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PRINCIPAL INVESTIGATOR: William Page, Ph.D.

CONTRACTING ORGANIZATION: National Academy of Sciences
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6. AUTHOR(S):
William Page, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
National Academy of Sciences
Washington, DC 20418

E-MAIL: WPage@nas.edu

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Between 1955 and 1975, the US Army enrolled volunteers in an experimental exposure program of chemical warfare and other agents at the Edgewood Arsenal, Maryland. In 1980 the National Research Council issued a report on the health status of test subjects which included 1,581 men exposed to anticholinesterase agents. The current study is a continued follow-up of the same subjects, including two control groups whose subjects were not exposed to anticholinesterase agents. The current study collected morbidity data via telephone survey on the following primary outcomes: somatization disorder, memory and attention problems, peripheral nerve disease, vestibular function, depression, generalized anxiety, sleep disturbance, and birth defects. In general, there were few statistically significant differences in these outcomes among the study groups. In contrast, self-reported non-experimental exposure was associated with higher levels of almost all outcomes, although this association could be due to reporting bias. This suggests that if there were any true long-term health effects associated with anticholinesterase exposure, they are probably smaller than those associated with self-reported non-experimental exposure to hazardous chemicals. These results were published in Military Medicine, Vol. 168, March 2003, pp. 239-45.

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Introduction

Between 1955 and 1975, the US Army enrolled 6,720 volunteers in an experimental exposure program of chemical warfare and other agents at the Edgewood Arsenal, Maryland. In 1980 the Army asked the National Research Council (NRC) to study the possible long term health effects of these exposures. A three-volume report was issued, the last volume dealing with the current health status of test subjects, including 1,581 men exposed to anticholinesterase compounds such as GA (tabun), GB (sarin), GD (soman), GF, and VX. The current study is a continued follow-up of the men exposed to anticholinesterase chemical agents as well as two control groups of approximately equal size whose subjects were not exposed to anticholinesterase agents. Based on research on the health effects of low level exposures of organophosphate pesticides—somewhat similar in their chemical action to the nerve agents tested at Edgewood—the current follow-up collected morbidity data via telephone survey on the following outcomes: general heath status, somatization disorders, cognitive impairment, peripheral nerve disease, vestibular function, depression, generalized anxiety, sleep disturbance, chronic medical conditions, and birth defects. The data have been analyzed to investigate whether there are differences in self-reported health between subjects exposed to anticholinesterase agents and non-exposed subjects. The results have been reported in an article for publication in a peer-reviewed journal, Military Medicine.

Background

Between 1955 and 1975, the US Army enrolled 6,720 volunteers in an experimental exposure program of chemical warfare and other agents at the Edgewood Arsenal, Maryland. In 1980 the Army asked the National Research Council to study the possible long term health effects of these exposures. A three-volume report was issued, the last volume dealing with the current health status of test subjects, including 1,581 men exposed to anticholinesterase compounds such as GA (tabun), GB (sarin), GD (soman), GF, and VX (1, 2, 3).

The current study is a continued follow-up of the men exposed to anticholinesterase chemical agents as well as two control groups of approximately equal size, composed of subjects who were not exposed to anticholinesterase agents. Based on research on the health effects of low level exposures of organophosphate pesticides—somewhat similar in their chemical action to the nerve agents tested at Edgewood—the current follow-up is focused on neurological and neuropsychological sequelae.

Materials and Methods

The subjects for this study were drawn entirely from rosters of previously-studied subjects. Of primary interest is the group of Edgewood subjects exposed to anticholinesterase agents. Edgewood subjects who were not exposed to any chemical agents will serve as the first comparison group. However, this is not an ideal comparison group because the original Edgewood protocol did not include a completely random assignment of subjects to treatment and control groups. In particular, it is thought that healthier men were more likely to have been assigned to chemical exposure groups and

less healthy men to the control group. To counteract the effect of this putative assignment bias, a second comparison group consisting of men who were multiply exposed to chemical agents other than anticholinesterase agents was included in the follow-up. The first comparison group," no chemical tests," and the second comparison group, "other chemical tests," are of approximately the same size.

Tracing subjects

Before undertaking the telephone survey, we located the test subjects and obtained their addresses and telephone numbers. Central to this effort was the use of the authority of the National Institute for Occupational Health and Safety (NIOSH) to provide address information from Internal Revenue Service (IRS) files. The entire file of study subjects was processed through the IRS address files, using Social Security Numbers (SSN) as the matching variable. SSNs were available for approximately 90% of the cohort. Further location efforts, such as credit bureau searches, were undertaken by the subcontractor.

Questionnaire development

Morbidity data were collected by telephone survey. We issued a request for proposals to select a subcontractor to design the questionnaire, obtain telephone numbers for the subjects in the study, and administer the questionnaire by telephone interview. Schulman, Ronca, and Bucuvalas, Inc. (SRBI) were chosen as the subcontractor to design and conduct the telephone survey.

The survey relied heavily on previously developed survey instruments. Subscales on memory and attention were taken from the Neuropsychological Impairment Scale (NIS), items dealing with peripheral nerve disease were adapted from a scale developed

by Dyck et al., and items on vestibular function were taken from an instrument by Roland et al. Items on depression, generalized anxiety, and somatization disorders were adapted from DSM-IV. General health was assessed, as well as the presence of various relevant chronic conditions (e.g., diabetes), using items from the National Health Interview Survey. Previous Department of Veterans Affairs (VA) surveys were the source of items on reproductive history, alcohol use, drug use and dependence, occupational history, and military experience.

Expert review of the questionnaire was provided by Dr. Peter Spencer of Oregon Health Sciences University and Dr. Dan Blazer of Duke University. Human Subjects review and approval of the protocol, the questionnaire, and associated materials was given by the National Academies' and the Army's Human Subjects Review Committees.

Mortality Follow-up

Crude mortality was determined prior to the telephone survey primarily to avoid attempting to contact decedents. However, we used VA records to determine vital status and also to obtain death certificates for deaths prior to 1979. For death in the years 1979 and after, the National Death Index (NDI Plus) was used to obtain cause-specific mortality data.

Analysis and Reporting

Rates of various health outcomes in the anticholinesterase group were compared to those for the two comparison groups. The primary outcomes of interest were as follows: NIS memory problem subscale; NIS attention problem subscale; peripheral

neuropathy score; sleep disturbance score; somatization score; presence of depression; presence of generalized anxiety disorder; frequency of vestibular dysfunction; and prevalence of birth defects. Risk estimates for these outcomes were calculated using linear and logistic regression analyses, adjusted for age at time of testing, test participation factors, race, and self-reported military and civilian exposure to chemicals outside the Edgewood program.

Overall, the response rate was 62% for all subjects and 77% for contacted subjects. During the interviewing process, one respondent called to say that he was having a nervous breakdown. When interviewers volunteered to put the subject in touch with a mental health professional or to call 911, the subject refused intervention. This adverse event was then reported to the National Academies' and Army's Human Subjects Committees. In response to this adverse event, the telephone survey instrument and associated procedure were modified, and Human Subjects approval for the modifications was received from The National Academies' and Army's Human Subjects Committees.

Demographics for the three groups were similar, with a slight difference in average age a survey: anticholinesterase group, 60 years; no chemical tests, 58 years; and other chemical tests, 56 years. Overall mortality was significantly lower in the anticholinesterase group, compared to the no chemical test group (hazard ratio=0.82). There were no statistically significant differences in cancer mortality.

With respect to the primary neurological and psychological endpoints, subjects exposed experimentally to anticholinesterase agents had a significantly lower rate of attention problems than those in other chemical tests group and a significantly higher rate of sleep disorders than those in the no chemical tests group. There were no statistically

significant differences among the groups with respect to the following endpoints: memory problems, peripheral neuropathy, somatization, depression, generalized anxiety, vestibular function (dizziness), or birth defects.

In contrast, subjects who reported exposure to hazardous chemicals outside their Edgewood experience reported significantly higher rates of attention problems, memory problems, peripheral neuropathy, sleep disorders, somatization, depression, generalized anxiety, vestibular function (dizziness), and birth defects. These significant associations were found regardless of experimental exposure. However, these associations could be due to reporting bias, i.e., men with health problems may have been more likely to recall hazardous chemical exposure outside the Edgewood experience.

In summary, there were few differences in health attributable to experimental exposures compared with many differences attributable to non-experimental exposures. The latter, however, may be due to reporting bias. This suggests that if there were any long-term health effects associated with experimental exposure to anticholinesterase agents, they were smaller than the statistically significant effects observed for non-experimental exposure.

The results of this study have been published in a peer-reviewed scientific journal, Military Medicine (4), and a copy of this report is provided in Appendix 1.

Key Research Accomplishments

During this study, the following key research accomplishments were achieved:

- the exposure cohort and two control cohorts were selected;
- vital status was obtained for all three study cohorts using VA records;

- death certificates were obtained from VA records and cause of death data from the National Death Index;
- requests for proposal were issued for the telephone survey and SRBI chosen as subcontractor to design the telephone survey questionnaire and administer the telephone survey;
- the telephone survey was designed by SRBI, reviewed by MFUA staff and expert technical advisors Drs. Dan Blazer and Peter Spencer, and put into final form;
- Human Subjects approval for conduct of the study was received from The National Academies' and Army Human Subjects Committees;
- the telephone survey was conducted with an overall response rate of approximately 62%;
- in response to an adverse event (see above), the telephone survey instrument and associated procedure were modified and Human Subjects approval for the modifications was received from The National Academies' and Army's Human Subjects Committees; and
- the data were analyzed and a final report was published in a peer-reviewed journal, Military Medicine.

Reportable Outcomes

No abstracts or presentations on the collected data have yet been made. Final results from this study have been published in a peer-reviewed journal, Military Medicine, March 2003 (4).

Conclusions

Final results from this study have been published in Military Medicine. These results will be of interest not only to researchers and participants in the original program, but may also be relevant to those studying health effects following contemporary chemical agent exposures of a similar nature. This study found few differences in health

attributable to experimental exposures compared with many differences attributable to non-experimental exposures. The latter, however, may be due to reporting bias. This suggests that it there were any long-term health effects associated with experimental exposure to anticholinesterase agents, they were smaller than the statistically significant effects observed for non-experimental exposure.

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Appendix Cover Sheet

MILITARY MEDICINE, 168, 3:239, 2003

Long-Term Health Effects of Exposure to Sarin and Other Anticholinesterase Chemical Warfare Agents

Guarantor: William F. Page, PhD
Contributor: William F. Page, PhD

In a telephone survey of 4,022 military volunteers for a 1955–1975 program of experimental exposures to chemical agents at Edgewood, Maryland, the current health of those exposed to anticholinesterase agents was compared with that of men exposed to no active chemicals (no chemical test) and to two or more other types of chemical agents (other chemical tests). The survey posed questions about general health and about neurological and psychological deficits. There were only two statistically significant differences: volunteers in anticholinesterase agent tests reported fewer attention problems than those in other chemical tests and greater sleep disturbance than those in no chemical tests. In contrast, volunteers who reported exposure to civilian or military chemical agents outside of their participation in the Edgewood program reported many statistically significant adverse neurological and psychological effects, regardless of their experimental exposure. In this study, the health effects of self-reported, nonexperimental exposure, which are subject to recall bias, were greater than the health effects of experimental exposure.

Introduction

Between 1955 and 1975, the U.S. Army enrolled military volunteers in an experimental program in Edgewood, Maryland, to test the effects of various chemical warfare agents, including sarin and other anticholinesterases. In the 1980s, the National Research Council's Committee on Toxicology used a roster of men who had participated in the program to examine the adverse long-term health effects of the known exposure.[1] This report presents results on the current health status of these same men. The previous National Research Council follow-up study found no marked health differences between men exposed to anticholinesterase chemical warfare agents and men who were either not exposed to any chemical agents or who were exposed to other types of chemical agents. In fact, almost 90% of the respondents reported no health problems related to their exposure and 79% reported good to excellent health. However, based on a review of Veterans Affairs hospitals (from 1963 to 1981), men who had been exposed to anticholinesterases at Edgewood were more likely to eventually be hospitalized for malignant neoplasms.[1]

In the wake of recent sarin exposures of both military and civilian populations, there is considerable current interest in the long-term or delayed health effects of such exposure. In 1991, some 100,000 U.S. troops were potentially exposed to sarin and cyclosarin after the detonation of the ammunition depot at Khamisiyah, Iraq.[2] In 1994, about 600 residents of Matsumoto, Japan, were exposed to sarin;[3] 1 year later, another 5,500 persons were exposed to sarin on the Tokyo subway.[4] It is far too early to study the long-term chronic effects of any of these recent, nonexperimental exposures, and there is very little other information available on the long-term health effects of this type of exposure. In the case of the 1991 Gulf War exposure, the effects may be difficult to determine since the level of exposure is believed to have been low (e.g., no chemical alarms sounded) and the determination of exposure is dependent on factors that are difficult to track (e.g., meteorological models and troop location data).[2] The roster of U.S. Army experimental subjects at Edgewood provides a unique opportunity to provide important information on the subject of long-term health effects following known, experimentally controlled exposure to anticholinesterase agents.

Because organophosphate (OP) pesticides resemble chemical warfare agents, one would expect the health effects of exposure to the latter to be similar to those of OP exposure. The long-term sequelae from low-level exposure to OP chemicals are unknown,[5] but reported short-term health effects from acute exposure include disorders of affect, emotion, and memory; persistent changes in electroencephalogram and behavior; and memory loss, irritability, and difficulty concentrating. Other evidence suggests that persons exposed to low levels of these chemicals for prolonged periods might also be at risk for mild polyneuropathy.[5] Based on these findings, the current follow-up study focused on self-reported neuropsychological impairment, including sleep disorders, anxiety, as well as depression and neurological deficits, including peripheral nerve disease and vestibular dysfunction. One would expect that these neurological and psychoneurological deficits would be more prevalent in the group of volunteers who were exposed to anticholinesterase agents.

Methods

Data Collection

Vital status was determined using mortality records from the Department of Veterans Affairs (VA) and the Social Security Administration, the combination of which generally accounts for about 96% of all veteran deaths.[6] Either a Social Security Number or military service number was used to identify the subjects.

After removing known decedents, a sample file containing 4,022 subjects was provided to Schulman, Ronca, and Bucuvalis, Inc., the subcontractor chosen to do the telephone survey. Addresses were obtained from the Internal Revenue Service or credit bureau searches. All subjects with current addresses were sent letters explaining the survey and requesting written

Medical Follow-up Agency, Institute of Medicine, 500 Fifth Street, N.W., Washington, DC 20001.

The opinions and assertions contained herein are those of the author and are not to be construed as reflecting the views or position of the National Academy of Sciences, the Institute of Medicine, or the National Research Council.

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informed consent. Letters were sent out at least twice to nonrespondents and, in some cases where there was more than one potentially valid address, as many as five letters were sent.

The survey was designed in consultation with outside experts (see "Acknowledgments") to measure the various types of outcomes that are expected to result from anticholinesterase exposure. Besides questions about general health, the survey included two subscales from the Neuropsychological Impairment Scale (NIS)[7] as well as items on peripheral nerve disease,[8] vestibular dysfunction, sleep disorders, and reproductive history. Neuropsychological scales included measures of somatization disorders, depression, generalized anxiety,[9] and the Illness Attitude Scales.[10] The prevalence of chronic medical conditions was assessed using items from the National Health Interview Survey.[11]

Volunteers were asked questions about schooling, marital status, general health, job history, living arrangements, birth of children, birth defects of children, smoking, drinking, treatment for alcoholism, use of illicit substances, medical care and hospitalizations within the past 5 years, number of days ill in bed in the past month, and limitations in activity. These are the same general areas that were covered in the 1985 survey, with one exception: the open-ended, general job history of the original survey was replaced by a series of items on specific occupations (e.g., Have you ever worked in farming?). The survey was also used to collect self-reported morbidity data, with an emphasis on neurological health (e.g., vestibular dysfunction) and neuropsychological health (e.g., depression and generalized anxiety). In the initial study, morbidity data were collected from Army and VA computerized records.

The study plan and survey were reviewed and approved by the Army's Human Subjects Research Review Board and the National Academies' Committee to Review Studies Involving Human Subjects. In lieu of a phone interview, approximately 254 subjects were sent a short form questionnaire with a limited number of items, but these data were not used in the analyses because of the low response rate and inconsistencies between the short form and the phone survey.

Study Cohort

Both the 1985 and this current study were comprised of the same three comparison groups: subjects exposed to anticholinesterase agents (anticholinesterase or ANTICHOL, N = 1,339), subjects not exposed to any chemical agents (no chemical test [NCT], N = 1,324), and subjects exposed to two or more chemical agents other than anticholinesterase agents (other chemical test [OCT], N = 1,359. The current study groups were identical in composition to those in the 1985 study,[1] except that decedents were removed before undertaking the telephone survey and that the OCT subjects were limited to those exposed to two or more agents (thus eliminating those who were exposed to only one other chemical agent).

In the 1985 study, individuals in the ANTICHOL group were exposed to at least 1 of 15 anticholinesterase substances, with sarin (N = 246), VX (N = 740), and eserine (N = 138) being the three most common. Individuals in the OCT group were exposed to anticholinergics (scopolamine [N = 534] and atropine [N = 444] being the two most common), cholinesterase reactivators (pralidoxime-2-chloride, being the most common, N = 607), psychochemicals (including lysergic acid diethylamide, N = 571), irritants (o-chlorobenzylidene malonitrile, being the most common, N = 1,366) and vesicants (mustard gas, N = 147), as well as drugs and innocuous chemicals (see Refs. 12 and 13 for further details).

The OCT comparison was added to the analysis because of a built-in selection bias and lack of a suitable control population. Prior to testing, volunteers had been screened for acceptable medical history, general intelligence, Minnesota Multiphasic Personality Inventory (MMPI) scores, and family history. Specifically, low general intelligence scores (below 90 or 80) were a reason for rejection as were certain patterns of MMPI scores. "Rules of thumb" were given for determining which MMPI score patterns were a cause for rejection, although "lacking a scientific basis for choosing, these [rules of thumb] represent advice rather than dogma."[14] For example, elevated MMPI scales (any 5 of Hs, D, Hy, Pd, Nf, Pa, Sc, Mc, or Si were above 65) were a cause for rejection as were Pd and Ma scores both above 65 if there was a history of "acting out."

Based on their health, the men were subsequently placed into one of four categories: A to D, with A the healthiest. The "A" rating indicated "OK for psychological testing"; a "B" rating "low-dose psychochemicals only"; a "C" rating "no psychochemicals"; and a "D" rating "equipment only".[14] Thus, healthier men were more likely to be exposed to active chemicals and less healthy men were more likely to be placed in the NCT control group. In fact, the NCT control group consisted only of subjects in category D. Because volunteers in the OCT group were exposed to a chemical agent and because healthier men were likely to be exposed to chemical agents, subjects in the OCT group were found to be healthier than men who were assigned to NCT. Furthermore, because OCT group members in this study were exposed to at least two agents (i.e., not just the one anticholinesterase), we believed they were likely also to be healthier than men assigned to ANTICHOL. Thus, ANTICHOL is "bracketed" between a control group likely to be less healthy (NCT) and one likely to be more healthy (OCT). Each comparative analysis described below included two sets of comparisons: ANTICHOL vs. NCT and ANTICHOL vs. OCT.

Statistical Analysis

Chi-square tests were used to compare interview response rates among the three comparison groups (Table I); characteristics of respondents vs. nonrespondents, based on data collected during the 1985 survey (Table II); and the demographics and military history of the three groups (Table III).

VA and National Death Index files were used to determine the cause of death for all decedents and proportional hazards analyses were conducted for total mortality (i.e., all causes of death), as well as for heart disease, cancer (i.e., all types), lung cancer, brain cancer, trauma (i.e., all types), suicide, and motor vehicle accidents (Table IV). Analyses of brain cancer and suicide were done because of their possible association with OP exposure and the expected similarities between the effects of OP and anticholinesterase exposure; the other specific causes of death were chosen simply because there were enough data to conduct the analyses. Hazards ratios were used to compare the relative survivals of ANTICHOL vs. OCT and ANTICHOL vs. NCT (Table IV). The time scale was time from the last testing at Edgewood until either death or the end of the follow-up period (i.e., December

TABLE I

SURVEY RESPONSE RATES

	ANTICHOL[a]	OCT	NCT	Total
Completed Telephone Interview	855 (63.9%)	871 (64.1%)	752 (56.8%)	2478 (61.6%)
Short form[b]	101 (7.5%)	75 (5.5%)	94 (7.1%)	270 (6.7%)
Not interviewed[c]	142 (10.6%)	151 (11.1%)	182 (13.7%)	475 (11.8%)
Not contacted[d]	45 (3.4%)	61 (4.5%)	49 (3.7%)	155 (3.9%)
Not located[e]	196 (14.6%)	201 (14.8%)	247 (18.7)	644 (16.0%)
Total	1339 (100%)	1359 (100%)	1324 (100%)	4022 (100%)

[a] Statistically significant difference between ANTICHOL and NCT (χ^2 = 17.75, 4 *df*, p = 0.001); no statistically significant difference between ANTICHOL and OCT (χ^2 = 6.60, 4 *df*, p = 0.16).

[b] Includes both short form mail questionnaires (N = 245) and partial telephone interviews (N = 25).

[c] Includes refusals and terminated interviews, subjects unable to be interviewed because of language or health problems, and deceased subjects.

[d] Includes wrong telephone numbers, fax numbers, answering machines, and nonreturned calls.

[e] No telephone number found.

TABLE II

COMPARISON OF SELECTED CHARACTERISTICS[a] OF RESPONDENTS AND NONRESPONDENTS

	Nonrespondents (N = 981)	Respondents (N = 1,831)
Education high school or less[b]	55.3%	45.6%
Hospital admission in previous 5 years[b]	35.5%	25.7%
Confined to bed during past month	19.7%	20.9%
General health excellent or good[b]	71.9%	83.2%
Regular smoker	82.5%	83.7%
Alcohol consumption (daily)		
Beer[b]	49.0%	41.9%
Wine	14.0%	11.0%
Whiskey[b]	30.0%	23.2%
Ever used drugs		
Amphetamines	17.0%	17.8%
Barbiturates/depressants	11.2%	9.7%
Cocaine	9.6%	8.9%
Heroin*	3.1%	1.6%
Marijuana	36.8%	36.9%

[a] Data on characteristics are taken from responses to the 1985 mail survey; thus, the analysis includes only volunteers who provided data in 1985.

[b] Statistically significant difference ($p < 0.05$) between nonrespondents and respondents.

TABLE III

DEMOGRAPHICS AND MILITARY HISTORY

	ANTICHOL (N = 855)	OCT (N = 871)	NCT (N = 752)
Mean age (years)	60.0	56.1[a]	58.1[a]
Caucasian race	88.7%	86.4%	81.2%[a]
College graduate	27.5%	30.0%	26.1%
Currently married	78.6%	77.1%	73.9%[a]
Household income $50,000 or greater	56.3%	62.5%[a]	55.1%
Vietnam theater service	21.6%	32.2%[a]	27.0%[a]
Exposed to combat situations	22.6%	31.9%[a]	27.3%
Reported participation in Edgewood testing	99.2%	99.7%	80.1%[a]
Ever had a civilian job with exposure to			
Defoliants/herbicides	8.6%	8.5%	8.2%
Insecticides	10.1%	9.3%	10.8%
Hazardous chemicals	14.7%	19.3%*	16.9%
Ever had military job where you handled			
Defoliants/herbicides	3.9%	4.2%	5.1%
Insecticides	3.4%	4.2%	4.7%
Hazardous chemicals	9.5%	8.2%	10.4%

[a] Statistically significant difference ($p < 0.05$) compared to ANTICHOL.

1998). Adjustments were made for age at testing as well as for exposure to psychochemicals and number of tests as described below.

The latter two adjustments were designed to compensate for the built-in selection bias and potentially different average health statuses of the three comparison groups. Unfortunately, the data provided by the Army did not indicate which of the four health categories (i.e., A–D) study participants had been assigned prior to testing; indeed, according to one source, these data had not even been written down because of their potential for misuse. Instead, the health fitness of the individual participants was characterized using two other sets of data: exposure to psychochemicals (i.e., lysergic acid diethylamide compounds, serynl [phencyclidine], and cannabis derivatives) and the total number of tests administered. The former was used because categories "A" through "C" were comprised only of individuals who were deemed suitable for psychochemical testing. The latter measure was included because a preliminary analysis of crude mortality showed that individuals who were exposed to more tests have experienced a lower mortality rate, which suggests that they were probably healthier and more likely to be placed in one of the healthier fitness categories.

Either χ^2 or t tests were used to compare both the long-term general health and neurological/psychological effects of exposure (i.e., the crude morbidity prevalence rates; Tables V and VI), and morbidity risk estimates were calculated by least-squares regression for the scaled outcomes (i.e., memory, attention, peripheral neuropathy, sleep disturbance, and somatization) and logistic regression for the categorical ones (depression, anxiety, vestibular dysfunction, children born with birth defects; Table VII). The risk estimates were adjusted for age at testing, race, and self-reported chemical exposure, as well as the two measures of health fitness described previously. Linear con-

TABLE IV

HAZARD RATIOS[a] COMPARING ANTICHOL WITH OCT AND ANTICHOL WITH NCT BY CAUSE OF DEATH

Cause of Death	ANTICHOL vs. OCT (N = 3,103)	ANTICHOL vs. NCT (N = 3,177)
All deaths	0.99 (0.79–1.23) [385]	0.82 (0.68–0.99) [516][b]
Heart disease	1.10 (0.70–1.73) [93]	0.77 (0.53–1.12) [136]
All cancer	1.18 (0.76–1.84) [102]	1.25 (0.85–1.85) [121]
Lung cancer	1.37 (0.66–2.83) [39]	1.56 (0.81–3.01) [44]
Brain	0.30 (0.03–3.59) [3]	0.18 (0.01–4.26) [3]
All trauma	0.90 (0.55–1.47) [71]	0.68 (0.41–1.13) [83]
Suicide	1.00 (0.37–2.74) [17]	0.91 (0.31–2.67) [18]
Motor vehicle accidents	1.09 (0.50–2.37) [28]	0.62 (0.29–1.34) [38]

[a] The hazard ratio for ANTICHOL vs. OCT expresses the relative risk of death for ANTICHOL subjects relative to OCT subjects; the hazard ratio for ANTICHOL vs. NCT expresses the relative risk of death for ANTICHOL subjects relative to NCT subjects. Ninety-five percent confidence intervals are in parentheses and number of deaths for a particular cause is in brackets.

[b] Statistically significant difference (i.e., 95% confidence limits exclude 1.0).

trasts were used in PROC GLM to compare the mean score responses of the least-squares regression, and dummy variables were used to compare the ANTICHOL group with each of the two comparison groups in the logistic regression. Calculations were performed using SAS.[15]

Lastly, health in relation to self-reported exposures (either civilian or military) to various types of chemicals outside of the Edgewood program was examined (data not shown), and risk estimates were calculated as described in the previous paragraph (Table VII). Because there were no specific associations between the different types of self-reported chemical exposures and the various health effects (the different types of self-reported chemical exposures are probably not well-differentiated because the survey questions were not specific enough), all types of self-reported exposures were combined into a single measure for the analyses. Likewise, all three comparison groups were combined for this analysis since they all have similar levels of self-reported chemical exposures (Table III). Although some dose data were available, they were not of sufficient quality for analytic use (see "Appendix").

Results

Survey response rates are shown in Table I. Overall, 62% of the volunteers who are still alive completed the telephone interview. The remainder either filled out a short form or completed only a partial interview (7%) or were contacted but not interviewed (12%), located but not contacted (4%), or not located (16%). Response rates were similar for the ANTICHOL and OCT groups (with completion rates of 63.9% and 64.1%, respectively; χ^2 = 6.60, 4 df, p = 0.16), while the NCT group had a significantly lower completion rate (56.8%; χ^2 = 17.75, 4 df, p = 0.001), attributable in part to lower location and higher noninterview rates. Overall, the completion rate for contacted subjects was 77%.

A comparison of selected characteristics of respondents vs. nonrespondents (i.e., based on data from the 1985 survey) is provided in Table II. Nonrespondents reported less education

TABLE V

GENERAL LONG-TERM HEALTH EFFECTS

	ANTICHOL (N = 855)	OCT (N = 871)	NCT (N = 752)
Do you have?			
Deafness in one/both ears	19.4%	18.4%	17.6%
Tinnitus/ringing in ears	36.3%	30.5%*	32.6%
Any trouble seeing when wearing glasses	8.0%	8.8%	7.7%
Repeated trouble with neck/back/spine	35.2%	34.2%	36.3%
Permanent stiffness/deformity of foot/leg/back	9.9%	9.8%	11.5%
Permanent stiffness/deformity of fingers/hand/arm	8.2%	7.8%	8.6%
Migraine/frequent headaches	11.1%	11.7%	13.6%
Has a doctor ever told you that you have?			
Thyroid problem	4.2%	5.0%	5.2%
Diabetes or "sugar" in the blood	14.8%	12.5%	17.6%
Cirrhosis of the liver	0.6%	<0.5%	1.1%
Cancer or leukemia	9.9%	8.9%	9.5%
Stroke	5.5%	4.0%	5.3%
Stomach/intestine problems	24.6%	21.8%	27.4%
Have you ever been diagnosed with?			
Parkinson's disease	<0.5%	<0.5%	<0.5%
Chronic fatigue syndrome	0.8%	1.6%	1.6%
Epilepsy	0.8%	0.8%	0.9%
Multiple sclerosis	<0.5%	<0.5%	<0.5%
Fibromyalgia	<0.5%	<0.5%	<0.5%
Carpal tunnel syndrome	7.4%	9.2%	8.4%
Nerve compression syndrome	2.5%	3.3%	4.3%[a]
Sciatica	11.2%	9.2%	10.6%
Diabetic neuropathy	2.7%	2.0%	3.5%
Other neurodegenerative disease	5.2%	5.7%	4.0%
How is your general health?			
Excellent	13.3%	17.3%	16.0%[a]
Very good	28.6%	28.1%	25.5%[a]
Good	35.6%	34.3%	32.8%[a]
Fair	16.2%	13.7%	16.3%[a]
Poor	6.3%	6.6%	9.5%[a]
Disabilities			
Activity limitation	17.7%	14.2%[a]	17.8%
Unable to work	25.3%	23.3%	25.8%
Limits vigorous activity	45.7%	42.4%	46.9%
Limits moderate activity	15.7%	14.5%	17.4%
Walking uphill or stairs	26.4%	21.4%[a]	25.1%
Bending, lifting, stooping	28.8%	25.1%	27.7%
Walking	9.0%	7.6%	9.5%
Eating, dressing, bathing, toilet	6.8%	6.4%	6.4%
Reproductive health outcomes			
Ever been a biological father?	78.9%	76.5%	76.7%
Mean number of live births	2.5	2.3	2.6
Number of birth defects (as proportion of live births)	6.4%	6.6%	6.3%

[a] Statistically significant difference (p < 0.05) compared to ANTICHOL.

TABLE VI

NEUROLOGICAL AND PSYCHOLOGICAL EFFECTS OF EXPOSURE

	ANTICHOL (N = 855)	OCT (N = 871)	NCT (N = 752)
Cognitive impairment (NIS)			
Attention scale			
Mean score	7.7	8.3	7.7
Raw score 14 or more (%)	14.9	20.1[a]	16.2
Memory scale			
Mean score	7.2	7.5	7.2
Raw score 14 or more (%)	11.7	13.5	12.5
Peripheral nerve symptoms (mean score)	2.6	2.5	2.7
Vestibular dysfunction			
Frequency of dizzy spells			
Every few months or less frequently (%)	51.8	50.2	51.5
Never (%)	48.2	49.8	48.5
Sleep Disturbance Index (mean score)	4.4	4.3	4.3
Somatization disorders (mean value)	5.15	5.00	5.33
Depression (%)	10.7	12.3	9.3
Generalized anxiety disorder (%)	2.9	3.0	2.4

[a] Statistically significant difference ($p < 0.05$) compared to ANTICHOL.

beyond the high school level; a higher rate of hospital admissions from 1980 to 1985; worse overall health; higher levels of beer and whiskey (but not wine) consumption; and a higher rate of heroin use (but not other drugs).

The demographics and military history of the three comparison groups are provided in Table III, with separate statistical comparisons of ANTICHOL vs. NCT and ANTICHOL vs. OCT. Although the groups are generally similar in composition, members of ANTICHOL are slightly older (mean age, 60 years) than those in either OCT (mean age, 56 years) or NCT (mean age, 58 years). This reflects the fact that different types of chemical agents were tested at different times: anticholinesterase experiments were among the earliest experiments conducted (see Table II of Ref. 1). Although virtually all members of the ANTICHOL and OCT groups reported that they had participated in chemical testing at Edgewood, a significantly lower proportion of NCT (80.1%) subjects reported such participation, perhaps because they were not exposed to active agents and thus did not consider themselves experimental subjects. Self-reported, nonexperimental civilian and military exposures to chemicals was generally similar across the study groups, except that fewer ANTICHOL subjects reported civilian exposure than did OCT subjects.

The results of the mortality rate analyses are provided in Table IV using hazard ratios, which are essentially estimates of relative risk of mortality. Based on the 95% confidence intervals of the hazard ratios, mortality rates of ANTICHOL are the same as for OCT and, with one exception, the same as for NCT. The exception is total mortality (i.e., all causes), which is significantly lower in ANTICHOL than in NCT (hazard ratio, 0.82; 95% confidence interval, 0.68–0.99). It is worth noting that without statistical controls for age and fitness, the differences in total mortality among ANTICHOL (14.5%), OCT (10.2%), and NCT (17.9%) would be highly statistically significant ($\chi^2 = 38.1$, 2 df, $p < 0.0001$). Although there are no statistically significant differences in cancer mortality among the groups, total cancer and lung cancer mortality are higher and brain cancer mortality is lower in ANTICHOL than in either OCT or NCT (Table IV).

The general long-term health effects are presented in Table V. There are few statistically significant differences between ANTICHOL and either control group. ANTICHOL has a higher rate of tinnitus than OCT and a lower rate of nerve compression syndrome than NCT. But the tinnitus finding may be age related, since the oldest group (i.e., ANTICHOL) has the highest prevalence rate (36%) and the youngest group (i.e., OCT) the lowest (31%). The distributions of general health are fairly similar across the study groups, although there is a statistically significant difference between ANTICHOL and NCT. Disability rates are similar, with members of the OCT having significantly lower rates of activity limitation and less trouble climbing stairs (again, this could be age related). Approximately 80% of the men

TABLE VII

RISK ESTIMATES (DIFFERENCES IN MEAN SCORES[a] AND ODDS RATIOS[b]) FOR SELECTED HEALTH OUTCOMES

	Experimental Exposure: ANTICHOL vs. OCT	Experimental Exposure: ANTICHOL vs. NCT	Nonexperimental Exposure
Memory subscale of NIS[a] (range, 0–32)	−0.34 (−0.87 to +0.19)	+0.31 (−0.31 to +0.93)	+0.92[c] (0.44–1.39)
Attention subscale of NIS[a] (range, 0–36)	−0.60[c] (−1.23 to −0.04)	+0.12 (−0.63 to +0.87)	+1.12[c] (0.55–1.70)
Peripheral neuropathy score[a] (range, 0–12)	+0.15 (−0.13 to +0.43)	+0.17 (−0.16 to +0.49)	+0.76[c] (0.51–1.01)
Sleep disturbance score[a] (range, 0–9)	+0.13 (−0.08 to +0.34)	+0.28[c] (+0.03 to +0.52)	+0.45[c] (0.26–0.64)
Somatization score[a] (range, 0–20)	+0.22 (−0.17 to +0.61)	+0.10 (−0.36 to +0.55)	+1.26[c] (0.91–1.61)
Depression[b] (SCID-based diagnosis)	0.89 (0.66–1.21)	1.11 (0.76–1.62)	1.39[c] (1.07–1.83)
Generalized anxiety disorder[b] (SCID-based diagnosis)	1.03 (0.58–1.83)	1.37 (0.68–2.74)	1.86[c] (1.15–3.02)
Vestibular dysfunction[b] (self-reported dizziness at least once a month)	1.09 (0.89–1.32)	1.07 (0.85–1.34)	1.41[c] (1.18–1.68)
Any children born with birth defects?[b]	1.17 (0.865–1.60)	1.10 (0.77–1.56)	1.36[c] (1.04–1.76)

[a] Mean difference in score adjusted for age at test, fitness, race, and self-reported chemical exposure; a risk estimate of "0" implies no difference between the two groups. Ninety-five percent confidence intervals in parentheses.

[b] Odds ratio adjusted for age at test, fitness, race, and self-reported chemical exposure; a risk estimate of "1" implies no difference between the two groups.

[c] Statistically significant difference (i.e., 95% confidence limits exclude 0.0 for a and 1.0 for b).

in each group reported having been biological fathers, with no significant differences in the mean number of live births or the proportion of live births with birth defects.

Long-term neurological and psychological effects of exposure are presented in Table VI. With the exception of a greater number of attention problems in OCT than in ANTICHOL, all other NIS scores are similar across groups. Vestibular dysfunction (frequency of dizzy spells), the mean number of peripheral nerve symptoms, and the mean sleep disturbance scores are similar across the three study groups. There are no statistically significant differences between ANTICHOL and either control group for any of the psychological effects, including somatization disorders, depression, and generalized anxiety. Additionally, rates of Illness Attitude Scale endorsements are virtually identical across the three groups (data not shown).

The risk estimates for both self-reported and experimental chemical exposures are summarized in Table VII. All estimates are adjusted for age at testing, health fitness (as described previously), and race. The experimental comparisons are between ANTICHOL and OCT and NCT, respectively, while the nonexperimental exposure comparison is between those who reported exposure to hazardous chemicals (regardless of group) and those who did not. There are only two statistically significant differences in risk estimates between ANTICHOL and either control group: attention problems are greater for OCT than ANTICHOL and sleep disturbance scores are higher for ANTICHOL than NCT. In contrast, all risk estimates for nonexperimental exposure are larger than their experimental counterparts. Clearly, men who self-reported chemical exposures (either civilian or military) outside of Edgewood have reported significantly greater health problems than men who did not report such outside exposure.

Discussion

The telephone survey was designed to collect information from representative samples of three study groups: ANTICHOL, OCT, and NCT. Although the response rates for ANTICHOL and OCT were similar, members of NCT were harder to locate and interview (Table I). The lower interview rate may be attributable, at least in part, to the fact that only about 80% of the NCT group members reported participation in the Edgewood program. The educational. health, and substance use differences between respondents and nonrespondents (Table II) are typical of surveys.

Demographic differences among respondents (Table III) from the three study groups may be attributable to the slight differences in age among the three study groups. Experiments with anticholinesterase agents occurred relatively early during the Edgewood program, and the subjects in ANTICHOL were, on average, 2 years older than the NCT subjects and 4 years older than OCT subjects. These age differences are also reflected in slight differences among the three groups in war era service and combat exposure. Although there are no large dissimilarities among respondents across study groups nor between respondents and nonrespondents, ANTICHOL and OCT appear to be less different with respect to baseline characteristics than ANTICHOL and NCT, as one would expect.

After adjusting for age and the two fitness factors described previously, there is only one statistically significant difference in mortality: ANTICHOL has lower overall mortality than NCT. Additionally, the risk of death because of cancer is proportionally slightly higher in ANTICHOL (17% higher than OCT and 31% higher than NCT), which parallels findings from VA hospitalization data in the original study. In that study, there were four VA hospital admissions for malignant neoplasms in ANTICHOL compared to one in OCT and none in NCT.[1] It is also worth noting that the adjustments for age and fitness yield risk estimates that differ radically from those based on crude, unadjusted data.

Morbidity differences between ANTICHOL and either control group are relatively small, and there is no clear, general pattern. For example, rates of tinnitus and activity limitation (Table V) are higher for ANTICHOL than OCT, but not NCT; this could merely reflect the age distributions of the three groups. There is only one statistically significant difference in neurological effects between ANTICHOL and either control group (attention problems; Table VI) and no significant differences in psychological effects.

Compared with published national data,[16] some of the rates in Table V are high. For example, the average national rates for tinnitus and diabetes among U.S. males are 7.7% and 5.7%, respectively, both of which are notably lower than the rates reported here. Approximately 59% of U.S. men between the ages of 45 and 64 years report excellent or very good health vs. 42% of ANTICHOL and NCT and 46% of OCT. In contrast, the rate of activity limitation in U.S. men between the ages of 45 and 64 years is 21% vs. rates of 17%, 14%, and 18% in ANTICHOL, OCT, and NCT, respectively. And the average rates for hearing and visual impairments (18.3% and 6.1%, respectively) among U.S. males between the ages of 45 and 64 years (the closest group for comparison) are comparable to those listed in Table V. Thus, although there may be some tendency to report higher rates of illness among survey respondents, this is not true of all measures of health.

There are only two statistically significant morbidity risk factor estimates associated with experimental exposure (Table VII): ANTICHOL has significantly fewer attention problems than OCT and significantly more sleep disturbance problems than NCT. The latter effect is consistent with reports of effects attributable to OP exposure.[6] Moreover, there is a uniform tendency for experimental exposure in ANTICHOL to be associated with higher (although not statistically significant) risks for all of the neurological and psychological health effects, except depression (compared with OCT) and the two NIS subscales (again, compared to OCT). Although the expectation was that the men in ANTICHOL would be healthier than the men in NCT but not as healthy as those in OCT, the only health measures for which this is true are the two NIS subscales.

In contrast, nonexperimental exposure is associated with higher, statistically significant risks for all of the major neurological and psychological health effects (Table VII). However, this general pattern may reflect a reporting bias; i.e., men who are ill may be more likely to recall having been exposed to chemical agents outside of their Edgewood program participation. Thus, it is unclear whether these pronounced effects of self-reported exposures are real. Indeed, even though the self-reported data are much more detailed than the record-based data of the 1985 study, the inability to adjust for recall bias is an important shortcoming of this study.

Also, and as noted in the initial study, the characteristics of the original testing program presented analytical problems with

respect to selection bias and multiplicity of chemical exposures. To deal with these issues, two measures of health fitness—exposure to psychochemicals and number of tests administered—were introduced to correct for some of these biases.

Other shortcomings include potential confounders such as age and race, which have also been accounted for with statistical adjustments. Finally, the large number of statistical comparisons present a possible "multiple comparisons" problem. However, by basing the risk estimate comparison on only eight of the study's primary end points, the number of comparisons in Table VII (18 total) has been substantially reduced.

Conclusion

In summary, there are few statistically significant differences in current health between ANTICHOL and either OCT or NCT, and the few differences in crude rates appear to reflect the slight age differences among the groups. After adjusting for age at testing, as well as initial fitness, race, and chemical exposure outside of Edgewood, ANTICHOL has a lower rate of attention problems than OCT and a higher rate of sleep disturbance problems than NCT. In contrast to these few and relatively small differences associated with experimental exposure, self-reported chemical exposure (either civilian or military) outside of the Edgewood program is significantly associated with all of the primary study end points. This suggests that if there are any true long-term health effects associated with experimental exposure to anticholinesterase compounds, they are probably smaller than the statistically significant effects attributable to self-reported, nonexperimental chemical exposure. But again, it is unclear whether these latter effects are a true consequence of nonexperimental exposure; they may simply reflect the possibility that volunteers who are currently ill are more likely to remember such exposure.

Appendix: Dose Data

Detailed information on doses in the Edgewood study is available from an earlier report.[7] Subthreshold doses were determined from animal studies and generally the intravenous route was preferred initially. Rarely did intravenous or intramuscular doses exceed 1.5 times the incapacitating dose, and although inhalation doses were higher, their potencies were lower. Acute effects were seen in some volunteers. For example, of a total of 246 subjects tested with sarin under various conditions, 25 were selected for a records review, with only 9 of them showing no acute symptoms (see "Appendix E" of Ref. 7 for more details).

Although there were no initial plans to use the data on experimental doses, we nonetheless undertook some investigations on the small number of subjects exposed to sarin. Of 287 such subjects, 67 had died before the second survey and only 147 of the remainder had useable dose data. Of these, only 67 responded to the second survey. Thus, the requirements of useable dose information and response to the second survey removed three-quarters of the original sample from consideration, a situation judged unacceptable. Moreover, sarin doses were measured differently for different kinds of exposure: intravenous exposures were measured in grams per kilogram of body weight, whereas aerosol exposures were measured in concentration time, i.e., chemical concentration in milligrams per cubic meter times length of exposure in minutes. Any analysis of the dose data would therefore need to find a way to reasonably combine the two types of exposure or to do separate analyses on even smaller groups.

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