1. AIMS

The Vietnam Era Study (VES) is a long-term follow-up of the study conducted in 1972 and 1974 by the Washington University School of Medicine (WUSM). The Original Study (P.I. Lee N. Robins) was aimed at assessing the extent of drug and other substance abuse and adjustment problems to civilian life among Vietnam War soldiers one year and three years after their departure from Vietnam. The major aims of the VES Phase III 25-year follow-up (R01DA09281) included: to complete in-person interviews with 830 Original Study respondents; to collect hair samples from all interviewed respondents who consented to hair sampling; to chart patterns of substance use over the 25-year period and factors predicting the course; to assess the long-term outcomes of substance abuse and trauma-related and other psychiatric disorders and their predictors; to examine patterns of health care utilization; and to validate self reports by drug-hair testing. This reporting period covers data analyses and death validity assessment corresponding to specific aims for Year 04.

2. STUDIES AND RESULTS

Remission from Drug Use (Attachment #1):
Patterns and psychiatric predictors of remission were analyzed using measures of remission obtained separately for sedatives, stimulants, marijuana, cocaine and opiates from year-to-year assessment. Among those who reported years of most frequent use since 1972, the mean duration per remission lasting 1 year or longer was lowest (10.5 years) for cocaine. The marginal success rate of continuous remission increased over time for cocaine, but the rate appeared stable for marijuana (Figure 1). Across 5 classes of drugs, more frequent use was detrimental to early remission. Alcohol dependence/abuse, childhood antisocial personality and war-time related post-traumatic disorder (PTSD) had negative impacts on early remission. A majority of illicit drug users (72-78% across 5 drugs) intentionally attempted to quit; however, most did not use traditional drug treatment when making the last quit attempt (no treatment from 65% for opiates to 90% for stimulants) (Table 1). Over 87% of remission without treatment was associated with continuous remission to present. A considerable portion of those maintaining remission reported the last year of most frequent use was prior to the last quit attempt. Health care was found to be underutilized. Less than 9% of drug users active during the past 5 years were treated for drug problems with hospitalization in this time period; 3% of current drug users received counseling/treatment in clinics during the past 6 months. The results suggest considerable unmet needs for chronic drug abusers. Comorbid PTSD increased the probability of psychiatric treatment, suggesting increased severity of psychiatric symptoms among drug users with PTSD may lead to treatment seeking. These results were presented at a poster session at the Annual Meetings of the College of Problems of Drug Dependence, Acapulco, Mexico in June, 1999.

Mortality: The data analyses to examine the patterns and predictors of mortality using available...
Continuing Work to Improve Prediction (Attachment #2): In conjunction with the P.I.’s Independent Scientist Award (K02 DA00221), newer techniques such as neural networks modeling were introduced. A manuscript using neural network multi-layer perceptron (MLP) modeling with information from Phase I mortality data has been accepted for publication in Psychological Assessment. Further exploration confirmed our suspicion that MLP outperforms logistic regression to a significantly greater extent when a substantial number of correlated measures are used as input variables. For example, when input variables consisting of 23 predictors were chosen separately for each of the pre-Vietnam, in-Vietnam and post-Vietnam periods, the value of the Complement of the Area Under the Curve (CAUC) was .04 using the MLP, compared to .21 using the corresponding multivariate logistic regression (Figure 2). The gain in prediction was attributable to a large extent to improvement in sensitivity, suggesting MLP’s suitability for extracting additional information from correlated variables in predicting the deceased. However, MLP’s performance was about the same as that of logistic regression when input variables were the reduced 8 predictors that were significant predictors at the p=.05 level across the three time periods. A total of 40 hidden neurons were required to maximize the prediction for the runs using 23 variables, while 5 hidden neurons were sufficient for the runs using 8 variables, indicating a complex architecture is merited when a large number of correlated input variables are used.

Mortality Validity Assessment: A sample of 32 deceased cohort members were chosen for informant interviews to obtain missing causes of death and assess the likelihood of effects of substance use on mortality, not apparent in death certificates. As of June 17, likely informants have been identified for all but two of these subjects. With 10 informant interviews completed, response from potential informants has been overwhelmingly positive. Missing causes of death were retrieved for two deceased subjects, including one heroin overdose death in 1972. In addition to the trauma from war experience, the prevalence of drug use in Vietnam and the lack of appropriate treatment were cited as problematic for the deceased subjects. The diagnosis of PTSD was reported for 4 cases, depression for 3 cases, illicit drug use for 6 cases, and drinking habit at time of death for 4 cases. Informant interviews appear to uncover substantial missing substance abuse and psychiatric information.

Assessing Generality of Suicidal Behaviors in VES Cohort (Attachments #3, #4): Comparative analyses were carried out using VES-III data and the National Longitudinal Alcohol Epidemiology Survey (NLAES) because a reliable general population estimate of increased risk for suicidal behavior among Vietnam veterans was lacking. Two issues were examined: whether or not Vietnam veterans are at an increased risk for suicidal behaviors when controlling for well-established demographic and psychiatric risk factors and protective factors; and whether or not parallel analyses using the VES database yield results similar to those of NLAES. In both datasets using multivariate logistic runs, Vietnam veterans were found to be at a significantly higher risk of lifetime suicidal attempt when demographic risk and protective factors were controlled for (Table 2). When substance use and depression were introduced, the Vietnam veteran variables still remained significant. However, Vietnam veteran status is not a significant predictor of suicidal behavior in the past year. The risk and protective factors are less predictive of past-year suicidal behavior across two datasets. The results indicate the existence of other factors such as situation-dependent protective factors and coping resources. The direction and magnitude of effects of the predictors are consistent across the two datasets. Where inconsistencies are found, some explanations can be offered. For example, the non-significant effect of age is due to the fact that the VES sample is more homogeneous with respect to age. The protective effect of being African American is clearly shown in the NLAES,
however, the effect is insignificant in VES-III. Continuing from earlier work, PTSD was also found to be a major predictor of lifetime and past-year suicide attempt in VES-III, independent of the effects of depression, physical illness and substance abuse. These and other results were presented at Epidemiology Seminar in the Department of Psychiatry in April, 1999.

### Table 2: Predictors of Suicide Attempt and Suicidal Behavior (Odds Ratios)

<table>
<thead>
<tr>
<th>Variable*</th>
<th>NLAES (N = 17,819, male) Lifetime</th>
<th>NLAES (N = 17,819, male) Past Year</th>
<th>VES-III (N = 839, male) Lifetime</th>
<th>VES-III (N = 839, male) Past Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Demographics</td>
<td>All Demographics</td>
<td>All Demographics</td>
<td>All Demographics</td>
</tr>
<tr>
<td></td>
<td>T score (P)</td>
<td>T score (P)</td>
<td>T score (P)</td>
<td>T score (P)</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>2.07** (p &lt; .01)</td>
<td>1.67** (p &lt; .01)</td>
<td>2.27* (p &lt; .05)</td>
<td>1.76 ** (p &lt; .1)</td>
</tr>
<tr>
<td>Drug use</td>
<td>2.72** (p &lt; .01)</td>
<td>1.21 (p &lt; .05)</td>
<td>3.18* (p &lt; .01)</td>
<td>NS</td>
</tr>
<tr>
<td>Depression</td>
<td>6.46** (p &lt; .01)</td>
<td>4.21** (p &lt; .01)</td>
<td>6.70** (p &lt; .01)</td>
<td>4.28** (p &lt; .01)</td>
</tr>
</tbody>
</table>

NLAES - National Longitudinal Alcohol Epidemiologic Survey (1992); VES-III - Washington University Vietnam Era Study - Phase III (1996-7). NS - p > .10; no asterisk - .05 < p < .1; * - .01 < p < .05; ** - p < .01. 1. Current year for NLAES; past year for VES. 2. For NLAES, current; for VES, not living with any of 4 most important people since 1972, and not married. 3. For NLAES, lifetime DSM-IV; for VES, since 1972, DSM-IV. 4. For NLAES, lifetime DSM-IV; for VES, since 1972. 5. Lifetime, meeting the DSM-IV criteria without suicidal behavior. 6. For NLAES, any of “attempt”, “suicidal thought”, “felt like dying”, or “thought of death”; for VES, any of “attempt”, “plan”, “frequent suicidal thought”.

**Predictors of Health Care Utilization (Attachment #5):**

A modified Anderson’s model was used to predict inpatient and outpatient VA use from the measures available in 1972/74 databases. Results were published in the Journal of Behavioral Health Services & Research.
Extending previous work, Drs. Virgo and Price are examining more recent utilization patterns of both private and public sectors and their predictors from self-reports obtained from VES-III interviews. Preliminary analyses indicate that the drug-positive status at discharge from Vietnam is still a powerful predictor of inpatient use in the past five years. However, physical illness and characteristics of health care systems also play a role in the use of inpatient facilities.

Cross-Validation of Self-Report and Hair Drug Testing: In collaboration with Drs. Bruce Goldberger and Susan Muldoon, a total of 613 hair samples are being analyzed to examine the validity of the past-three-month self-reported use of marijuana, cocaine, opiates, and methamphetamine, compared to results of hair drug testing. The impact of cut-offs imposed on the quantitative values of drug detection in hair was examined for both screening and confirmation tests. The ROC curves for cocaine and marijuana confirmation test drug values assuming self-report as the gold standard show that cut-offs recommended by Psychemedics (5+ ng cocaine/10 mg hair, >0 ng marijuana/10 mg hair) are indeed adequate (Figure 4). For both classes of drugs, sensitivity was maximized at these levels, while loss of specificity was minimized. Using the industry standard cut-offs, further preliminary analyses indicate a considerable under-reporting of cocaine use (5.2% self-report vs. 12.3% hair screening test), a slight under-reporting for marijuana and some over-reporting for opiates.

Kappas range from .293 for methamphetamine and .642 for marijuana in screening tests. Results are comparable between screening tests and confirmation tests (Tables 4a, 4b). A substantial proportion of those hair samples where quantity was not sufficient for testing (QNS) were self-report positives. This occurred because multiple confirmation testing for four classes of drugs led to an insufficient amount of hair for some polydrug users. There still appears to be unexplained false negatives in drug-testing, except for cocaine, which may be due to misclassification of drugs on the part of respondents, insufficient detection of THC in hair, or segmented use of hair samples for confirmation testing.

3. SIGNIFICANCE

The results indicate remission patterns appear rather stable over this 24-year period across 5 classes of drugs. Hardest to remit in this sample was marijuana. The success rate for continuous remission increased over time for cocaine, but the rate appeared stable for marijuana. Drug use frequency was most detrimental to early remission across 5 classes of drugs. Only sporadic negative impacts were observed for modes of administration, alcoholism, childhood ASP and PTSD from war-time trauma. A majority of chronic drug users identified in our study did not obtain help from traditional drug abuse treatment, for the most part. When a sample is ascertained from a community, spontaneous remission is the rule, not an exception, for major

Table 4. Preliminary Results Comparing Self-Report and Hair Testing of Drug Use Past 3 Months

<table>
<thead>
<tr>
<th>Table 4a. Screening Test Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>% Hair Positive</td>
<td>% Self Positive</td>
<td>% QNS</td>
<td>%QNS Positive</td>
<td>Spec</td>
<td>Sens</td>
<td>Kappa</td>
</tr>
<tr>
<td>Marijuana</td>
<td>556</td>
<td>19.1</td>
<td>16.9</td>
<td>9.3</td>
<td>15.8</td>
<td>94.9</td>
<td>70.0</td>
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<tr>
<td>Cocaine</td>
<td>612</td>
<td>12.3</td>
<td>5.2</td>
<td>.2</td>
<td>0</td>
<td>100</td>
<td>42.7</td>
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<tr>
<td>Opiates</td>
<td>613</td>
<td>1.5</td>
<td>2.6</td>
<td>-</td>
<td>-</td>
<td>98.5</td>
<td>77.7</td>
</tr>
<tr>
<td>Meth</td>
<td>613</td>
<td>2.3</td>
<td>2.0</td>
<td>-</td>
<td>-</td>
<td>98.7</td>
<td>28.6</td>
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</table>

<table>
<thead>
<tr>
<th>Table 4b. Confirmation Test Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>% Hair Positive</td>
<td>% Self Positive</td>
<td>%QNS</td>
<td>%QNS Positive</td>
<td>Spec</td>
<td>Sens</td>
<td>Kappa</td>
</tr>
<tr>
<td>Marijuana</td>
<td>542</td>
<td>13.3</td>
<td>15.7</td>
<td>13.2</td>
<td>64.3</td>
<td>93.6</td>
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</tr>
<tr>
<td>Cocaine</td>
<td>606</td>
<td>10.1</td>
<td>4.5</td>
<td>8.0</td>
<td>83.3</td>
<td>100</td>
<td>44.3</td>
</tr>
<tr>
<td>Opiates</td>
<td>613</td>
<td>1.3</td>
<td>2.6</td>
<td>0</td>
<td>-</td>
<td>98.3</td>
<td>75.0</td>
</tr>
</tbody>
</table>
of chronic drug users looks bleak. As they grow older, their needs for substance abuse and psychiatric care may continue to be undermet. Understanding their perception about the existing systems of care and how actual decisions regarding care are made may be important to improve the access to health care and detection of problems among chronic drug users.

Our continuing work in classification methods suggests that even those measures obtained over two decades ago have substantial power for predicting mortality. A traditional approach relying on significance level of predictor’s effect may perhaps have undermined the predictive ability of epidemiologic measures in the past. With two years of exploration, we now are able to specify the conditions under which neural networks surpass the ability of linear models for classification problems, and why such superior performance occurs.

The mortality validity assessment so far shows that informant interviews can be very helpful in retrieving information about the deceased. Our observations further suggest that prevalence estimates of substance abuse and psychiatric comorbidity obtained from surviving members are likely to be underestimated due to loss of information on the deceased.

Analyses of suicidal behaviors show that epidemiologic measures identified in the literature are indeed predictive of suicide attempts and other suicidal behaviors in this sample. Unique to this sample, however, appears to be a strong and independent impact of PTSD on suicidal behaviors. The impacts of risk and protective factors appear to be non-linear. Integration of qualitative information into quantitative analyses may prove useful in understanding the inner working of protective factors.

Preliminary analyses of hair drug testing results suggest a considerable under-reporting of recent cocaine use. For other drugs, discrepancies may be due to the quantitative nature of drug detection, misinformation of drugs taken by respondents, and instability of metabolites in hair.

4. PLANS

We plan to continue analyses related to remission, including examination of life events and interpersonal and occupational predictors of remission. Year-to-year assessment is available for these measures, therefore, Generalized Estimation Equation (GEE) modeling is particularly suitable. We also plan to examine the dynamics of remission regarding cessation sequence of drugs and alcohol, using log-linear models. These sets of analyses should result in two additional manuscripts (Part II, Part III).

The mortality validity assessment should be completed in the next few months. The results will be useful to revise the results on the causes of death. We currently are exploring new analytical schemes to integrate informant information to correct for estimates obtained from the surviving members. It is likely that this line of exploration will lead to a new submission of a small-size grant application.

Extending the considerable amount of work already done on suicidal behaviors, a manuscript is planned to report the generality of our findings to the general population and the nature of unique findings which may be attributable to traumatic experiences. Using the quantitative-qualitative approach, we expect our research to eventually fold into R01 activities involving qualitative interviews of subsamples of the VES cohort.

Examinations of health care utilization and hair drug testing results will continue as planned. Dr. Virgo will take a lead for the second manuscript preparation on health care utilization. Two manuscripts are planned for hair testing results: one reporting on validity of self-reports and the utility of drug hair testing; the other, predictors of discrepancies of self-report vs. hair testing. Dr. Muldoon, Dr. Goldberger and Dr. Edward Spitznagel, the project’s biostatistician, will work closely with the P.I. and her team.

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