), and 12.4 (± 1.9) parts per trillion on a lipid weight basis, respectively. The mean levels for these groups were not significantly different from each other with or without adjustment for age of individuals,

* Han K. Kang, Dr.P.H., and Kevin Watanabe, M.S., are with the Department of Veterans Affairs in Washington, DC; Joseph Breen, Ph.D., Janet Remmers, M.S., and Margaret G. Conomos, M.P.H., are with the U.S. Environmental Protection Agency in Washington, DC; John Stanley, Ph.D., is with the Midwest Research Institute in Kansas City, Missouri; and Michele Flicker, Ph.D., M.D., is with the VA Medical Center in Leavenworth, Kansas. Correspondence to Dr. Han K. Kang, VA Office of Environmental Epidemiology, 1825 K Street, NW, Suite 322, Washington, DC 20006. This paper is copyrighted by the *American Journal of Public Health* and appeared in the January 1991 issue.

body mass index, and specimen collection year. In addition, none of the surrogate measures of Agent Orange exposure such as military branch, service within specific geographic region, military occupation, and troop location in relation to recorded Agent Orange spraying was associated with the dioxin levels in adipose tissue of Vietnam veterans. Our results suggest that heavy exposure to Agent Orange or dioxin for most U.S. troops was unlikely.

INTRODUCTION

From 1965 to 1970, the U.S. Air Force sprayed more than 40 million liters of Agent Orange in South Vietnam.[1] Approximately 2 million American soldiers served in Vietnam during this period. Agent Orange was the name used for a phenoxy herbicide consisting of a mixture of 2,4-dichloro-phenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The 2,4,5-T contained 1–50 parts per million of the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), also known as dioxin. Dioxin is extremely toxic in laboratory animals, promotes liver tumors in rats, and is teratogenic in mice.[1,2] The two parent herbicides, 2,4-D and 2,4,5-T are very short-lived in the human body and do not persist in the environment.[3] Because of these characteristics and their relatively low toxicity in humans, attention has been focused on the highly persistent and toxic chemical, dioxin.

Many Vietnam veterans believe that they were heavily exposed to Agent Orange and that the exposure is responsible for health problems such as skin rashes, rare types of cancer, and birth defects of their children. Since 1979, two hundred thousand Vietnam veterans have come to Department of Veterans Affairs (VA) hospitals for an Agent Orange Registry medical examination because of concerns about exposure to Agent Orange.

Two questions are paramount in dealing with the veterans' concerns. The first is whether dioxin causes birth defects, immune deficiencies, cancers, or other chronic health problems in humans. The second is whether Vietnam veterans, in general, received substantial exposure to dioxin while they served in Vietnam. This study addresses the second question.

Dioxin accumulates preferentially in the body fat of animals and man. The dioxin half-life in humans is estimated at 5 to 11 years. [4,5,6,7] Among the many 2,3,7,8-substituted polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) found in the environment and in samples of human adipose tissue, only 2,3,7,8-TCDD or dioxin was present in Agent Orange.[7] Dioxin levels in adipose tissue could, therefore, serve as a biological marker of exposure to Agent Orange.

In fact, several studies have reported that even after approximately 20 years, dioxin levels were elevated markedly in the adipose tissue or blood serum of Vietnam veterans who handled Agent Orange.[6,7,8] More recently, however, the Centers for Disease Control (CDC) reported that current serum dioxin levels of Army Vietnam combat troops did not differ significantly from those of non-Vietnam veterans and that dioxin levels in Vietnam veterans did not increase with increased exposure levels estimated from military records.[9] This study was criticized on the basis that blood specimens taken almost 20 years after exposure could not represent what happened in Vietnam and that veterans selected for the study were limited to Army enlisted men who served in only one geographic region of Vietnam.[10]

The purpose of our study was twofold: (1) to determine if a group of individuals with military service in Vietnam have significantly higher levels of dioxin in adipose tissue than either a similar group of non-Vietnam veterans or civilian peers, and (2) to determine if dioxin levels in adipose tissue were associated with specific demographic and military service characteristics.

METHODS

Selection of Study Subjects

Our study used adipose tissue specimens that had been collected from the general population by the U.S. Environmental Protection Agency (EPA). The EPA has conducted the National Human Adipose Tissue Survey (NHATS) since 1970 to monitor the human body burden of pesticides and other selected chemicals. Up to 1,000 adipose tissue specimens have been collected annually from pathologists and medical examiners across the country and analyzed by the EPA for the selected chemicals. After analysis, the unused tissue specimens were sent to a central facility to be stored at 0°C to-20°C.

The NHATS utilized a probability sample of the Standard Metropolitan Statistical Areas (SMSA) that is designated to represent a sample of the U.S. population in terms of age, sex, and race.[11] The target population for the NHATS program was all non-institutionalized persons in the conterminous United States. However, due to the invasive nature of collecting adipose tissue samples, the sampling population was limited to individuals who died from external causes (90%) and surgical patients (10%). Within each SMSA, hospitals or medical examiners were identified and asked to contribute tissue specimens according to the design specifications of age (0–14 years, 15–44 years, 45+ years), sex, and race (white, non-white). Since the vast majority of Vietnam veterans were men

born between 1936 and 1954, this study was restricted to specimens from men born in that period.

An Inventory File was created for the 8,000 specimens that were recorded to have an adequate amount of tissue. It was found that 528 of 8,000 specimens were from males born between 1936 and 1954. The hospitals or medical examiners who originally collected the 528 specimens were recontacted to obtain enough identifying information on the donors to determine their military service status. The collection effort yielded information for 494, or 94%, of the 528 specimens.

The military service status for these 494 men, including any Vietnam service, was determined by reviewing records archived at the National Personnel Records Center (NPRC) in St. Louis and military records maintained at other locations. From this effort, 134 men (or 27% of 494) were initially found to have served in the military, 40 of whom served in Vietnam. According to the 1980 Census, one would expect about 34% of men in this age group to be veterans. All 40 Vietnam veterans were selected for the study. From the 94 remaining veterans, 80 were selected randomly for the non-Vietnam comparison group. Two civilians were closely matched to each Vietnam veteran by birth year (±2 years) and sample collection year (±2 years). Age and sample collection year were considered important matching variables because of probable accumulation of dioxin in the body with each year of exposure and the possibility of degradation of fat or dioxin while in storage. All adipose tissue specimens were analyzed during 1987. Demographic data were taken from the NHATS file and the official death certificates. Body mass index (BMI) was calculated from weight and height as follows: BMI = weight in kg/height in m^2.

Determination of Opportunity for Agent Orange Exposure

A precise estimate of the exposure of each Vietnam veteran to Agent Orange is not considered feasible based on either military records or self-reported data. In this study the probable opportunity for exposure was determined from the following: branch of service, military occupational specialty code (MOSC), and location of the individual's unit in Vietnam in relation to recorded Agent Orange spray. Ground troops in Vietnam might have had a higher probability of contact with Agent Orange than other Vietnam veterans due to the nature of their military operations. Ground troops engaged in combat were assumed more likely to be in herbicide-sprayed areas. As another surrogate for exposure, a veteran's military unit was assigned to one of the four broad military regions in Vietnam. According to the records of the U.S. Air Force Ranch Hand Operation, 20 million liters of Agent Orange were sprayed in Military

Region III from 1965 to 1970. During the same period, Military Regions II, I, and IV received 9.5, 8.3, and 4.5 million liters, respectively. Finally, troop locations (company size units) were determined on a 100-meter grid map of Vietnam at intervals of 90 days or less. Computer matching of troop location with respect to time and distance from recorded herbicide spray tracts was carried out using the HERBS tape and services HERB tape databases. The HERBS tape contained information on most of the herbicide missions flown by fixed-wing aircraft from 1965 to 1971, and on crop destruction missions flown by helicopter between 1968 and 1971. The tape contained information on the type of herbicide, gallons, dates, and where spray runs started and ended. Services HERBS Tape prepared by U.S. Army and Joint Services Environmental Support Group identified and documented an additional 6 million liters of herbicide sprayed mainly by Army personnel around the perimeter of base camps, fire bases, airbases and other fixed military installations. The opportunity for Agent Orange exposure was determined in two ways: an individual's company was ever located either within 2 kilometers (km) of a recorded Agent Orange spray tract within 3 days of application or within 8 km of a spray tract within 90 days application.

Laboratory Analysis

Specimens from the three groups were assigned randomly to one of 20 batches. Each batch typically consisted of 10 study specimens and 4 quality control (QC) samples. The QC samples provided data on method accuracy and precision. In addition, the external quality control audit samples were prepared by another laboratory and incorporated as blind samples into the various batches. Study specimens and QC samples were coded with a unique laboratory number and submitted to the analysts as blind samples. Following sample cleanup and preparation, instrumental analyses were achieved using a high-resolution gas chromatograph coupled to a high-resolution double-focusing mass spectrometer. Overall method accuracy and precision for 2,3,7,8-TCDD analyses of spiked lipid samples were 113% recovery and 8.8% coefficient of variation.

The analytical protocol provided for the detection and quantitative determination of 17 congeners of 2,3,7,8-substituted polychlorinated dibenzo-p-dioxins (PCDD) and dibenzofurans (PCDF). The minimum measurable concentration ranged from 1 picogram per gram (pg/g) for 2,3,7,8-TCDD and 2,3,7,8-TCDF, to 5 pg/g for OCDD and OCDF based on a 10-gram aliquot of human adipose tissue. This protocol was evaluated for method performance prior to being used in this study.[12]

Statistical Considerations

Multiple comparisons and testing for differences were done by using the F test in one way analysis of variance (ANOVA) and analysis of covariance with adjustments for demographic variables such as age, collection year, and body mass index.[13] A paired t-test was conducted to compare the means of Vietnam veterans with their matched civilian controls.14 In all analyses, the dioxin values were transformed to a natural logarithmic scale because the dioxin values were found to have approximately log-normal distributions in this study and another study.[15]

A stepwise linear regression model was also used to determine whether dioxin levels were associated with demographic and military service characteristics.[16] Factors considered a priori as covariates were age, adipose tissue sample collection year, race, and body mass index. A regression model specific to Vietnam veterans included such covariates as military occupation, calendar year of tour in Vietnam, geographic region in Vietnam, time of and distance from recorded Agent Orange spray, and adipose tissue sample collection year. All statistical tests were conducted at the .05 level of significance.

RESULTS

Table 1 presents the arithmetic and geometric means, and various percentile values for dioxin for the three study groups. One-way analysis of variance did not demonstrate a statistically significant difference in the mean dioxin levels among groups ($p = 0.35$). Analysis of covariance, testing the effect of Vietnam service on dioxin levels after adjusting for age, sample collection year, or body mass index, did not indicate a statistically significant association between service in Vietnam and dioxin levels. A paired t-test between Vietnam veterans and their matched civilian pairs did not show a significant difference in mean dioxin levels ($p = 0.52$; 95% confidence interval for the difference between two means =-1.32, 1.16).

For Vietnam veterans, dioxin levels were also evaluated by four factors related to the likelihood of Agent Orange exposure (Table 2). None of the surrogate measures of Agent Orange exposure was associated with the dioxin levels in adipose tissue of Vietnam veterans. Furthermore, the mean dioxin level of 7 Vietnam veterans whose specimens were taken within 4 years (less than one dioxin half-life estimated for humans) since their last service in Vietnam were compared with 19 non-Vietnam veterans whose tissue specimens were collected on or before 1974 (the last sample collection year for the 7 Vietnam veterans), and also with their matched civilian pairs. The geometric mean dioxin levels (± standard deviation) for

the Vietnam group (n = 7), non-Vietnam veteran group (n = 19), and civilian controls (n = 14) were at the levels of 16.6 (± 1.6), 15.5 (± 1.5), and 18.4 (± 1.6) parts per trillion (ppt) respectively. The difference among the means was not statistically significant (p = 0.56). The 95% confidence limits for a mean dioxin difference between Vietnam veterans and civilian controls were-1.59 and 1.31. Stepwise linear regression analysis for 36 Vietnam veterans indicated that Vietnam service characteristics could account for only 14% of the variation in dioxin levels (p = 0.3), whereas collection year alone could account for 21% of variance (p = 0.005). Five other 2,3,7,8-substituted dioxins and 10 other dibenzofurans were measured, and their mean levels were calculated from specimens with levels above the detection limit (Table 3). There were no group differences in the mean level of any of the dioxin congeners. The differences in TCDD levels in the three groups were also evaluated while adjusting for levels of other 2,3,7,8-substituted dioxin congeners not found in Agent Orange by a stepwise multiple regression technique. TCDD levels were taken as the dependent variable and Vietnam service status and other PCDD congener levels as independent variables. There was a significant association between the TCDD levels and the levels of PCDD congeners ($R^2 = 0.54$, p = 0.0001), but not with the Vietnam service status ($R^2 = 0.0025$, p = 0.3).

The levels of dioxins increased with an increase in the number of chlorine except for 1,2,3,7,8,9-HxCDD. Levels of dibenzofurans were always lower than their dioxin counterparts. In each study group, the levels of dioxin tended to be inversely related to the specimen collection year, i.e., the earlier the collection year, the higher the dioxin levels (p = 0.0001, n = 195).

DISCUSSION

In this study, military service in Vietnam was not associated with elevated dioxin levels in adipose tissue with or without adjustment for demographic variables. In addition, no Vietnam service characteristic measured singly or in combination was a good predictor of dioxin levels in adipose tissue. There were no consistent trends in the dioxin levels according to the surrogate measures of Agent Orange exposure. The mean levels of dioxin did rise slightly with combat MOSC and having been within 3 days/2 km of sprayed areas. But the other two surrogates, branch of service and service location in Vietnam, were not associated with the dioxin levels. The small magnitude of the mean difference and the variation within each group suggest that the small difference in mean values could have been easily due to the sampling and measurement variation.

Analyses of adipose tissue from the general populations of industrialized countries have indicated the presence of a number of 2,3,7,8-substituted dioxins and dibenzofurans at ppt level.[17,18,19,20,21] These dioxins and dibenzofurans could have originated from a number of sources: incineration of municipal waste and wood products; manufacturing, use and disposal of pesticides, herbicides, and wood preservatives; and PCBs from electric transformers and capacitors. Because 2,3,7,8-TCDD was the only congener found in Agent Orange as a contaminant,[1,7] knowing the levels of other dioxins and dibenzofurans would help determine whether TCDD levels in adipose tissue of Vietnam veterans were the result of Agent Orange exposure in Vietnam or exposure to other sources. For example, if most dioxins and dibenzofurans as well as 2,3,7,8-TCDD levels were found to be elevated among Vietnam veterans, contribution from sources other than Agent Orange should not be ruled out. However, if only the 2,3,7,8-TCDD level remained elevated and other PCDD levels were comparable to the comparison groups, Agent Orange would be considered as the contributor. There were no group differences in the mean levels of any PCDD congeners. The lack of group differences suggested that sources other than Agent Orange may have contributed to the Vietnam veterans' levels of 2,3,7,8-TCDD. In a study by Kahn et al.,7 of 10 Vietnam veterans with heavy potential for exposure to Agent Orange (e.g. Ranch Hand personnel, Army Chemical Corps specialists), the levels of 12 other 2,3,7,8-substituted dioxins and dibenzofurans were similar to the levels found among 10 Vietnam veteran controls and 7 non-Vietnam veteran controls. Only 2,3,7,8-TCDD levels were elevated approximately 10-fold among Vietnam veterans with a heavy exposure potential.

This study may have failed to detect a small difference in mean dioxin levels among groups because of the relatively small sample size. The study had an adequate statistical power (90%) to detect a mean difference of 5 ppt or more between groups. Elimination of dioxin from the body after Vietnam service is an unlikely explanation because dioxin levels of seven Vietnam veterans whose specimens were taken within four years from their return from Vietnam (which was considerably less than the estimated half-life of dioxin in humans) were not significantly different from their appropriate comparison groups.

Although the NHATS sampling scheme was designed to collect a representative sample of the SMSA in terms of age, sex, and race, subjects selected for the study may not have represented their respective groups for several reasons. First, over 90% of the NHATS sample were collected from deceased persons whose deaths in most instances were due to traumatic injury. Second, tissue samples for this study were selected from the archived NHATS specimens rather than original NHATS samples. Third, 6% of the men who were eligible for the study had to be excluded

because of missing personal identifiers. Despite these problems, demographic and military characteristics of the Vietnam veterans selected for the study did not differ substantially from the overall Vietnam veteran population. They were predominantly white (75%), draft eligible during the Vietnam war (age 18 to 25), enlisted men (89%), who served in the Army and Marine Corps (72%) with military occupational specialties related to combat support roles (67%). None of the Vietnam veterans in the study had a record of routinely handling or spraying Agent Orange.

The mean background levels of dioxin reported here were generally higher than the values reported by others.[6789] It is unlikely that this difference is due solely to an interlaboratory variation. Our laboratory (the Midwest Research Institute) participated in an interlaboratory validation study for dioxin measurement and produced a satisfactory result. Furthermore, external quality control audit samples prepared by the Battelle Columbus Division were incorporated as blind samples into the various batches and analyzed for dioxin and dibenzofuran congeners. The analytical results were found to be acceptable. We believe that the difference in sampling years between this study and several other studies could account for the higher values reported in our study. We found that the dioxin levels in adipose tissue were significantly associated with the sample collection year ($p = 0.0001$); the earlier the collection year, the higher the levels of dioxin irrespective of veteran status. In fact, this general trend was observed for other dioxins. The median sample collection year in our study was 1978, whereas in other studies the specimens were mostly collected in the mid-1980s or later. The observed dioxin decline from 1971 to 1982 is consistent with the general trend for chlorinated hydrocarbon chemical compounds in human adipose tissue. The U.S. Environmental Protection Agency's National Human Adipose Tissue Survey Program indicates that the median levels of BHC, HCB, and PCB had been steadily decreasing over time between 1970 and 1983.[7] In Sweden, the levels of dioxins and dibenzofurans in human milk decreased significantly from 1972 to 1985.[22] The Swedish authors attributed the decline to the reduction in use of certain organochlorine compounds such as PCBs, PCP and 2,4,5-T. A study involving a large sample of specimens representative of the U.S. population will be needed to confirm this observation.

We concluded that the results of our study did not support the hypothesis that most U.S. troops were heavily exposed to dioxin in Vietnam. Furthermore, none of the surrogate measures of Agent Orange exposure based on military service characteristics was associated with the dioxin levels in adipose tissue of Vietnam veterans. These results are consistent with those of CDC[9] and not inconsistent with Kahn et al.[7] and Schecter et al.[8]

REFERENCES

1. Young AL, Kang HK, Shepard BS: Chlorinated dioxins as herbicide contaminants. Environ SCi Technol 1983; 17: 530A–540A.
2. Neal RA, Olson JR, Gasiewicz TA, et al: The toxicokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian system Drug metabolism Review 1982; 13: 355–385.
3. World Health Organization: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. V. 15. Lyon, France, 1977.
4. Poiger H, Schlatter C: Pharmacokinetics of 2,3,7,8-TCDD in man. Chemosphere 1986; 15: 1489–1494.
5. Pirkle JL, Wolff WH, Patterson DG Jr, et al: Estimates of the half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Vietnam veterans of Operation Ranch Hand. J Toxicol Environ Health 1989; 27: 165–171.
6. Centers for Disease Control: Serum 2,3,7,8-tetra-chlorodibenzo-p-dioxin levels in Air Force Health study participants-Preliminary report. JAMA 1988; 259: 3533–3535
7. Kahn PC, Gochfeld M, Nygren M, et al: Dioxins and dibenzofurans in blood and adipose tissue of Agent Orange exposed Vietnam veterans and matched controls. JAMA 1988; 259: 1661–1667.
8. Schecter A, Constable JD, Arghestani S, et al: Elevated levels of 2,3,7,8-tetrachlorodibenzodioxin in adipose tissue of certain U.S. veterans of the Vietnam war. Chemosphere 1987; 16: 1997–2002.
9. Centers for Disease Control: Serum 2,3,7,8-tetra-chlorodibenzo-p-dioxin levels in US Army Vietnam era veterans . JAMA 1988; 260: 1249–1254.
10. Taubes G: Unmasking Agent Orange. Discover April 1988; 9: 42–48.
11. US Environmental Protection Agency: Baseline Estimates and time trends for betabenzene hexachloride, hexachlorobenzene, and polychlorinated biphenyls in human adipose tissue 1970–1983. EPA No. 560/5-85-025, Office of Toxic Substances, Washington, D.C., September 30, 1985.
12. U.S. Environmental Protection Agency: Analysis for Polychlorinated Dibenzo-p-dioxins (PCDD) and Dibenzofurans (PCDF) in Human Adipose Tissue: Method Evaluation Study. EPA-560/5-86-020, Washington, D.C., October 1986.
13. SAS Institute Inc: The GLM Procedure. In: SAS User's Guide: Statistics, Version 5 Edition. Cary, N.C., SAS Institute, Inc., 1985.
14. SAS Institute Inc: The MEANS Procedure. In: SAS User's Guide: Basics, Version 5 Edition. Cary, N.C., SAS Institute, Inc. 1985.
15. Patterson DG, Hoffman RE, Needham LL, et al: 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in adipose tissue of exposed and control persons in Missouri. JAMA 1986; 256: 2683–2686.
16. Dixon WJ, Jennrick R: Stepwise regression. In: BMDP Statistical Software. University of California Press, 1983.
17. Patterson DG, Holler JS, Smith SJ, et al: Human adipose data for 2,3,7,8-tetrachlorodibenzo-p-dioxin in certain U.S. samples. Chemosphere 1986; 15: 2055–2060.
18. Graham M, Hileman FD, Orth RG, et al: Chlorocarbons in adipose tissue from a Missouri population. Chemosphere 1986; 15: 1595–1600.
19. Ryan JJ, Lizotte R, Lan BP: Chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans in Canadian human adipose tissue. Chemosphere 1985; 14: 697–706.
20. Rappe C, Nygren M, Lindstrom G, et al: Dioxins and dibenzofurans in biological samples of European origin. Chemosphere 1986; 15: 1635–1639.
21. Stanley JS, Boggess KE, Onstot J, et al: PCDDs and PCDFs in human adipose from the EPA FY82 NHATS repository. Chemosphere 1986; 15: 1605–1612.

22. Noren K: Changes in the levels of organochlorine pesticides, polychlorinated biphenyls, dibenzo-p-dioxin and dibenzofurans in human milk from Stockholm, 1972–1985. Chemosphere 1968; 17:39–49.

ACKNOWLEDGMENT

We are grateful to Aaron Blair, Ph.D. (National Cancer Institute), Carl Keller, Ph.D. (formerly, National Institute of Environmental Health Sciences), Donald Patterson, Ph.D. (Centers for Disease Control), Linda Pickle, Ph.D. (Georgetown University), and John Ryan, Ph.D. (Canada) for their review of a study report from which the manuscript was prepared. The guidance provided by Alvin Young, Ph.D. (U.S. Department of Agriculture) and Joseph Carra and Mary Frankenberry (U.S. Environmental Protection Agency) in planning for the study is greatly appreciated.

TABLE 1 DISTRIBUTION OF 2,3,7,8-TCDD LEVELS IN ADIPOSE TISSUE BY MILITARY SERVICE STATUS, IN PG/G OF THE TOTAL EXTRACTABLE LIPID (PPT)

				Percentile				
Status	N	Arithmetic Mean + SD[a]	Geometric Mean	25th	50th (median)	75th	90th	95th
Vietnam Veterans	36[b]	13.4 ± 7.4	11.7	7.8	10.0	17.3	26.8	30.4
Non-Vietnam Veterans	79[c]	12.5 ± 7.2	10.9	7.6	11.4	14.8	19.8	25.3
Civilians	80	15.8 ± 14.5[d]	12.4	7.9	11.8	18.0	30.5	43.4

[a] Standard deviation

[b] Four of the 40 men initially classified as having served in Vietnam were excluded from analysis because two veterans' specimens had less than 20% extractable lipid content, one veteran did not have adequate amount of tissue for analysis, and one veteran served only in Thailand.

[c] One of the 80 men initially classified as having served in the military was excluded because his military service could not be documented unequivocally.

[d] The large standard deviation was attributed to an outlier with a value of 106. The value was verified. The occupational history of this individual is unknown. He was listed as a "laborer" on his death certificate. Analyses conducted without this value resulted in an arithmetic mean of 14.7 (± 10.3) and a geometric mean of 12.2. There was still no statistically significant difference between the groups (p = 0.49).

TABLE 2 GEOMETRIC MEAN 2,3,7,8-TCDD LEVELS IN ADIPOSE TISSUE BY VIETNAM SERVICE CHARACTERISTICS, IN PG/G OF THE TOTAL EXTRACTABLE LIPID (PPT)

Service Characteristics	No. of Vietnam Veterans	2,3,7,8-TCDD	
	Mean	SD[a]	
Branch			
Army	20	11.6	1.7
Marine	6	12.3	1.8
Air Force	1	6.7	—
Navy	9	12.4	1.5
MOSC[b]			
Non-Combat	24	11.1	1.7
Combat	12	13.1	1.6
Military Region[c]			
I Corp	11	12.4	1.6
II Corp	4	6.9	1.3
III Corp	9	11.9	1.9
IV Corp	3	14.3	1.9
Sea Duty	8	13.3	1.4
Time and Distance From[d] Recorded Herbicide Spray			
a. 3 days / 2 KM			
no	31	11.5	1.7
yes	4	14.3	1.6
b. 90 days / 8 KM			
no	16	11.8	1.5
yes	19	11.8	1.8

[a] Standard deviation
[b] Military Occupation Specialty Code (MOSC)
[c] Missing Military Region information for one veteran
[d] Missing information on time and distance from recorded herbicide spray for one veteran due to unknown unit location

TABLE 3 ARITHMETIC MEAN LEVELS OF DIOXINS AND FURANS DETECTED IN ADIPOSE TISSUE BY MILITARY SERVICE STATUS, IN PG/G OF THE TOTAL EXTRACTABLE LIPID (PPT)

			Status
Chemicals	Vietnam Veterans	Non-Vietnam Veterans	Civilians
Dioxins			
2378-TCDD	13.4 (36)*	12.5 (79)	15.8 (80)
12378-PeCDD	20.6 (36)	18.3 (78)	18.3 (80)
123478/123678-HxCDD	170.4 (36)	152.9 (79)	165.1 (80)
123789-HxCDD	19.4 (35)	17.2 (79)	17.9 (79)
1234678-HpCDD	276.2 (36)	244.6 (79)	300.3 (80)
OCDD	1261.8 (36)	1108.9 (79)	1392.9 (80)
Furans			
2378-TCDF	2.9 (25)	2.4 (52)	3.3 (51)
12378-PeCDF	1.7 (8)	1.1 (17)	1.9 (16)
23478-PeCDF	23.1 (35)	22.2 (78)	23.3 (80)
123478-HxCDF	21.5 (36)	19.3 (78)	23.2 (79)
123678-HxCDF	10.7 (34)	9.9 (77)	12.0 (79)
234678-HxCDF	3.8 (26)	3.2 (73)	3.6 (78)
123789-HxCDF	1.5 (3)	0.9 (2)	0.9 (4)
1234678-HpCDF	37.4 (36)	32.9 (79)	39.1 (80)
1234789-HpCDF	2.2 (14)	1.9 (35)	2.2 (41)
OCDF 3.6	(27)	4.5 (54)	3.4 (60)

* The number in parentheses represents the number of cases in that category.

Radiation Risk Studies in Military Populations

S. Jablon*

As an introduction, it will be useful to consider why it is desirable to do studies of radiation risk, for which of the possible purposes military populations are appropriate, and why. It has been well known for many years that ionizing radiation is a cause of subsequent cancer, which may not occur until several decades after exposure. What, then, is the need for studies?

There are two principal reasons for doing more studies of radiation risk in humans. First, although we know about the late effects of exposure to radiation in a general way, our quantitative information is somewhat uncertain; we can specify the cancer risk per unit of radiation dose only with an accompanying uncertainty of at least a factor of two. Second, some persons who have been exposed to radiation and who subsequently develop cancer, in the belief that the radiation was the cause of the cancer, claim compensation from the author of the exposure, whether the federal government, a national laboratory, a commercial nuclear power generating utility, or a physician.

We need better and less uncertain quantitative information about the risks of radiation carcinogenesis—how many extra cases of cancer will develop per unit of radiation exposure, and when. The information is necessary in order to set 'safe' limits on exposure for persons who are exposed occupationally; so that populations involved in an event like the accident at the Three Mile Island generating plant can be informed, warned, or reassured, depending on the exact circumstances; and to enable physicians to balance risk versus benefit when considering the advisability of a radiological examination such as mammography as a screening procedure for early breast cancer. We need to know what are the kinds

* Seymour Jablon is with the National Cancer Institute in Bethesda, Maryland.

of cancer that are induced by radiation; leukemia is certainly a late effect, as are cancers of the lung and of the stomach, but we are still uncertain about the lymphomas or liver cancer or many others. What are the risks imposed by various levels of radon concentrations in homes, schools, or work places? To obtain more and better data concerning these points we need large-scale studies in which there is good quantitative data concerning the magnitude of individual exposures. Studies of the kind just described can be characterized as "scientific studies."

The second class of studies, for lack of a better term, can be called 'population studies." Such studies as those of persons who lived near Three Mile Island; of residents of southwest Utah in the 1950's, at the time of above-ground testing of nuclear weapons at the Nevada Test Site; or of veterans who, while in service, were present at nuclear weapons tests belong to this class. Studies of the population around Chernobyl will also be of this kind, since the possibility of deriving reasonably accurate estimates of individual radiation doses seems remote. In all of these instances it seems quite possible that estimates of the probable range of individual radiation doses, and their average, can be obtained, but the results of such studies, considered for their scientific value, will probably be no more than confirmatory, in a general way, of the risks obtained from other studies. If such studies have, at best, marginal value for science, why should they be done? For two reasons:

1. The people involved are concerned, or at least many of them are, since it is general knowledge that radiation is a cause of cancer.
2. Many of those who have been exposed, no matter how low the radiation doses may be in individual cases, will attribute any cancer that may develop to the previous exposure.

Since about 20 percent of all deaths in the United States are caused by cancer, and at least 30 percent of all people have some form of cancer diagnosed during their lifetimes, the potential for claims is enormous. This has been demonstrated with respect to the off-site residents of Utah, veterans who were present at nuclear tests, and the veterans who participated in the occupation of Hiroshima and Nagasaki just a few weeks after the atomic bombings of those cities. The statement that, in some instances at least, the exposure levels were too low to result in detectable effects is met with skepticism. Population studies, if they show that the populations in question have cancer rates that are no different from those of the general population, may demonstrate that claimed excesses of cancer are not well founded; alternatively, they may show that the estimated exposure levels are erroneous or that the generally accepted estimates of risk per unit exposure have been drastically underestimated.

Studies of veterans generally fall into the second class; that is, they are not primarily designed to produce scientific information about cancer risks per rem, if for no other reason than that reasonably accurate information about radiation exposures is hardly ever available. While many of the participants in tests at the Nevada Test Site and at the Pacific test area had film badges, the primary purpose of the badging procedure was to ensure that the participants were not exposed to radiation fields that exceeded certain maximum "allowable" limits, not to lay the foundation for future estimates of radiation risk per rad. Accordingly, the badges were not handled with the care that would otherwise have been mandatory, records of readings were sometimes lost or otherwise mishandled, and there was little effort at quality control. Great care in handling and reading the film badges, in fact, would not have been appropriate—the procedures that were followed accomplished the task that they were designed for: to ensure that the exposures were less than some stated amount, not to lay the foundation for future studies.

It is clear why little thought was given to obtaining scientific information. The recent BEIR V report (1) estimates that a radiation dose of 0.1 Sv (10 rem) to a population of 100,000 young men would result, roughly, in about an extra thousand deaths from cancer, over the remaining lifetimes of that population. That is, the population's cancer mortality would be increased by about 5 percent from the 20,000 cancer deaths that can be expected in an unselected population, and to observe the excess, the population would have to be followed for 60 years or more. Given that few veterans who were present at nuclear weapons tests had exposures approaching 10 rem, it seems clear that science would have little to gain from a study of those veterans.

If the risks to the veterans are so small as to be unobservable in a scientific study, what is the problem? Why are we, or they, concerned? Because although we, as scientists, believe, and think we know, that the risks are so small as to be unobservable, members of the general public, including veterans, do not know that, and attempts to persuade them are met with blank disbelief; it is claimed that government officials are liars and that there is a conspiracy to "cover up" the damage that has been done to innocent people. Since, in fact, some officials did, for whatever reasons, conceal from the affected populations facts concerning the magnitude of radioactive fallout, the distrust is understandable.

The purpose of studies of veterans, then, is to determine whether large classes of veterans who have been exposed to ionizing radiation are, on that account, subject to larger risks of subsequent cancer than they otherwise would have been.

So much for the objectives, and the problems, of studies of veterans. What are the advantages? There are two:

1. Individuals are well identified in military files. In addition to the name, a military identifying number, which is now the Social Security number (SSN), is available, which facilitates tracing to learn outcomes.
2. The files of the Veterans Administration, chiefly the Beneficiary Identification and Records Locater Subsystem (BIRLS), are resources that enable a quick and relatively easy determination of whether a given veteran is alive or dead. A statement of the cause of death, transcribed from the death certificate, is often available, and when it is not, there is usually sufficient information to enable a request to the state in which death occurred to obtain a copy of the death certificate itself. Information available from the BIRLS file can be supplemented by resort to the files of the Social Security Administration (SSA), which similarly, provides the information required to enable resort to the state of death. This is an enormous advantage, compared with the difficulty of tracing ordinary civilian rosters, which usually involve long, arduous, and expensive procedures that are not completely successful.

Studies of veterans that have been done usually have been of weapons test participants, but one study of veterans who had occupational exposures has been reported.

X-RAY TECHNOLOGISTS

Thousands of soldiers served as x-ray technologists during World War II. Many of these technologists were trained in Army technical training schools so that it was possible to identify them from school records. A roster that included 6,560 former technologists was created along with rosters of pharmacy and medical technologist controls, for whom the educational qualifications were similar to those for the x-ray technologists. Information regarding exposures of the x-ray technicians was, as might be expected, not available. However, by means of a mailed questionnaire for which the response rate was about 65 percent, some information related to exposure was obtained, such as number of months service in the occupation, occupation after military service (19 percent continued to work as x-ray technologists after an average of three years of occupational exposures while in military service), whether or not there was a history of x-ray therapy, the number of children, and their sex.

Two reports were published. The first (2) concerned follow-up data through 1963, that is, eighteen years after 1945, and the second report (3) extended the follow-up by eleven years, to 1974, making a total 29-year experience after separation from service.

Table 1 shows the results concerning mortality derived from the first survey. Attention focuses primarily on leukemia, since that is the

bellwether for late health effects following ionizing radiation exposure. There were 8 deaths among the technicians, while 6.4 would have been expected at concurrent U.S. rates. The technicians did have excessive mortality from lung cancer, whether compared with the United States or with the controls. However, in the absence of information on cigarette smoking, it is difficult to interpret this. The controls had a deficit of lung cancer deaths, which no doubt, reflected the fact that the different occupational groups had different backgrounds.

Table 2 displays the data concerning sex ratio of children. Six to 8 percent of the men on each roster reported having x-ray therapy, usually for such conditions as acne or bursitis, and strangely, among the technologists who reported such therapy, but not among the corresponding controls, the sex ratio of the offspring was significantly reduced . Among those who did not report x-ray therapy there was no evident effect on the sex ratio.

The later report (3) concerned only mortality; there was not a second round of questionnaires. The number of leukemia deaths increased between 1963 and 1974 from 8 to 12 among the technologists, and from 5 to 7 among the controls (Table 3). Although there was a small excess of leukemia deaths among the technologists, as might be expected to result from radiation exposure, the differences were not statistically significant on either occasion. In fact, mortality was very similar in the two rosters; the excess of respiratory cancer mortality that had been seen in the earlier follow-up had disappeared by 1974.

NUCLEAR TEST PARTICIPANTS

In 1980 Caldwell and colleagues at the Centers for Disease Control (CDC) published a report (4) that showed highly significant excesses of both the incidence of and mortality from leukemia in a group of 3,224 veterans who had participated at a test code-named Smoky at the Nevada Test Site in 1957 (Table 4). The report stirred considerable interest, but seemed unexplainable. Although 4 of the 9 men diagnosed with leukemia had radiation doses estimated to be more that 0.5 rem, none were as large as 3 rem. Conventionally accepted risk estimates for the induction by radiation of leukemia could not explain the excess of about 5.5 incident cases above expectation, given the average radiation dose of perhaps 0.5 rem to the entire group. A second report, in 1983 (5), was concerned with mortality from all causes among the former Smoky participants, both from malignant neoplasms and from other causes of death. The veterans had quite low mortality from diseases other than cancer, as has been generally true for groups that have been selected initially for good health (Table 5). The cancer mortality experience, however, was remarkably close to

expectation at national death rates. Examining the experience with respect to particular kinds of malignant disease (Table 6), there were no remarkable findings except for leukemia where, as had been previously observed, the number of deaths was significantly high.

In view of the reports from CDC it seemed important to review the experience of participants at other weapons tests, both of fission devices at the Nevada Test Site and of thermonuclear weapons at the Pacific Proving Ground. It will be recalled that the Bravo test shot of the Castle series in 1956 exceeded the expected yield, and large amounts of radioactive debris were released into the atmosphere. Several Japanese crew members aboard the fishing boat Lucky Dragon were rather heavily dusted; symptoms of acute radiation injury were reported, and one man died. Similarly, some Marshallese on Rongelap and other atolls in the group were also exposed to radioactive fallout severe enough to cause symptoms, and in fact, during follow-up examinations, an increased incidence of thyroid nodules and, later, of thyroid cancer was found.

At the request of the Defense Nuclear Agency a study was undertaken with the objective of learning whether the findings following the Smoky shot were unique to that test or whether similar excesses of leukemia or other cancers might be found among those who had been present at other tests (6).

Five test series were selected, three from the Pacific and two from the Nevada Test Site (NTS); nearly 50,000 participants were identified (Table 7). Radiation doses could be determined only for about two-thirds of the participants (Table 8), but from the available data it was clear that the doses varied greatly among the series, with the Pacific series attended by radiation doses much larger than those at the NTS. Substantial numbers of men had doses estimated at more than 3,000 mrem (3 rem) and several hundred had more than 5 rem.

The excess of leukemia among Smoky participants that had been reported by Caldwell et al. was confirmed (Table 9), but mortality from no other form of cancer was increased, and in fact, there was actually a deficit in total cancer mortality. When the data for the men in all test series were combined, despite the increase among the men who had been at Smoky, there was no excess of deaths due to leukemia (56 deaths, 56.4 expected) and a very sizable deficit of deaths from all forms of cancer, as compared with the number of deaths expected from contemporary U.S. mortality rates (1,046 deaths observed, 1,243.5 expected).

In summary, studies of radiation carcinogenesis in veterans, rooted in their experiences while in military or naval service, are of strategic importance:

- Very large population groups are needed, and these can be supplied by the military.
- Very long intervals of follow-up are necessary, and with the aid of such indexes as the VA BIRLS system, it is feasible to study rosters of tens of thousands of veterans over a span of more than 30 years.
- The federal government undertakes to be responsible for injury to veterans that has its cause in experiences while in military service. Since there is no general consensus regarding the cancer risks that may follow relatively low doses (under 5 rads), only actual study of the experience of veterans can define those risks in relation to background "normal" cancer mortality rates.

REFERENCES

1. National Academy of Sciences, National Research Council. Health effects of exposure to low levels of ionizing radiation. Washington DC: National Academy Press; BEIR V Report; 1990.
2. Miller, R.W.; Jablon, S. A search for late radiation effects among men who served as x-ray technologists in the U.S. army during World War II. Radiology 96:269–274; 1970.
3. Jablon, S.; Miller, R.W. Army technologists: 29-year follow-up for cause of death. Radiology 126:677–679; 1978.
4. Caldwell, G.G.; Kelley, D.B.; Heath, C.W. Jr. Leukemia among participants in military maneuvers at a nuclear bomb test. JAMA 244:1575–1578; 1980.
5. Caldwell, G.G.; Kelley, D.; Zack, M.; Falk, H.; Heath, C.W.Jr. Mortality and cancer frequency among military nuclear test participants, 1957 through 1979. JAMA 250:620–624; 1983.
6. Robinette, C.D.; Jablon, S.; Preston, T.L. Studies of participants in nuclear tests. National Research Council, Medical Follow-up Agency, 1985.

TABLE 1

	X-Ray		Pharmacy		Medical	
Category	Obs.	Exp.	Obs.	Exp.	Obs	Exp.
Deaths from trauma	66	63.9	10	15.3	53	49.8
Suicide	18	16.2	2	4.1	12	11.7
Homicide	3	3.8	1	0.8	4	3.4
Other	45	...	7	...	37	...
Deaths from all diseases	223	208.5	52	52.8	141	154.7
All cancer	55	52.3	13	13.0	37	39.7
Leukemia	8	6.4	0	1.5	5	5.0
Other lymphatic	4	7.5	5	1.8	6	5.7
Respiratory	17	10.5	1	2.8	3	7.8
Digestive	13	12.1	3	3.1	8	8.9
Other	13	15.8	4	3.8	15	12.3
Vascular, CNS	14	11.7	3	3.0	6	8.3
Arteriosclerotic & degenerative heart disease	83	76.7	11	19.8	59	56.6
Peptic ulcer	1	1.0	1	0.3	0	0.7
Cirrhosis, liver	14	11.1	4	3.0	4	7.9
Nephritis and nephrosis	4	4.5	1	1.2	4	3.3
Other	52	51.3	19	12.6	31	38.2
Total in sample	6,560		1,522		5,304	

Source: Miller and Jablon (2).

TABLE 2 SEX RATIO IN OFFSPRING BORN IN 1946 OR LATER

Category	Number of Children	Proportion of Male Births
Men who reported radiotherapy		
X-ray technologists	539	0.4712*
Pharmacy technologists	78	0.5641
Medical lab technologists	423	0.5130
Men who did not report radio therapy		
X-ray technologists	6,539	0.5178
Pharmacy technologists	1,510	0.5211
Medical lab technologists	6,033	0.5173
TOTAL	15,168	

* Difference between this ratio and the total ratio significant at the 5% level, two-tail test.
Source: Miller and Jablon (2).

TABLE 3 NUMBER AND PERCENTAGE OF DEATHS BY CAUSE, 1946–1974

	X-ray Technicians		Controls	
Cause of Death (ICD 7th Revision)	No.	%	No.	%
Total	6,560	100.0	6,826	100.0
Deaths, all causes	792	12.10	792	11.60
Deaths by cause				
Accidents, poisonings, and violence (E800–E999)	107	1.63	109	1.59
Disease (001–796)	657	10.02	656	9.61
Malignant neoplasms (all 140–205)	145	2.21	158	2.31
Leukemia (204)	12	0.18	7	0.10
Other lymphatic and hematopoietic (200–203,205)	11	0.17	16	0.23
Respiratory system (160–164)	41	0.62	42	0.62
Digestive system (150–159)	38	0.58	47	0.69
Other malignant neoplasms (remainder 140–205)	43	0.66	46	0.67
Vascular lesions of CNS (330–334)	37	0.56	42	0.62
Arteriosclerotic and degenerative heart disease (420–422)	283	4.31	266	3.90
Cirrhosis of liver (581)	35	0.53	33	0.48
Other disease (remainder 001–795)	157	2.39	157	2.30
Unknown cause	28	0.43	27	0.40

Source: Jablon and Miller (3).

TABLE 4 LEUKEMIA MORTALITY AND INCIDENCE IN SMOKY PARTICIPANTS

	No. of Leukemia Cases			
Leukemic Cell Type	Observed	Expected	Observed/ Expected Ratio	Probability (Poisson)
Mortality				
(all types)	8	2.9	2.4	.01
Incidence				
All types	9	3.5	2.3	.01
AML only	4	1.1	3.6	.03
CML only	3	0.7	4.3	.03
AML and CML	7	1.8	3.8	.003

Source: Caldwell et al. (4).

TABLE 5 CAUSES OF DEATH IN SMOKY PARTICIPANTS, 1957–1979

	Deaths		
	Observed	Expected	Ratio
All causes	320	364.8	0.88
Trauma	103	84.9	1.21
Neoplasms	64	64.3	1.00
Other disease	153	215.6	0.71

Source: Caldwell et al. (5).

TABLE 6 DEATHS FROM NEOPLASMS AMONG SMOKY PARTICIPANTS, 1957–1979

	Deaths		Ratio
	Observed	Expected	
All neoplasms	64	64.3	1.00
Leukemia	8	3.1	2.58
Lymphoma	3	4.2	0.71
Multiple myeloma	0	0.7	0.00
Digestive cancer	15	15.6	0.96
Respiratory	21	22.2	0.94
Brain & nervous system	5	2.9	1.72
Other	12	12.7	0.94

Source: Caldwell et al. (5).

TABLE 7 TEST SERIES INCLUDED IN THIS STUDY, DATES, AND NUMBERS OF PARTICIPANTS

Series	Date	Location	Number of shots	Number of participants
Greenhouse	1951	Pacific	4	3,093
Upshot-Knothole	1953	Nevada	11	10,365
Castle	1954	Pacific	6	11,674
Redwing	1956	Pacific	17	10,564
Plumbob	1957	Nevada	30	15,165
Total				49,148*

* The total is lees than the sum because there were 1,713 multiple test participants.
Source: Robinette et al. (6).

TABLE 8 GAMMA RADIATION DOSES (MREM) BY SERIES, PERCENTAGE OF PARTICIPANTS, AND MEAN VALUES

Series	Number with Known Dose	Mean Dose	Percent more than				
100	300	1,000	3,000	5,000			
Greenhouse	2,099	1,291	87.6	81.7	55.9	8.2	3.0
Upshot-Knothole	5,741	291	10.3	9.1	7.1	3.9	1.2
Castle	7,595	1,493	91.3	78.7	45.2	13.6	3.7
Redwing	9,205	1,534	88.3	79.2	47.0	17.6	2.8
Plumbob	9,477	538	57.1	35.9	13.4	3.8	1.4
Smoky*	(3,440)	571	62.5	38.8	14.1	2.8	1.1
Total**	32,577	934	66.1	54.1	29.3	8.8	1.7

* Included in total for Plumbob.
** Includes 1,540 men with known doses present at more than one series who are counted in each.
Source: Robinette et al. (6).

TABLE 9 OBSERVED AND EXPECTED MORTALITY FROM CANCER BY CALENDAR YEAR: SMOKY

Cohort Size: 3,554

		Follow-up year			
Kind of cancer	Deaths	1–10	11–20	21+	Total
Digestive	Observed	0	12	5	17
	Expected	3.51	9.36	7.92	20.96
	SMR	—	1.28	0.63	0.81
Respiratory	Observed	6	9	11	26
	Expected	3.83	14.68	13.21	32.00
	SMR	1.57	0.61	0.83	0.81
Leukemia	Observed	1	5	4	10
	Expected	1.12	1.69	1.14	3.97
	SMR	0.89	2.96	3.51	2.52
Other	Observed	5	13	6	24
	Expected	6.54	13.60	10.51	30.86
	SMR	0.76	0.96	9.57	0.78
Total	Observed	12	39	26	77
	Expected	15.00	39.33	32.78	87.78
	SMR	0.80	0.99	0.79	0.88

Abbreviation: SMR, standardized mortality ratio.
Source: Robinette et al. (6).

Resources for Epidemiologic Research in Vietnam Era Veteran Populations within the Department of Veterans Affairs

Han K. Kang*

The Department of Veterans Affairs (VA) maintains three large automated databases that provide the opportunity for studying long-term health effects of military service in Vietnam. These databases were created for administrative and management purposes, not for research purposes. Nevertheless, these resources can be used either as sampling frames for studies of diseases or as tools for health surveillance and vital status follow-up activities.

The Beneficiary Identification and Record Locator Subsystem (BIRLS)

VA maintains an automated system to identify veterans and their dependents and to keep track of where their claims folders are located. The system includes records for veterans and dependents of veterans who have or are receiving compensation, pension, education, and other VA benefits. This computerized database, created in 1972, replaced the manual Veterans Administration Master Index. There are approximately 40 million records in the database. The BIRLS is an excellent source of vital status information on veterans. VA pays a lump sum death benefit to eligible survivors of deceased veterans. At the present time up to $300 is paid toward a veteran's burial expenses, and an amount not exceeding $150 is paid for a plot or interment allowance if the veteran is not buried in a national cemetery. Until October 1981, survivors of all Vietnam era veterans who were discharged under conditions other than dishonorable were eligible to receive burial benefits. The BIRLS file offers several advantages in ascertaining veteran deaths:

* Han K. Kang, Dr.P.H., is with the Office of Environmental Epidemiology of the Department of Veterans Affairs in Washington, DC.

a. It is considered to be relatively complete in its roster of veteran deaths. Beebe and Simons (1) showed that up to 98% of WWII veterans whose deaths in 1962 were independently ascertained were known to VA. A more recent study by the National Academy of Sciences (NAS) Medical Follow-up Agency (2) indicated that 88% of Vietnam era veteran deaths that occurred in 1980 were recorded on the VA BIRLS files. The ascertainment rate was somewhat higher (93.4%) for those who served two or more years on active duty.
b. It has a built-in linkage, through the VA claims folder, to the veteran's death certificate. The BIRLS file, as its name suggests, is a records locator system. The location of a veteran's claim folder is indicated in the BIRLS, and the claim folder holds some kind of notification of death, usually a death certificate.
c. The BIRLS file contains data that can facilitate linkage to a veteran's military records. It contains all or some of the following information: name, Social Security number (SSN), military service number, date of birth, dates of military service, and branch of service.

We have used BIRLS for many of our mortality follow-up studies of Vietnam veterans:

1. Marine Corps Vietnam Veterans Mortality Study
2. Women Vietnam Veterans Mortality Study (3)
3. Army Chemical Corps Vietnam Veterans Mortality Study (4).

We have also used BIRLS to develop a roster of Vietnam era veteran deaths (5–7). The Vietnam Veterans Mortality Study published in 1988 (5) is entirely based on BIRLS information, which was used to select 90,000 potential study subjects. Over 85% of the death certificates for these veterans were obtained from VA claims folders. A state normally charges a fee of $2–$10 per death certificate. It would have cost VA approximately $300,000 to purchase these death certificates, had they not been in VA claim folders.

We are concerned with the potential impact of Public Law 97-35, which became effective on October 1, 1981, on the reporting of veterans' deaths to VA. The new eligibility requirement of the law may have caused underreporting of veterans' deaths to VA.

In a preliminary attempt to assess the impact of the law, we have compared the total numbers of each of the three types of death benefits awarded for the three fiscal years (FY's) prior to the eligibility changes

(FY's 1979–81) and for the three fiscal years following the changes (FY's 1982–84). The estimated number of veterans alive in each of the fiscal year periods ranged from 28 to 30 million. The total number of basic burial benefit claims has declined substantially since the passage of the law and has remained depressed despite the growing number of aging veterans. However, the number of claims for other death benefits such as plot interment allowance and burial flags has not changed substantially during the entire 6-year period. Because the basic burial benefit claim is one of several ways by which a veteran's fact of death is reported to VA and because other death benefit programs do not appear to be affected by the law, the overall impact on the reporting of veteran deaths may not be as severe as one may assume.

Nonetheless, we plan to reassess the completeness of death reporting to the BIRLS file for two post-1981 years and to evaluate the demographic and military characteristics of deceased veterans included and not included in the BIRLS file. This study will be a replication of an earlier NAS/VA study of deaths occurring in 1980 among Vietnam era males (2). As before, eight selected states will be approached for magnetic tape copies of their 1982 and 1987 death records for males born during the years 1936 through 1955. Their veteran status will be determined by matching against the registry of the National Personnel Record Center. A total of 4,000 men who are identified as veterans will be matched to BIRLS by "batch processing." Veterans not matched during this trial will be researched through individual BIRLS inquiries. The data collected will be analyzed to determine whether death reporting rates differ according to such factors as cause of death, Vietnam service, race, rank, and discharge status.

Although VA maintains the BIRLS file for administrative and management purposes, it can serve as an important national source of vital status information for adult males. After all, the 1980 census showed that one in three males above 16 years old was a veteran (8). A detailed characterization of deaths reported and not reported to the BIRLS will be useful to the epidemiologist who plans to tap this national resource.

The VA Patient Treatment File (PTF)

The PTF is a computerized hospital discharge abstract system of inpatient records, including patients' demographic data, surgical and procedural transactions, and patient movements and diagnosis. One PTF record is prepared for each discharged VA in-patient by the medical records librarian at the discharging station. The VA Data Processing Center in Austin updates the PTF each week. The PTF record contains information on such variables as name, SSN, date of birth (DOB), place of residence, marital status, period of military service, radiation exposure,

self-reported Agent Orange exposure, prisoner of war status, discharge diagnosis, length of stay, surgical and other procedures, and compensation and pension status. Nearly 1.5 million veterans are treated as in-patients in the VA hospitals each year.

The PTF provides an excellent sampling frame for a study of disease. We have conducted three case-control studies based on the veteran patients in the PTF: soft tissue sarcomas (9), non-Hodgkin's lymphoma (10), and Hodgkin's disease (11). To those who want to consider using the PTF for any future study, we would like to share our experience with the data file. Beginning in July 1982, the PTF added a Vietnam Service Indicator or Agent Orange Exposure Indicator to the record. We thought it would be an expedient and practical way to evaluate Vietnam veterans' health problems by comparing discharge diagnoses of Vietnam veterans to those of non-Vietnam veterans. If there is no Vietnam effect, the distribution of various categories of health conditions recorded in the PTF should be similar after adjustment for certain demographic variables between these two patient groups. Since there is a built-in Vietnam service indicator for each patient and his discharge diagnosis is already coded using ICD 9, it would have been a relatively simple process. Before we started this project, we thought we would check the accuracy of the indicator. We randomly selected 1,000 Vietnam era veterans from the PTF for FY 1983. We were able to locate and retrieve military service records for 914 of the veterans from the National Personnel Records Center in St. Louis. We had their military service records abstracted by a contractor and compared Vietnam service against the PTF indicator for such service. The results were more than disappointing. Of 370 veterans who were identified as Vietnam veterans by the PTF, only 196 veterans were determined to have served in Vietnam by the military record. Similarly, of those 544 veterans who did not serve in Vietnam according to the PTF, 159 patients were found to have served in Vietnam. Therefore, the percentage of false positives and false negatives were 31% and 45%, respectively.

Coding for discharge diagnosis was not any better for certain types of cancer. A few years ago we conducted a case-control study of soft tissue sarcoma using veteran patients in the PTF (9). We identified a total of 418 patients with an ICD 171 diagnosis, i.e., malignant neoplasm of connective and other soft tissue, by a complete search of the PTF for Vietnam era veterans who were hospitalized between 1969 and 1983. A pathology report for each ICD 171 case was requested from each treating VA hospital. A review of the 394 pathology reports that we received by an expert pathologist, who during the review had no knowledge of Vietnam service status of any of the patients, yielded the following results. He excluded 151 cases from the study because of miscoding or misclassi

fication. Nine cases were considered doubtful, leaving only 234 cases that met the classification system for soft tissue sarcoma. That was almost a 40% loss.

We had a similar experience with malignant lymphoma cases among Vietnam era veterans in the PTF (10). In preparation for a case-control study of lymphoma among Vietnam era veterans, we identified the recorded lymphoma cases (ICD 200–202), and as before retrieved the pathology reports and had them reviewed by an expert pathologist. Only one-half (or 450) of the cases coded ICD 200 and 202 were determined to be consistent with the diagnosis of non-Hodgkin's lymphoma. We have not reviewed the PTF for other coded diagnosis. But it was clear to us that you can't rely on ICD coding recorded in the PTF without further verification at least for a study of cancer. The PTF can provide an excellent sampling frame for study of diseases among veterans. But one has to be well aware of the possibility of substantial coding errors.

In order to further evaluate the PTF, we arranged for a pathological review of tissue slides from the cases described as soft tissue sarcomas (ICD 171) in the pathology reports. We obtained the services of the Armed Forces Institute of Pathology (AFIP). The AFIP was provided with sets of slides that VA Medical Centers forwarded to us along with information on the sex and age of the patient and the anatomical site from which the specimen was taken. The AFIP knew neither the Vietnam service status of the patients nor the contents of their VA clinical records and pathological diagnosis. Among the 181 cases the AFIP reviewed, the AFIP disagreed with the VA diagnosis in 10 cases (5.5%).

I believe, therefore, that the major problem with the PTF is the miscoding by medical clerks rather than misdiagnosis by VA clinicians.

The Agent Orange Registry

The Agent Orange Registry was initiated by the Department of Veterans Affairs in mid-1978 in response to concerns expressed by Vietnam veterans who were increasingly worried that they may have been exposed to Agent Orange and other herbicides that might be causing a variety of ill effects. It provides the veteran an opportunity to receive a complete health evaluation and answers to questions concerning the current state of knowledge regarding the relationship between herbicide exposure and subsequent health problems. The computerized Agent Orange Registry data include veteran's name, address, some information on military service, and findings at the time of his physical examination.

Because of the self-selected nature of the registry participants, this group of veterans cannot be viewed as being representational of Vietnam

veterans as a whole. There are approximately 200,000 participants in the Registry; that is almost one-tenth of all Vietnam veterans.

Because of the possibility of coding and keying errors in the Agent Orange Registry, we have assessed the overall accuracy of the data in the registry by randomly reexamining original microfilmed medical records of Agent Orange examinations and comparing this information to the data on the code sheet. We then compared the data on the code sheet with the data contained in the computerized registry.

Coding and keying errors do exist in the Registry, especially in the diagnosis and complaint fields. Upon reviewing the records for 200 Agent Orange examinations, it was found that 11% of the diagnoses were miscoded and 2.7% of the diagnoses were miskeyed.

We are conducting two case-control studies using information in the Registry (12,13). Because of the limitations that I described earlier, we are verifying military service data by reviewing the study subjects' military records and also the diagnosis by reviewing their Agent Orange Registry abstracts. As I stated earlier, the Registry contains the demographic and medical data for approximately 200,000 Vietnam veterans. With appropriate caution and appreciation of its limitations, the Registry can serve as another useful resource for future health studies of Vietnam veterans.

REFERENCES

1. Beebe GW, Simon AH. Ascertainment of mortality in the U.S. veteran population. Am J Epidemiol 1969; 89:636–643.
2. National Academy of Sciences Commission on the Life Sciences Medical Follow-up Agency. Ascertainment of Mortality in the U.S. Vietnam veteran population. A report to contract V101(93)P-937. Washington, D.C.: 1985
3. Thomas TL, Kang, HK Mortality among Women Vietnam-era veterans: a preliminary analysis. Presented at the 23rd Annual Meeting of the Society for Epidemiologic Research, June 12–15, 1990, Snowbird, Utah.
4. Thomas TL, Kang, HK Mortality and Morbidity Among Army Chemical Corps Vietnam veterans: A preliminary report. AM J Ind Med 1990; 18: in print.
5. Breslin P, Kang HK, Lee Y et al. Proportionate mortality study of US Army and US Marine Corps veterans of the Vietnam war. J Occup Med 1988; 30: 412–19,
6. Bullman TA, Kang HK, Watanabe KK. Proportionate Mortality among US Army Vietnam veterans who served in military region I. Am J Epidemiol 1990; 132: in print.
7. Watanabe KK, Kang HK, Thomas TL. Mortality among Vietnam veterans: with methodological considerations. J Occup Med 1991; in print.

8. Veterans Administration. Veterans in the United States. A statistical portrait from the 1980 census. Office of Information Management and Statistics. Washington, D.C; 1984.
9. Kang HK, Weatherbee L, Breslin P, et al. Soft tissue sarcomas and military service in Vietnam: A case comparison group analysis of hospital patients. J Occup Med 1986; 28: 1215–18.
10. Dalager NA, Kang HK, Burt VL et al. Non-Hodgkin's lymphoma among Vietnam veterans. J Occup Med 1991; in print.
11. Dalager NA, Kang HK, Burt VL et al. Malignant lymphoma among Vietnam-era veterans. Presented at the 9th International Symposium on chlorinated dioxins and related compounds. September 17–22, 1989, Toronto, Canada.
12. Thomas TL, Kang HK. Health status of a self-selected group of 104,000 Vietnam veterans. Presented at the 22nd Annual Meeting of the Society for Epidemiologic Research. June 14–16, 1989, Birmingham, Alabama.
13. Bullman T, Kang HK. A case control analysis of Vietnam veterans from the Agent Orange Registry for post-traumatic stress disorder. Presented at the 23rd Annual Meeting of the Society for Epidemiologic Research, June 12–15, 1990, Utah.