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The effects of long-term abstinence on biochemical and hematologic markers for alcoholism

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The Effects of Long-Term Abstinence on

Biochemical and Hematologic Markers for Alcoholism

A Thesis Submitted to the Yale University

School of Medicine in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Medicine

by

Lynne Valencia Perry

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ABSTRACT

Researchers have tried for years to develop an
early biochemical screening test for alcoholism.
The most accurate method thus far is the quadratic
discriminant function analysis (QDA) model developed
by the Ryback group at the National Institute of Alcoholism
and Alcohol Abuse which uses 25 commonly ordered
laboratory tests to classify alcoholics with greater
than 90% accuracy. No other group has reproduced the
data. Most other researchers prefer linear discriminant
function analysis (LDA) because of wider availability.
Hence while discriminant function analysis (DFA) may
prove a useful tool in the diagnosis of
alcoholism, further questions need to be answered before
routine clinical practice.

We used DFA to study long-term abstinence in a
treatment program. We divided the N=125 alcoholics who
had all completed a 28-day alcoholism treatment program
several months ago into groups of abstainers (N=95) for at
least 6 months and nonabstaining controls (N=30).

Based on 7 predictive variables from the pre-
treatment blood data, LDA correctly predicted 69% of
the abstainers and 57% of the nonabstainers. QDA correctly
predicted about 76% of the abstainers and 79% of the
nonabstainers.

With 7 different variables to distinguish abstainers from nonabstainers based on current posttreatment data, LDA correctly predicted 79% of the abstainers and 67% of the nonabstainers. QDA correctly predicted 73% of the abstainers but only 40% of the nonabstainers.

The predictive accuracy would have been higher if we had been able to attract more equal numbers of nonabstainers. The posttreatment results suggest DFA is a useful tool to follow abstinence. The pretreatment results are interesting since all patients were drinking yet the model could detect the future abstainers. This ability to distinguish between the two groups in the pretreatment phase suggests the presence of a biological trait for alcoholism probably detected by serum biochemical markers.

INTRODUCTION

Alcohol has a wide sphere of influence on society. Medically, this influence is demonstrated by the involvement of alcohol in three of the major causes of death in the U.S. today (accidents, cirrhosis, suicide) and by the variety of pathophysiology alcoholism can cause. The reported hospital prevalence of alcoholism ranges from 9% to 70%. In one study, alcoholism was present in 25% of admissions to a large community hospital.[1] The 1980 census survey of VA hospitals (based on medical record data) found 26% of all beds occupied by veterans with alcohol problems (35% under 35 year old age group).[2]

Early recognition of alcohol abuse could reduce the multiple complications of alcoholism. Members of the medical profession have traditonally found early recognition difficult since psychological and social deterioration usually occur before significant biological abnormalities. In one large population of non-skid row alcoholics, 7% showed no evidence of physical disease on hospital admission and 33% had asymptomatic physical disease.[3] The presence of nonbiological deterioration before clinically evident biological abnormalities forces the physician to rely on psychosocial events to make the diagnosis. Hence effective communication in the doctor-patient relationship becomes more important, and the physican is required to use psychosocial data to make a

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medical diagnosis.   Not all physicians are prepared to do the latter.[4]

Many alcoholics cannot or do not willingly provide evidence of alcohol abuse or dependence, as defined by the Diagnostic and Statistical Manual for Mental Disorders, third edition.[5] Alcohol abuse is a pattern of pathological use for at least a month that causes impirment in social and occupational functioning. "Pathological use" refers to the need for daily use of alcohol for adequate functioning and an inability to cut down or stop drinking despite repeated attempts to control or reduce drinking.   Alcohol dependence includes the same criteria as for alcohol abuse and in addition includes the presence of tolerance or withdrawal.   The term alcoholism is more general, often encompassing both alcohol abuse and dependency.

In attempting statistically to classify alcoholics, the two main approaches have been the typological and the dimensional.   According to Skinner, the typological approach focuses on attempts to identify discrete categories of individuals, i.e. the personality types most susceptible to alcoholism, while the dimensional approach emphasizes quantitative relationships such as laboratory and clinical data.[6]   The former approach has been demonstrated to elicit important clinical and descriptive information about alcoholism but the predictive validity of this method has not been shown.

In alcoholism, the dimensional approach has been researched in depth over the past decade. From studies of single laboratory tests and diagnostic procedures to the multivariate approach (using several frequently abnormal blood tests to separate alcoholics from nonalcoholics), attempts have been made to develop an early biochemical screening test for alcoholism. In the landmark group of studies involving multivariate analysis, the Ryback group found that by using only a patient's 18 blood chemistry and 7 complete blood count values (to be listed later), they could correctly classify 100% of medical ward alcoholics, 94% of treatment program alcoholics, and 100%[7] of medical control nonalcoholics. These impressive data have been difficult to reproduce and have raised multiple questions about the use of discriminant function analysis as a diagnostic tool for alcoholism.[26,27,31]

We planned to further evaluate the mechanics of discriminant function analysis by studying abstinence in an alcoholism treatment program over time. The goal of the project was to identify a large population of abstinent and nonabstinent alcoholics still in treatment. We planned first to distinguish their current blood chemistry and complete blood count values from the lab values determined when they first entered treatment while drinking; second to distinguish current lab values of nonabstainers from their lab values when they initially entered the program; and third to distinguish current lab values of abstinent alcoholics from current lab values of

nonabstainers. All patients entered the 28-day West Haven Veteran Administration Medical Center's alcoholism treatment program at least four months prior to initiation of the project. All were in active alcoholism follow-up treatment when they participated in the current study.

REVIEW OF LITERATURE

Numerous attempts have been made to find a
biochemical marker for alcoholism. Elevated erythrocyte
mean corpuscular volume (MCV), often secondary to Vitamin
B12 or folate deficiency, common in alcoholics, provided
some promise as a marker for alcoholism. Unger and
Johnson in 1974 reported MCV greater than 95 cu. microns[8]
as suggestive of alcoholism. However, the elevated MCV
test is not sufficiently sensitive, since many alcoholics
who are iron as well as Vitamin B12 - or folate-deficient
(from poor dietary intake or chronic gastrointestinal
blood loss) may have a normal or low measured MCV.

More recently, since the serum gamma glutamyl
transpeptidase (GGTP) level was known to be elevated in
patients who consumed excessive amounts of alcohol, this
enzyme was considered as a marker for alcohol-related
liver pathology. GGTP values average two to three times
the upper limit of the reference interval in hospitalized
alcoholics and up to twice the upper limit in outpatient
alcoholics.[10] Yet the GGTP level was not found
clinically useful since it lacked specificity for
alcoholic liver disease and sensitivity for detecting
alcoholics. For example, GGTP is also elevated in all
cases of cholestasis, in some cases of advanced
nonalcoholic liver disease, in use of drugs which

stimulate hepatic endoplasmic reticulum in their metabolism (such as phenobarbital), in porphyria cutanea tarda as well as in both acute and chronic ingestion of alcohol.[11,12] In various studies the sensitivity for GGTP for alcohol-related liver pathology has been reported to range from 35 to 62%.[13] This wide differential and varying sensitivity create the potential for a medically unacceptable number of false positives and false negatives.

Another potential biochemical marker for alcoholism was the level of certain aminotransferases. The serum activities of alanine and aspartate aminotransferase are frequently elevated in alcoholism but may also be raised in myocardial infarction patients or patients with muscular complaints. Elevation of these levels reflects liver involvement in alcoholism and in the chronic alcoholic may eventually normalize presumably because of either increased individual resistance to alcohol toxicity or to decreased hepatic reserve of these enzymes. Clark has also reported that these enzymes are much less sensitive markers for alcoholism than GGTP.[10]

The single biochemical marker approach has largely been replaced with methods using combinations of variables to improve accuracy. One of the first multivariate biochemical markers for alcoholism to be studied was the ratio of plasma amino-n-butyric acid to leucine (AANB:L) as suggested by Shaw, Stimmel, and Liebner in 1976.[14]

Not only did this test lack specificity (in that abnormal elevations could be due to liver disease), but since the test requires specialized equipment, it does not follow the requirement that a screening test be relatively cheap and readily available.

Another group, Jankowski and Drum, in 1977 moved outside of the laboratory and suggested using a combination of positive clinical findings as variables to ident. alcoholics, such as history of seizures, hepatomegaly, and selected laboratory tests such as mean corpuscular volume greater than 95 cu. microns, serum glutamic oxalic transaminase greater than 32 mU/mL, and gamma glutamyl transpeptidase greater than 55 mU/mL.[15] Unfortunately, this approach did not overcome the problem of specificity to alcoholic liver disease noted previously. Papoz et al. in 1981, using GGTP and MCV in combination, correctly identified 75% of self-reported "heavy-drinking" (greater than 80 grams of pure alcohol a day) from a population of otherwise healthy men.[16] When the Ryback group used the same variables (GGTP, MCV) in their quadratic discriminant function analysis method to discriminate between a population of known alcoholics presenting for treatment and of nonalcoholic control outpatients in a venereal disease clinic, they found that they could correctly identify 94% of nonalcoholics but only 36% of the alcoholics.[17] Since the sensitivity rate approached that of the GGTP test alone, it was therefore unsuitable.

For the past several years with the advances in computer and statistical technology, researchers have been able to include a much larger number of variables in different combinations than previously possible in attempting to develop a screening test for alcoholism. Such multivariate methods have included multiple regression analysis and linear and quadratic discriminant function analysis. Discriminant function analysis (DFA) as a screening tool for alcoholism was first proposed in 1980 by Ryback, Eckardt, and Pautler at the National[7] Institute for Alcohol Abuse and Alcoholism. DFA is a complex mathematical form of pattern recognition whose purpose is to demonstrate whether two or more distinct conditions can be differentiated on the basis of multiple variables. Because of its ability to separate out fine differences between two groups, DFA has become popular with researchers studying other medical conditions such as anorexia nervosa, schizophrenia, and prognosis one year[18,19,20] after myocardial infarction.

The two basic types of DFA are linear (LDA) and quadratic (QDA). Although most medical researchers have used LDA, the Ryback group preferred QDA for several reasons. LDA assumes that variability of the discriminant variables (in this case the routinely requested laboratory tests) is the same for all subjects. LDA relies on mean differences to discriminate; QDA makes no assumption about the homogeneity of the discriminant variables for each

condition. Hence in studying a condition such as alcoholism with the potential for a high degree of variablility, according to Ryback, QDA is more appropriate. Other researchers have preferred LDA to QDA. Although distinguishing alcoholics from nonalcoholics may violate the LDA assumption of homogeneity, LDA still yields accurate results. In addition, since the calculations performed in LDA are simpler, they do not require the detailed memory and considerable processing power needed for QDA and are becoming available on micro- and mini-computers.

Several features of QDA may appear as drawbacks when compared to the more simple LDA but actually allow for more independence of each variable. For example, the QDA model is not simply a quadratic equation built by squaring the independent variables, but applies a complex set of different calculations for each variable.[21] The purpose of these calculations is to measure how closely the values of a new subject's independent variables resemble the mean values of the independent variables of previous alcoholic and nonalcoholic patients. In addition, since this is a quadratic function, distribution of all variables taken together approximate a bell-shaped curve and not a straight line as in LDA. With this assumption of multivariate normality, QDA may be more sensitive to nonnormality than LDA.[22] The required sample size must be larger in QDA than LDA to account for the larger numbers of parameters estimated in QDA from the greater amount of

observations made.

Since many alcoholics do not present for treatment until late in the course of alcoholism as noted above, significant biological abnormalities often have begun to occur. Accordingly, the Ryback group decided to use DFA based on routinely requested laboratory tests to attempt to differentiate alcoholics from nonalcoholics.

In 1980, Ryback et al. published the prototype for the use of QDA in screening for alcoholism. The first phase consisted of establishing subjects:

1. alcoholic patients in VA medical wards (N=63)
2. alcoholic patients who were parti-
   cipants in an alcoholism treatment
   program (N=412)
3. nonalcoholic medical inpatients (N=40)
4. nonalcoholic medical inpatients with
   biopsy-verified nonalcoholic liver
   disease who had been abstinent for   7
   at least one year prior to biopsy (N=12)

In selecting these groups, Ryback et al. satisfied the need for a heterogeneous patient population which would serve as a model population for the potential screening test. In any DFA model which will later be used as a template on which to apply new patient populations (e.g. as a screening device), it is important to find a "control" population as similar to the prospective screening population as possible.

The second phase tests the ability of the discriminating variables to identify correctly each patient as belonging to the alcoholic or nonalcoholic

group.   The   discriminating   variables   included   only
laboratory values commonly obtained in American hospitals:
total protein, albumin, calcium, phosphorus, cholesterol,
uric   acid,   creatinine,   total   bilirubin,   alkaline
phosphatase, lactic dehydrogenase, serum glutamic oxalic
transaminase, serum glutamic phosphoryl transaminase (all
included in the SMA-12); sodium, chloride, potassium, urea
nitrogen, carbon dioxide, glucose (the SMA-6); white blood cell
count, red blood cell count, hemoglobin, hematocrit, mean
corpuscular volume, mean corpuscular hemoglobin, mean
corpuscular hemoglobin concentration (the CBC).   In this
Ryback study, 100% of the medical ward alcoholics, 94% of
the   treatment   program   alcoholics,   and   100%   of
nonalcoholic medical inpatients were classified correctly
using all 25 parameters, above but less accurate results
were obtained when all parameters were not employed simultaneously.
For example, if the SMA-12 was used alone, 59% of the
combined alcoholic group and 90% of the nonalcoholics
were correctly identified. If the SMA-6 were used alone,
55% of the combined alcoholic group and 86% of the
nonalcoholics were correctly identified.   If the CBC were
used alone, 57% of the combined alcoholic group and 91% of
the nonalcoholics were correctly identified. Combinations
of the above yielded better results as expected:

        SMA-12 + SMA-6   67% combined alcoholic
                          92% nonalcoholic

        SMA-12 + CBC   72% combined alcoholic
                          96% nonalcoholic

SMA-6 + CBC   74% combined alcoholic
                95 % nonalcoholic6

The third phase involves the use of QDA to classify
prospectively new patients who were not members of the
original two groups. A new patient population including
an expanded control group (N=63) with 12 elderly patients
known to be nonalcoholic was then compared to the combined
medical ward/treatment program alcoholic group. A total
of 50% of the elderly patients were incorrectly classified
as alcoholic. The Ryback group hence states that the
model may not be applicable to persons over the age of
65.[7] They tend to blame the inaccurate classification of
the new patient population on age rather than on the
predictive ability of the model itself. As stated
previously age may indeed be a significant factor in
abnormal blood values, but the Ryback QDA model must be
testd on other predictive patient populations.

In 1982, the Ryback group published their results on
using the QDA model to distinguish between different types
of liver disease. 100% of nonalcoholics without overt liver
disease, 98% ofalcoholism treatment program alcoholics with
mild liver involvement, 96% of alcoholics with liver disease,
and 89% of nonalcoholics with liver disease were correctly
classified. On a predictive population of 18 patients
with biopsy-pending liver disease, 83% were correctly
classified as alcoholic liver disease patients later
proven by biopsy.[23] The data have improved over the 1980
data probably because the predictive population more

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closely resembled the test population in the latter study.

Although the Ryback group may appear to have successfully completed the projected three phases, their results have been difficult for other researchers to reproduce. In 1982 Beresford selected a socioeconomically and culturally diverse population of 104 patients from admissions to a county teaching hospital. 37% of the patients were defined as alcoholic based on results of a brief interview and the presence of DSM-III criteria for alcohol dependence. Using the two-tailed t-test and LDA on 29 variables (additonal variables included GGTP, triglycerides, and calculated anion gap), the Beresford group detected the 7 most discriminating variables (MCV, MCH, BUN, total protein, direct bilirubin, SGOT, SGPT). Then by LDA, 79% of the alcoholics were correctly classified (21% incorrectly classified) and 80% of the nonalcoholics were correctly classified (20% incorrectly classified).[24] These results compared favorably to earlier results of Drum and Jankowski and Eckardt and Feldman ranging from 70 to 96% correct classification of alcoholics and 52 to 79% correct identification of nonalcoholics in VA populations.[15,17]

Beresford's data appear to support Hansert and the Ryback groups's contention that compared to LDA, QDA provides a more accurate diagnosis.[25] One could also argue that the reason the Beresford research did not yield as good results as Ryback's QDA study is that the patient population may have been more diverse than in the Ryback

study. Patients in a county teaching hospital assigned the diagnosis of alcoholism by DSM-III criteria of alcohol dependence and a questionnaire are probably more heterogeneous than a VA population of alcoholic treatment program patients. Beresford's approach also demonstrates the utility of the more accesible and convenient LDA method.

After carefully identifying two separate populations (alcoholic and nonalcoholic), Schnitt and Dove in 1984 used both QDA and LDA models as potential screening methods for alcoholism. They found little difference in their results, despite the Ryback group's conclusion that QDA yields more accurate results. The patient population included N=163 patients: 78 relatively healthy ambulatory alcoholics hospitalized in a 28-day inpatient alcoholism treatment program and 85 outpatient nonalcoholics with Michigan Alcoholism Screening Test scores less than 2. The first model correctly classified 95% of the alcoholics and 92% of the nonalcoholics. Another model was built on half the subjects (N=82; 39 alcoholics and 43 nonalcoholics) and was then tested on the other half of the sample. This model correctly classified 86% of the alcoholics but only 60% of the nonalcoholics. Through these results, the Schnitt group recognized the difficulty in testing the Ryback method. The loss in predictive accuracy of the second model compared to the first suggests the first model tends to overstate the predictive accuracy while the

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second underestimates the predictive accuracy. One reason the first model overstated the predictive accuracy could have been because of the homogeneous nature of the nonalcoholic control group which enhanced the discriminating ability of the equations. A second reason is "shrinkage," the well-known loss of predictive capacity in DFA when a model is applied to new subjects.[35]

In another Schnitt group study (unpublished data), 92 known alcohol-dependent patients were run through the larger model. All but 6 were correctly classified. Three of those incorrectly classified as nonalcoholic had either severe diabetes mellitus or severe hypertension. These patients too closely resembled the treated hypertensive control subjects for the model to discriminate. This points out the ability of a DFA model to use any abnormal variables in the control group as discriminators. The authors concluded that a model built on hypertensive controls would only be suitable to discriminate alcoholics from nonalcoholics in a hypertension clinic setting and would not have broader applicability.

Other researchers such as Freedland, Frankel, and Evenson have found that linear discriminant models generally outperform quadratic models.[27] They attribute the impressive Ryback findings to the use of identical samples for derivation and classification purposes. The Freedland group's derivation population sample included N=407 alcoholics and N=1068 nonalcoholic psychiatric patients. Assignment was performed randomly by

statistical software. The best results were obtained with an equal stepwise LDA model which used SGOT, calcium, albumin, inorganic phosphate, and BUN together as the best predictors. In the cross-validation sample, 59% of the alcoholics and 72% of the nonalcoholics were correctly classified by stepwise LDA. QDA correctly classified 32% of the alcoholics and 88% of the nonalcoholics creating a high false-negative rate.

Hawkins, Silsby et al. concur with the Freedland group that LDA has greater promise than QDA as a screening test for alcoholism.[28] Their all-male patient population included N=252 clinically confirmed alcoholics and N=142 nonalcoholic controls selected from the general medical population. On this derivation population, the quadratic yielded better results: 94% of the alcoholics and 81% nonalcoholics by QDA vs. 79% alcoholics and 81% of the nonalcoholics by LDA were correctly predicted. On the validation sample of 56 alcoholics and 36 medical nonalcoholic controls, the LDA yielded more accurate results, correctly predicting 77% of the alcoholics and 81% of the nonalcoholics by LDA vs. 80% of the alcoholics and 57% of the nonalcoholics by QDA. Note that the linear analysis was done with 11 of the most predictive blood chemistry variables - calcium, MCV, inorganic phosphorus, carbon dioxide, total bilirubin, uric acid, triglycerides, cholesterol, lactic dehydrogenase, SGOT, and albumin.

Although the Freedland and Hawkins groups had

different types of patients, population sizes, and different predictor variables, they both found that LDA generally outperformed QDA on predictive populations. The slightly less accurate results of the Freedland group may be attributed to the much larger sample size (N=1385 vs. N=92) of the predictive population.

The Ryback group has also used their QDA model in a study on the effect of abstinence on biochemical tests. With an all-male patient population of N=412 alcoholism treatment program alcoholics without significant medical disease, N=63 alcoholic inpatients with clinically apparent complications of alcoholism, and N=41 nonalcoholic inpatients without a history of alcohol-related problems, QDA was applied to the 25 commonly ordered laboratory tests used in previous Ryback studies. 100% medical ward alcoholics, 95% treatment program alcoholics (N=274) and 100% nonalcoholics were correctly identified. In the random population of an additional N=138 alcoholism treatment program patients, 96% were correctly classified and after 27 days of hospitalization, 94% were still classified as alcoholic despite improvement in hematologic and hepatic parameters.[29] Classification remained unchanged after 7 and 24 months for the 15 abstaining patients regardless of the fact that there was no obvious and persistent medical complication detected from blood values. When compared to N=39 patients who continued to drink, the abstainers did have improved blood

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values.

The Ryback study on abstinence suggests a new role
for DFA in alcoholism but did not have a large enough
sample of long-term abstinent alcoholics to make
conclusions about abstaining alcoholics compared to
nonabstaining alcoholics. The purpose of the present
study was to attempt to identify a large enough population
of abstinent alcoholics and characterize them by the
statistical methods described above.

METHODS

Subjects

The two experimental groups consisted of 125
sequentially approached relatively healthy ambulatory
alcoholics in treatment at the West Haven Veteran
Administration Medical Center Alcoholism Ambulatory Service, an
outpatient follow-up clinic in the Alcoholism Program.
These patients met the following criteria: 1. clinically
evident alcoholism (alcohol dependence as defined by DSM-
III criteria); 2. voluntary entrance into and participation
in a 28-day intensive alcoholism inpatient treatment unit
at least 4 months prior to data collection; 3. successful
completion of the inpatient program and participation in
ongoing outpatient follow-up treatment.

Each patient completed a questionnaire (see Appendix 1)
which asked specific information about demographics of
drinking such as age of first drink, age of first alcohol-
related problems, first-degree relatives who were
alcoholic, smoking history, brief medical history,
quantity and frequency of drinking since completion of the
inpatient program and more than six months ago, within the
past six months until a month ago, and within the last
month.   The last part of the test was designed after the
Veteran's Alcoholism Screening Test.   This test includes
the 25 basic questions asked in the Michigan Alcoholism
Screening Test but classifies scores into groups of within

the past year, within the past 1 to 5 years, and more than 5 years ago in addition to the standard MAST classification. With its specific reference to time periods, the VAST provides a greater opportunity to separate actively drinking from abstinent alcoholics. While soewhat controversial, the MAST has been reported to provide the highest levels of sensitivity and specificity (when ease of administration is considered) of any screening test so far developed.[31]

Questionnaire information about abstinence was corroborated by the subjects' primary clinicians in the alcoholism outpatient clinic; these clinicians had followed their patients from the time of successful completion of the 28-day intensive inpatient program. Clinicians were considered to have reliable impressions of the patients' drinking patterns. In addition, we contacted 100 of the participants by telephone to clarify answers on the questionnaire.

From questionnaire data and clinician confirmation, the patients were classified as either abstainers or nonabstainers from alcohol. Group 1 (N=95) included alcohol abstainers who had been dry for at least six months prior to the time their bloods were drawn for this study. Group 2 (N=30) included nonabstaining controls who continued to drink at least once in the past six months prior to the time their follow-up blood samples were drawn for this study. Ten participants (N=12) spent time in a halfway house after inpatient alcoholism treatment.

Patients consumed no alcohol within the three days prior to the day blood was drawn for this study. Numerous attempts were made to recruit more participants in order to increase the number of nonabstainers; this instead attracted mainly abstainers.

Along with the questionnaire, the medical records of each patient were inspected to form an accurate medical profile and obtain blood values upon entrance into the inpatient program. For alcoholics, most participants were relatively healthy. There were 23 treated hypertensives, 6 diabetics (2 insulin-dependent), 5 patients with biopsy-proven alcohol-related cirrhosis, 1 patient with biopsy-proven nonalcoholic cirrhosis. According to patient report by questionnaire, 45 patients (including the 6 liver disease patients above) had been told they had "liver trouble or cirrhosis." By questionnaire report, 64 patients recalled having had "delirium tremens, DT's, severe shaking, or had heard voices or seen things that really weren't there." Medical records indicated 5 patients had a history of withdrawal seizures.

With respect to psychiatric history, 10 patients were currently being medically treated for depression and 2 patients had been diagnosed as having a bipolar disorder. No other psychiatric Axis I disorders were noted.

Blood analysis

Blood samples were obtained from all patients to determine serum levels of the SMAC (18 values at the West Haven VA) and the complete blood count. The following blood chemistry values were used because of their standard inclusion in the SMAC profile. Along with the CBC, these are the usual tests obtained to accompany the history and physical examination in hospital admissions. A semiautomatic blood cell multiple counter was used to determine the white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration. The SMAC Technicon, an automated multiple analysis computer, was used to determine total protein, albumin, calcium, phosphorus, cholesterol, uric acid, creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, lactic dehydrogenase (LDH), serum glutamic oxalic transaminase (SGOT), serum glutamic phosphoryl transaminase (SGPT), sodium, chloride, potassium, urea nitrogen (BUN), carbon dioxide (CO_2), and glucose.

Values obtained on the day of entry to the inpatient program (pre-TSE) were obtained from the medical record; all subjects were drinking alcoholically. Post-TSE values were obtained when all patients had been abstinent for at least 3 days prior to venipuncture.

Statistical Analysis

The data were coded, keypunched, verified, and screened for errors. Basic statistics were first obtained for all data. This included determinations of frequencies and means for the blood values listed above as well as for the questionnaire data. Correlation matrices were then determined to find relationships between questionnaire data and current laboratory values.

Multivariate analysis may include all 28 variables as in the Ryback study[7,17,22] or the least significant predictors may be left out as in the Beresford[24] and Freedland[27] studies. After deciding whether or not to leave out non-predictive variables, according to Schnitt and Dove, one must then decide whether to include statistically significant but clinically spurious variables.[32] This is the choice of the investigator since discriminant function analysis (i.e. LDA and QDA) can only distinguish between two groups and not give information about clinical relevance of these distinctions. We decided to keep these variables in the model upon the recommendation of the Schnitt group and because the issue of abnormal laboratory values secondary to alcoholism is still being researched.

Stepwise regression was performed to find the most discriminating parameters of the pre-TSE and post-TSE blood data. Using LDA and then QDA, the diagnostic accuracy of the most discriminatory variables was tested.

The models were developed with the quadratic discriminant analysis program of the SAS-82 package supplied by the SAS Institute, Inc. of Raleigh, North Carolina on the IBM 4341 at the Yale Computer Center. This technique was used because it has been shown through previous studies described above to provide the best discrimination in similar analyses.

The prior probabilities were set at .50 and the procedure terminated when a reasonable model was obtained that separated abstainers from nonabstainers. One model separated pre-TSE values of abstainers from pre-TSE values of nonabstainers. Note that all patients were drinking pre-TSE and the term "abstainer" refers only to post-TSE drinking history. Another model separated post-TSE values of abstainers from post-TSE values of nonabstainers. Paired and unpaired t-tests were performed to compare pre-TSE values of abstainers to post-TSE values of abstainers; pre-TSE values of nonabstainers to post-TSE values of nonabstainers; and pre-TSE values of both groups to post-TSE values of both groups.

RESULTS

Of 125 participants, all were male except for one nonabstaining female. The mean age for this study was 54.1 ($\pm$10.2) years with a range from 31 to 84. There were no statistically significant differences in ages between the abstainers and nonabstainers. Age tended to correlate most strongly (p<.001) with later onset of alcohol-related problems; that is, older subjects had a later-life onset of alcohol problems than did younger patients. This may be a spurious finding. Older patients tended to have their first drink later in life and to drink primarily hard liquor (p<.01). Other statistically important age-related data of the p<.05 level were: older patients tended to smoke fewer packs of cigarettes, have fewer alcoholic family members, take more prescribed medications, and have lower VAST scores in the past year. With respect to individual blood values, older patients had higher alkaline phophatase levels (p<.01), lower albumin (p<.01), higher BUN (p<.05), and lower cholesterol (p<.05).

In the next correlation matrix, abstainers (76%) were compared to nonabstainers (24%). Continuing to consume alcohol was most strongly correlated (p<.001) with having drunk between one and six months ago (rather than earlier or more recently) and as expected, higher VAST scores in the one year and 1-5 year categories.

The average time out of TSE was 58.3 ($\pm$39.1) months. The more recently a subject had completed the alcoholism inpatient program, the more likely that veteran was to be a nonabstainer. These sets of findings are relatively expectable; the clinical setting from which subjects were drawn has found that patients who remain in therapy more than 6 months are less likely to resume drinking. Those both abstinent and in therapy for more than one year are increasingly unlikely to return to drinking.

Blood data

Significant blood test correlations were that nonabstainers tended to have higher SGOT levels ($p<.01$), MCH ($p<.05$), LDH ($p<.05$), SGPT ($p<.05$), and MCV ($p<.10$) levels in the post-TSE blood data. The higher MCH and the higher SGOT,SGPT, and MCV levels of nonabstainers over abstainers are consistent with earlier findings of the Eckardt group.[33] That prospective study was designed to determine the effects of posttreatment alcohol consumption by 56 male alcoholics (abstainers N=17) seven months after participation in a 28-day alcoholism treatment program.

For the multivariate analysis of laboratory values, blood data was divided into 2 groups: pre-TSE and post-TSE. Pre-TSE blood data was available for only N=114 participants (86 later became abstainers, 28 continued to drink). The mean values for the SMA-18 and CBC profiles are located in Table 1. Stepwise regression revealed 7

statistically significant variables (i.e. accounting for >1% of the variance): BUN, MCHC, total cholesterol, total protein, potassium, chloride, inorganic phosphorus. These variables accounted for a total of 18% of the variation in the pre-TSE blood data (see Table 2) and are listed in order of their discriminating abilities.

LDA of pre-TSE values of abstainers and nonabstainers was performed based on the 7 variables deemed significant by stepwise regression. Of 114 patients, 69% were correctly classified as belonging to the abstainer group (i.e. they were correctly predicted to become abstainers later in time) and 57% were correctly classified as nonabstainers. QDA correctly classified 76% of these patients who later became abstainers and 79% of those patients who continued to drink (see Table 3).

Post-TSE blood values were obtained for all (N=125) participants. This included 95 abstainers and 30 nonabstainers. Stepwise regression of post-TSE data revealed 7 completely different statistically significant variables: SGOT, MCH, SGPT, RBC, hemaglobin, MCV, and hematocrit. These variables accounted for 21% of the variation in the post-TSE blood data (see Table 4) and are listed in terms of their discriminating abilities.

With these 7 statistically significant variables, LDA of post-TSE values of abstainers and nonabstainers was performed and 79% of the abstainers were correctly identified as well as 67% of the nonabstainers. When QDA was applied to the 7 variables, the results changed

dramatically: 93% abstainers were correctly identified

while only 40% of nonabstainers were correctly identified

(see Table 5).

Table   1. - Biochemical   and   Hematologic   Values   -
        Means ± Standard Deviations

Test	Pre-T5E (N=114) Mean +/- S.D.	Post-T5E (N=125) Mean +/- S.D.	Reference
Chloride mEq/L	100.4 ± 4.4	103.4 ± 3.4	97-108
Carbon dioxide mEq/L	28.1 ± 2.6	29.1 ± 2.7	24-30
Potassium mEq/L	4.2 ± 0.5	4.2 ± 0.4	3.5-5.0
Sodium mEq/L	140.6 ± 3.1	141.2 ± 3.1	135-145
BUN mg/dL	13.3 ± 4.2	14.2 ± 4.2	8-23
Glucose mg/dL	106.3 ±42.3	108.6 ±45.4	70-130
Tot. protein g/dL	7.2 ± 0.6	6.9 ± 0.4	6.7-8.7
Albumin g/dL	4.3 ± 0.4	4.5 ± 0.3	3.9-5.0
Calcium mg/dL	9.7 ± 0.5	9.6 ± 0.4	9.0-10.5
Phosphorus mg/dL	3.6 ± 0.7	3.4 ± 0.5	2.4-4.5
Tot. chol. mg/dL	208.3 ±46.7	216.5 ±46.9	130-270
Uric acid mg/dL	5.7 ± 1.3	6.1 ± 1.4	4.2-8.2
Creatinine mg/dL	1.0 ± 0.3	1.1 ± 0.2	0.8-1.5
Tot. bili. mg/dL	0.9 ± 1.0	0.5 ± 0.2	0-1.6
Dir. bili. mg/dL	0.3 ± 0.5	0.1 ± 0.1	0-0.3
Alk. phos. mU/ml	95.0 ±33.5	87.8 ±36.6	35-100
LDH mU/ml	204.5 ±65.5	158.1 ±35.4	110-220
SGOT mU/ml	60.9 ±66.5*	23.6 ±17.1	0-41
SGPT mU/ml	54.3 ±67.7*	27.2 ±30.8	0-41
WBC 1000/cu mm	7.7 ± 2.7	8.0 ± 2.3	4.8-10.8
RBC million/cu mm	4.6 ± 0.6*	4.8 ± 0.4	4.7-6.1
Hemoglobin g/dL	14.8 ± 1.8	14.8 ± 1.2	14-18
Hematocrit vol %	43.8 ± 5.3	44.1 ± 3.6	42-52
MCV cu microns	95.7 ± 6.4*	93.0 ± 4.4	80-94
MCH pg	32.3 ± 2.3*	31.3 ± 1.8*	27-31
MCHC g/dL	33.8 ± 1.1	33.7 ± 0.9	32-36

* = items where group means exceed reference values

Table 2. — Pre-TSE Predictive Variables (N=114)

Variable	$*r^2$	cumulative r^2
BUN	4	4
MCHC	5	9
Total cholesterol	2	11
Total protein	3	14
Potassium	1	15
Chloride	2	17
Phosphorus	1	18
Total	18%	18%

$*r^2$ = % of explained variation

Table 3. — Multivariate Analysis of Pre-TSE Blood Data

Classification	LDA	QDA	N
ABS correctly predicted	69%	76%	
ABS error	31%	24%	86
NABS correctly predicted	57%	79%	
NABS error	43%	21%	28

ABS — alcohol abstainers for at least the past 6 months (Group 1)
NABS — nonabstainers from alcohol (Group 2)

Table 4.- Post-TSE Predictive Variables (N=125)

Variable	$*r^2$	cumulative r^2
SGOT	8	8
MCH	2	10
SGPT	3	13
RBC	1	14
HGB	5	19
MCV	1	20
HCT	1	21
Total	21%	21%

$*r^2$ = % of explained variation

Table 5. - Multivariate Analysis of Post-TSE Blood Data

Classification	LDA	QDA	N
ABS correctly predicted	79%	93%	
			95
ABS error	21%	7%	
NABS correctly predicted	67%	40%	
			30
NABS error	33%	60%	

ABS - alcohol abstainers for at least the past six months (Group I)
NABS - nonabstainers from alcohol (Group 2)

While the mean values of all tests but the MCH returned to be within the reference values in the post-TSE sample, unpaired and paired t-tests were performed to compare more accurately the total pre-TSE blood data to post-TSE blood data. Statistically significant changes in mean values are noted in Table 6. The decreases in bilirubin, alkaline phosphatase, LDH, SGOT, SGPT indicate improving hepatic function while the increase in red cell count and decreases in MCV and MCH indicate hematologic improvement. SGOT and SGPT normalized (i.e. decreased to be included in the reference value range) in comparing pre-TSE to post-TSE blood data. For the hematologic values, MCH improved but remained out of the reference value range while red cell count increased and MCV decreased so that they were within reference value range.

Unpaired and paired t-tests were then performed to compare pre-TSE blood data of abstainers (N=86) to post-TSE blood data of abstainers (N=95). Statistically significant changes are noted in Table 7. These data represent significant hepatic and hematologic improvement for the abstainers. The increase in urea nitrogen may reflect the effect of age as suggested by the age correlation matrix. The mean values for the abstainers pre-TSE and post-TSE are shown in Table 8. SGOT and SGPT normalized. For the hematologic values, MCH improved but the mean remained slightly out of reference value range

normalized.   For the hematologic values, MCH improved but the mean remained slightly out of reference value range while red cell count and MCV normalized to within the reference value range.

Table 6.   — Mean Differences in Pre-TSE and Post-TSE Blood
           Data as Determined by Paired T-Test

Variables	Mean diff.	p-value	no signif. change
Chloride	3.0	p<.001	Potassium
Carbon dioxide	1.0	p<.001	Sodium
Tot. protein	-0.3	p<.001	BUN
Albumin	0.2	p<.001	Glucose
Calcium	-0.1	p<.05	Tot. chol.
Phosphorus	-0.2	p<.05	Creatinine
Uric acid	0.3	p<.01	WBC
Tot. bili.	-0.4	p<.001	Hemoglobin
Dir. bili.	-0.2	p<.001	Hematocrit
Alk. phos.	-7.4	p<.10	MCHC
LDH	-47.6	p<.001	
SGOT	-36.6	p<.001	
SGPT	-25.9	p<.001	
RBC	0.2	p<.01	
MCV	-2.5	p<.001	
MCH	-0.9	p<.001	

For units, reference values, please refer to Table 1.

Table 7. — Mean Differences in Pre-TSE and Post-TSE Blood
Data of Abstainers as Determined by Paired T-Test

Variables	Mean diff.	p-value	no signif. change
Chloride	3.6	p<.001	Potassium
Carbon dioxide	1.2	p<.01	Glucose
Sodium	0.9	p<.06	Total chol.
BUN	1.2	p<.05	Creatinine
Tot. protein	-0.3	p<.001	Alk. phos.
Albumin	0.2	p<.001	WBC
Calcium	-0.2	p<.05	Hemoglobin
Phosphorus	-0.2	p<.01	Hematocrit
Uric acid	0.3	p<.06	MCHC
Tot. bili.	-0.4	p<.001	
Dir. bili.	-0.2	p<.01	
LDH	-53.0	p<.001	
SGOT	-39.3	p<.001	
SGPT	-27.7	p<.001	
RBC	0.2	p<.001	
MCV	-3.3	p<.001	
MCH	-1.2	p<.001	

For units, reference values, please refer to Table 1.

Table 8. — Mean Values ± Standard Deviations for Abstainers
Pre-TSE and Post-TSE

Test	ABS Pre-TSE (N=86)	ABS Post-TSE (N=95)	Reference
Chloride mEq/L	100.0 ± 4.3	103.6 ± 3.3	97-108
Carbon dioxide mEq/L	28.0 ± 2.6	29.2 ± 2.8	24-30
Potassium mEq/L	4.2 ± 0.6	4.3 ± 0.4	3.5-5.0
Sodium mEq/L	140.5 ± 3.0	141.3 ± 3.1	135-145
BUN mg/dL	12.8 ± 3.5	14.3 ± 4.2	8-23
Glucose mg/dL	107.3 +45.8	110.7 +46.8	70-130
Tot. protein g/dL	7.2 ± 0.6	6.9 ± 0.4	6.7-8.7
Albumin g/dL	4.3 ± 0.4	4.5 ± 0.3	3.9-5.0
Calcium mg/dL	9.7 ± 0.6	9.5 ± 0.4	9.0-10.5
Phosphorus mg/dL	3.6 ± 0.7	3.4 ± 0.5	2.4-4.5
Tot. chol. mg/dL	205.7 +41.8	214.9 +47.1	130-270
Uric acid mg/dL	5.7 ± 1.4	6.0 ± 1.4	4.2-8.2
Creatinine mg/dL	1.1 ± 0.4	1.1 ± 0.2	0.8-1.5
Tot. bili. mg/dL	0.9 ± 1.0	0.5 ± 0.2	0-1.6
Dir. bili. mg/dL	0.3 ± 0.5	0.1 ± 0.1	0-0.3
Alk. phos. mU/ml	93.8 +33.4	89.0 +40.0	35-100
LDH mU/ml	206.4 +62.3	154.4 +35.2	110-220
SGOT mU/ml	60.0 +61.8*	20.9 +13.4	0-41
SGPT mU/ml	51.5 +64.9*	24.2 +24.7	0-41
WBC 1000/cu mm	7.9 ± 2.8	7.9 ± 2.4	4.8-10.8
RBC million/cu mm	4.5 ± 0.6*	4.8 ± 0.4	4.7-6.1
Hemoglobin g/dL	14.7 ± 1.8	14.8 ± 1.2	14-18
Hematocrit vol %	43.6 ± 5.3	44.0 ± 3.6	42-52
MCV cu microns	96.2 ± 5.8*	92.6 ± 4.2	80-94
MCH pg	32.4 ± 2.0*	31.1 ± 1.7	27-31
MCHC g/dL	33.6 ± 1.1	33.6 ± 0.9	32-36

* = items where group means exceed reference values

Unpaired and paired t-test analysis of nonabstainers pre-TSE (N=28) and post-TSE (N=30) revealed considerably less significant mean differences than that of the abstainers. The statistically significant changes are noted in Table 9. As expected, these data do not reflect the hepatic and hematologic improvement noted for the abstainers since these patients continued to drink. The nonabstainers consumed an average of 10.9 ($\pm$ 10.3) ounces of pure alcohol daily during each drinking episode. This amount represents roughly 3 six-packs of beer or 2 pints of 80 proof "hard" liquor such as gin, whiskey, and vodka. Compared to the abstainers, the nonabstainers also showed a significant decline in LDH ($p<.01$) but less significant decreases in total bilirubin, SGPT, uric acid ($p<.05$), and direct bilirubin, SGOT, alkaline phosphatase ($p<.10$). The mean values for the nonabstainers pre-TSE and post-TSE are located in Table 10. As with the abstainers, SGOT, SGPT normalized. For the hematologic values, MCH and MCV means were higher than the reference value range in pre- and post-TSE nonabstainer blood data while red blood cell count remained within reference value range for both sets of nonabstainer data.

Table 9. – Mean Differences in Pre-TSE and Post-TSE Blood
Data of Nonabstainers as Determined by Paired T-Test

Variables	Mean diff.	p-value	no signif. change
Uric acid	0.4	p<.05	Chloride
Tot. bili.	-0.5	p<.05	Carbon dioxide
Dir. bili.	-0.2	p<.10	Potassium
Alk. phos.	-12.1	p<.10	Sodium
LDH	-31.3	p<.01	BUN
SGOT	-28.8	p<.10	Glucose
SGPT	-21.7	p<.05	Tot. protein
WBC	0.6	p<.10	Albumin
			Calcium
			Phosphorus
			Tot. chol.
			Creatinine
			RBC
			Hemoglobin
			Hematocrit
			MCV
			MCH
			MCHC

For units, reference values, please refer to Tables 8 or 1.

Table 10. - Mean Values ± Standard Deviations for Nonabstainers
        Pre-TSE and Post-TSE

Test	NABS Pre-TSE (N=28)	NABS Post-TSE (N=30)	Reference
Chloride mEq/L	101.3 ± 4.5	102.8 ± 3.6	97-108
Carbon dioxide mEq/L	28.4 ± 2.5	28.9 ± 2.6	24-30
Potassium mEq/L	4.1 ± 0.4	4.2 ± 0.4	3.5-5.0
Sodium mEq/L	140.8 ± 3.6	141.0 ± 3.1	135-145
BUN mg/dL	14.9 ± 5.8	13.8 ± 4.3	8-23
Glucose mg/dL	103.2 ±29.4	102.0 ±32.4	70-130
Tot. protein mg/dL	7.0 ± 0.4	6.9 ± 0.4	6.7 - 8.7
Albumin g/dL	4.4 ± 0.4	4.5 ± 0.3	3.9-5.0
Calcium mg/dL	9.7 ± 0.5	9.7 ± 0.5	9.0-10.5
Phosphorus mg/dL	3.5 ± 0.7	3.4 ± 0.6	2.4-4.5
Tot. chol. mg/dL	216.2 ±59.5	221.5 ±47.0	150-270
Uric acid mg/dL	5.9 ± 1.1	6.3 ± 1.2	4.2-6.2
Creatinine mg/dL	1.1 ± 0.2	1.1 ± 0.2	0.8-1.5
Tot. bili. mg/dL	1.0 ± 1.1	0.5 ± 0.2	0-1.6
Dir. bili. mg/dL	0.3 ± 0.6	0.1 ± 0.0	0-0.3
Alk. phos. mU/ml	96.6 ±32.5	84.1 ±22.4	35-100
LDH mU/ml	203.4 ±67.6	169.6 ±34.2	110-220
SGOT mU/ml	63.0 ±80.7*	32.2 ±23.7	0-41
SGPT mU/ml	61.0 ±74.1*	37.1 ±44.1	0-41
WBC 1000/cu mm	7.3 ± 2.5	8.2 ± 2.2	4.8-10.8
RBC million/cu mm	4.7 ± 0.6	4.7 ± 0.4	4.7-6.1
Hemoglobin g/dL	15.1 ± 1.9	15.0 ± 1.1	14-18
Hematocrit vol%	44.4 ± 5.3	44.6 ± 3.7	42-52
MCV cu microns	94.3 ± 7.8*	94.2 ± 4.8*	80-94
MCH pg	32.1 ± 2.9*	31.9 ± 2.0*	27-31
MCHC g/dL	34.1 ± 1.0	35.9 ± 1.0	32-36

* = items where means exceed reference values

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Demographics

Scores on the 25-question MAST ranged from 2 to 55 with a mean of 31.7±12.1. Scores greater than 5 indicate probable alcoholism, scores between 3 and 5 are only suggestive of alcoholism, and scores less than 3 indicate a lack of alcoholism. VAST scores showed a decline over time: more than 5 years ago mean = 26.7±12.9, from 1 to 5 years ago mean = 17.0±12.7, and within the past year mean =10.8±9.0. This is consistent with a population which has many members dry for several years.

Smoking statistics proved of some interest since 90% of participants reported having smoked cigarettes for an extended period of time. The mean age of onset of smoking was 14.4±3.3. The heaviest amount smoked averaged 2.2±0.9 packs of cigarettes per day. 73% of patients report still smoking although the average amount smoked declined to 1.4±0.7 packs of cigarettes per day. A total of 30% of patients used other forms of tobacco such as cigars, pipe, and snuff. Smokers tended to start drinking at younger ages (p<.001), have earlier onset of alcohol-related problems (p<.05), drink larger amounts of alcohol than nonsmokers (p<.01). They also tended to have family members who were alcoholic (p<.05). The only significant blood variable associated with smoking was that smokers tended to have higher albumin levels (p<.05).

An average of 70% of participants reported having had first degree relatives who were alcoholic. Table 11 identifies which family members were alcoholic. Unfortunately the twin data was uninterpretable. Although 2 patients reported having twins who were alcoholic, we do not have statistics on how many patients in the study had twins. Patients with alcoholic family members tended to start drinking at a younger age (p<.01), have an earlier onset of alcohol-related problems (p<.05), have higher MAST scores (p<.01), higher VAST scores in the last 1-5 years (p<.05), and higher VAST scores more than 5 years ago (p,.05) Nonabstaining patients with alcoholic family members tended to drink more than nonabstainers without a family history of alcoholism (p<.01).

Table 11. - Alcoholic First-Degree Relatives

Classification	N	Percent
At least a parent	53	59.5%
At least a sibling	42	47.7%
At least one grandparent	17	19.3%
At least an aunt or an uncle	31	35.2%
Identical twin	2	2.3%
Other	6	6.8%
Total	88	*70.4%

*indicates percentage of total participants in study
(N=125) who reported having alcoholic family members.
(other percentages refer to N=88)

DISCUSSION

The patient sample in this study (N=125) represents a
self-selected sample of known veteran alcoholics who had
successfully completed a 28-day inpatient alcoholism
treatment program and were currently in outpatient follow-
up care. The time requirement of having entered the
program at least 4 months prior to data collection was
decided upon because of the expectation of significant
improvement in hepatic and hematologic parameters after at
least 4 months of abstinence from alcohol. We wanted to
allow each patient an adequate period of time after
completing the inpatient treatment program for improvement
of serum biochemical markers. 93% of the participants
(N=116) completed the inpatient program more than 5 months
ago.

The patient population was heterogeneous with respect
to age, drinking, smoking, medical histories, and time out
of the inpatient treatment program. The two study groups
(abstainers and nonabstainers) did not differ from each
other significantly in age, medical, or smoking histories.
and original MAST scores. Since their recent drinking
histories differed in that the abstainers had had no
alcohol for at least the past six months. as expected the
abstainers had lower VAST scores in the last year and 1 to
5 year categories. Current blood values (i.e. post-TSE)
were used to find correlations between continuing to drink

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and serum biochemical markers. The lower levels of SGOT, SGPT, LDH, MCH, and MCV for the abstainers compared to nonabstainers represent improved hepatic and hematologic function for the abstainers. Along with alkaline phosphatase, these are the same variables noted by previous researchers to be increased in actively drinking alcoholics.[34]

Some of the age-related correlations may not prove significant for several reasons. For example, the observation that older patients tend to have the first drink and first alcohol-related problems later in life excludes younger patients who may have had an earlier onset of alcoholism and hence presented for treatment earlier in life. That older patients tend to take more prescribed medications suggests these patients are understandably more ill than the younger ones. The older patients may suffer increased pulmonary incapacity and may be too sick to smoke as much as the younger ones. We did not find the decrease in red blood cell count and the increase in MCV and MCH with age as reported by Halman and Rubinstein in 1974.[4]

Our multivariate analysis results were comparable to those of previous researchers but could be improved with the inclusion of more nonabstaining controls. (We had roughly 3 times as many abstainers as nonabstainers.) It is preferable to have roughly equal numbers of abstainers and nonabstainers. In addition, Fletcher reports that in

a discriminant function analysis model, the number of subjects should be at least 5 times the number of variables to be tested.[35] This is primarily to prevent "shrinkage," i.e. the loss of discriminating ability when used on a patient population. Shrinkage occurs when a discriminant function analysis model loses some of its predictive accuracy when applied to a new group of subjects. We did satisfy the DFA requirement of a large heterogeneous patient population but could not obtain equal numbers of abstainers and nonabstainers since primarily abstainers were willing to participate in the study and since nonabstainers tend to leave treatment over time.

The pre-TSE multivariate analysis findings are interesting since both patient groups were drinking at that time. The model appeared able to predict with a modest degree of accuracy who the future abstainers were (recalling that a flip of the coin would produce 50% predictive accuracy over time). QDA was more predictive than LDA (76% vs. 69% correctly predicted). For the nonabstainers, QDA also outperformed LDA (79% vs. 57%). Those results were obtained with the 7 most predictive variables determined by stepwise regression. None of the predictive variables are commonly associated with actively drinking alcoholics. Since all of the patients were drinking pre-TSE, there appeared to be no statistically significant difference between the abstainers and nonabstainers in hepatic and hematologic markers for

alcoholism such as SGOT, SGPT, LDH, MCV, red blood cell count, and MCH. It is difficult to determine why these 7 most significant variables (Table 2) were selected. The slightly lower means for total protein and phosphorus of the nonabstainers may indicate a greater problem with chronic alcoholism than the abstainers. These biochemical markers are often lower in chronic alcoholics due to poor nutrition. While attractive, there is no direct evidence that the ability to distinguish between the two groups even though they were both actively drinking may suggest the presence of a biological trait for alcoholism possibly detected by serum biochemical markers.

The post-TSE blood data is more reliable for separating the abstainers and nonabstainers since it reflects current differences in drinking patterns. The predictive variables proved to be some of those commonly associated with alcoholism and active drinking such as SGOT, SGPT, MCH, red blood cell count, and MCV. For the abstainers, QDA outperformed LDA with a predictive accuracy of 93% vs. 40%. This appears to reflect the Ryback assumption that QDA may be more sensitive to non-normality and hence requires larger sample population sizes for predictive accuracy. The sample size of N=30 nonabstainers with 7 predictive variables may have been to small for accurate classification.

The most significant improvement for all patients since treatment in the inpatient program was in hepatic

parameters (SGOT, SGPT, LDH, bilirubin) and in MCV and MCH. The reasons are multifold and reflect less active drinking at the time the post-TSE blood data collection. For example, all patients were asked to remain abstinent for at least 3 days prior to venipuncture to allow for a more accurate comparison between long-term consequences of remaining abstinent and continuing to drink. Second, most patients (76%) were abstinenct post-TSE but had presented to and had their bloods at the inpatient program while actively drinking. Third, all patients were abstinent during their month on TSE and most patients appeared to have cut down on drinking throughout the months after their participation in the program according to clinician-verified questionnaire data.

The mean decrease in phosphorus and increases in chloride and red blood cell count are consistent with the Eckardt findings of 1983 on biochemical consequences of posttreatment alcohol consumption (N=56).[33] We did not observe a significant change in potassium, urea nitrogen, white blood cell count, and MCHC as did the Eckardt group but we did note significant improvement in other blood chemistry and hematologic data. For example, in the Eckardt study, SGOT, SGPT, alkaline phosphatase and glucose remained out of the reference value range whereas in the present study SGOT and SGPT normalized and the other variables remained within the reference value range. This may be because the mean time out of the inpatient treatment program was greater in our study (58.3 months

compared to 7 months) and because a larger proportion of abstainers (95 out of 125 compared to 17 out of 56). The Eckardt group may also have had more diabetics with abnormal glucose values.

As expected, the abstainers demonstrated the most significant improvement in biochemical and hematologic parameters. Compared to the pre-TSE data, the post-TSE blood data showed highly significant (p<.001) mean decreases in variables found by the Eckardt group to be consistent with active drinking. As patients consumed greater amounts of alcohol, they had higher elevations of alkaline phosphatase, total protein, SGOT, SGPT, MCV, MCH, and lower red blood cell count. Except for total these were the variables which were out of the reference value range pre-TSE but normalized post-TSE. Along with the significant decreases in LDH (p<.001), total bilirubin (p<.001), and direct bilirubin (p<.01), the decreases in SGOT and SGPT indicate improvement of hepatic function. Although MCH remained slightly out of the reference value range (mean = 31.1±1.7, range = 27-31), the statistically significant decrease in the levels of this variable and MCV, along with the increase in the red cell count, suggests hematologic improvement.

These findings are similar to the latest Eckardt study on long-term abstinence in which 15 male alcoholics remained abstinent for 7 months after participation in a 27-day alcoholism treatment program and then had their

bloods drawn. Statistically significant (p<.05) decreases were noted in phosphorus, total bilirubin, LDH, SGOT, MCV, and MCH levels. Significant (p<.05) increases in red cell count, chloride, potassium, and MCHC were also noted.[29] In our study, we noted no significant difference in potassium. Our subjects tended to show greater improvement in hepatic markers than Eckardt's subjects. This could have been because our subjects remained abstinent for a longer period of time. Our findings suggest that the longer patients remain abstinent, the more their blood values tended to normalize.

A comparison analysis of the blood variables which improved significantly with abstinence may provide a helpful manner in which to follow alcoholics after inpatient treatment. The t-test is one method. Another potentially helpful method would be to use discriminant function analysis; a model could be constructed to attempt to separate the pre-TSE blood values (reflecting active drinking) from the post-TSE blood values (reflecting long-term abstinence). We wanted to do this but the method proved too time-consuming for the present study. This will be attempted in a later study. Should the model separate the two with significant predictive accuracy, DFA could provide another way of following abstinence. A group of individuals' hepatic and hematologic improvement may be followed by comparing their posttreatment blood values to their pretreatment values rather than comparing posttreatment blood values to those

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of other nonabstaining patients.

The nonabstainers showed less significant improvement in the variables listed above associated with both short-term and long-term abstinence. Although most of these patients had their last drink between 1 and 6 months ago as suggested by the drinking history correlation matrix (p<.001), they did not experience the significant reductions in total protein, cholesterol, MCV, and MCH as the Ryback group's nonabstainers did (N=136). (The Ryback group's nonabstainers had not consumed any alcohol for the 27 days they participated in the inpatient program and then had their bloods drawn.)

For the nonabstainers in the present study, the most significant decrease was in LDH (p<.01). Along with the less significant decreases in SGPT, total bilirubin (p<.05), SGOT, and direct bilirubin (p<.10), these changes reflect some hepatic improvement although not nearly as much as that appreciated for the abstainers. There was no significant improvement in MCV, MCH, or red cell count which suggests that improvement in hepatic function may precede improvement in hematologic function as patients start abstaining from alcohol.

The demographic data is of interest because of the majority of smokers (currently 73%) and the high degree of familial alcoholism. The tendency of smokers to start drinking at earlier ages (p<.001) and consume larger amounts of alcohol than nonsmokers (p<.01) may suggest a

real problem of cross-addiction. It might also just reflect the fact that the smokers outnumbered the nonsmokers by 9 to 1 in the past and 3 to 1 at the present time. We did not find the tendency for higher hemoglobin, hematocrit, or MCH associated with smoking as noted by Helman and Rubinstein.[9] These changes are thought to be due to increased blood viscosity from increased erythrocyte size relative to arterial hypoxemia from smoking.

Studies have been done to try to determine the etiology of the high incidence of familial alcoholism Most reports suggest 25% of male relatives and 5-10% of female relatives of known alcoholics are also alcoholic.[36]

The familial data is impressive in that it suggests a much higher incidence of positive family history of alcoholism than traditional reports. Most patients reported having at least one parent who was alcoholic (Table 11). Alcoholism in such an important role model as the parent may explain why these patients tended to start drinking at an earlier age. This finding is mentioned in previous studies.[36] The greater degree of alcohol-related problems and higher MAST scores in patients from alcoholic families reflects the significance of the unhealthy environment surrounding alcoholism.

Researchers are now studying the biological components of alcoholism quite closely; many are looking for a possible genetic marker for alcoholism. Adoption studies and twin studies, two of the most reliable methods

for studying family heritance patterns, suggest a definite familial predisposition towards alcoholism. In addition to proposing a possible method of following abstinence, the data from this study also demonstrate that the biological abnormalities seen in alcoholism change sufficiently with abstinence hopefully to permit discriminant function analysis to separate abstinenct from nonabstinent alcoholics.

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PROJECT QUESTIONNAIRE

NAME: _____   DATE: _____

SOCIAL SECURITY # __ __ __ - __ __ - __ __ __ __
                   (1) (2) (3) (4)

Date you were first on T5E (inpatient alcoholism unit in this program)? _____
                                                                          (5-8)

If ever a halfway house resident (T6W), dates you were there? _____
                                                                (9-16)

FOR "YES AND NO" QUESTIONS, PLEASE CIRCLE YOUR BEST ANSWER.
FOR OTHER QUESTIONS, GIVE YOUR "BEST GUESS" ANSWER.
==

PART I

Since you completed T5E, have you developed any new medical problems? YES NO   (17)
If YES, please list below:_____
                                                                                (18-23)

_____

_____

Do you now take any prescribed medicines?   YES   NO   (24)

If YES, please list below. _____   (25-30)

_____

_____

What was you age at your first drink? _____   (31-32)

At what age did you have your first alcohol-related problems?_____   (33 34)

Do you think you have any biologically related family members   (35)
who are/were alcoholic? YES NO
If YES, circle all that apply: Father Mother Grandfather Grandmother Aunt   (36-46)
Uncle Brother Sister Twin Son Other:_____
                        (identical)

The following questions involve tobacco smoking.

Have you ever smoked cigarettes for an extended period of time?   YES NO   (47)
(If NO, please skip to QUESTION #14)
(If YES, please answer the following questions)
What was your age at your first smoke?   _____   (48-49)

The heaviest you ever smoked, in packs/day? _____   (50-52)

Were you smoking when you were on T5E?   YES NO   (53)

1a

f YES, how many packs/day did you smoke? _____ (54-56)

o you smoke now? YES NO (57)
f YES, how many packs per day do you smoke? _____ (58-60)

ave you ever smoked a pipe for an extended period of time? YES NO (61)
f YES, how many years did you smoke a pipe? _____ (62-63)

ave you ever smoked cigars for an extended period of time? YES NO (64)
f YES, how many years did you smoke cigars? _____ (65-66)

ave you ever used snuff (smokeless tobacco) for an extended period of time? YES NO (67)
f YES, how many years did you use snuff? _____ (68-69)

PART II

)id you complete T5E more than 5 months ago? YES NO (70)
(If NO, please skip to QUESTION #21)
(If YES, please answer the next question)

Have you had any alcohol since you completed T5E? YES NO (71)
(If NO, please skip to QUESTION #32)
(If YES, please answer the following questions):

e following questions apply to the time period after you left T5E up to 6 months ago.
NOT INCLUDE any information from the MOST RECENT 6 MONTHS in this section.

How many drinking episodes did you have after leaving T5E and before 6 months ago? (72)
(By "drinking episode" we mean a period when you drank alcohol;
for example, if you drank every day for 2 weeks and then were dry,
that would be 1 episode). _____

How long were these drinking episodes, usually? (Specify hours, days, weeks, or months (74-77)
_____

Were you usually a "binge" drinker? (By "binge" we mean did you
drink over a pint a day or over 2 six packs a day for 1 to 5   (78)
days and then stay dry for at least a week?). YES NO

What type of alcohol did you usually drink? Circle all that apply: (79-84)
Beer or ale   Wine   Fortified wines (sherry, port)
Liquor (distilled spirits)   Alcohol-containing medicines (like cough syrups)
Non-beverage alcohol (like mouthwash, aftershave, rubbing alcohol)

How much did you drink in a day when you drank? (Pick a typical drinking day and (85-87)
list all that apply for that day--please specify size of bottle, can or glass):
BEER/Ale:_____
WINES: _____
LIQUOR: _____
ALCOHOLIC MEDICINES/NON-BEVERAGE ALCOHOL:_____

he following questions apply only to the period from 6 months ago to 1 month ago.
NOT INCLUDE any information from BEFORE 6 MONTHS ago or FROM THE LAST 30 DAYS.

2a

ave you had any alcohol to drink between 6 months and one month ago? YES   NO   (88)
F NO, PLEASE SKIP TO QUESTION #32. If YES, please answer the following questions.

ow many drinking episodes did you have during the past 6 months?_____   (89-90)

ow long were these drinking episodes usually? Specify hours, days, weeks, months. (91-94)
_____

ere you usually a "binge" drinker? (By "binge" we mean did you
rink over a pint a day or over 2 six packs a day for 1 to 5
ays and then stay dry for at least a week)?   YES NO   (95)

hat type of alcohol did you usually drink? Circle all that apply: (96-101)
eer or ale   Wine   Fortified wines (sherry, port)
iquor (distilled spirits)   Alcohol-containing medicines (like cough syrups)
on-beverage alcohol (like mouthwash, aftershave, rubbing alcohol)

ow much did you drink in a day when you drank? (Pick a typical drinking day and (102-104)
ist all that apply for that day--please specify size of bottle, can or glass):
EER/Ale: _____
INES: _____
IQUOR: _____
LCOHOLIC MEDICINES/NON-BEVERAGE ALCOHOL:_____

following questions apply only to THE LAST 30 DAYS. DO NOT INCLUDE ANY INFORMATION from
ORE A MONTH AGO.

ave you had any alcohol to drink in the past 30 days?   YES   NO   (105)
F NO, PLEASE PROCEED TO QUESTION #32.
f YES, please answer the following questions. Circle your best guess.

ow many drinking episodes have you had in the last 30 days?_____ (106-107)

hat was the length of the episodes in days? _____ (108-111)

hat type of alcohol did you drink? Circle all that apply:
eer or ale   Wine   Fortified wine (sherry, port) Liquor (distilled spirits)   (112-117)
lcoholic medicines (like cough syrups) Non-beverage alcohol (mouthwash, aftershave)

ow much did you drink in a day when you drank? (Pick a typical drinking day and (118-120)
ist all that apply for that day--please specify size of bottle, can or glass):
EER/Ale: _____
INES: _____
IQUOR: _____
LCOHOLIC MEDICINES/NON-BEVERAGE ALCOHOL:_____

PART III

o you feel you are now a normal drinker? (that is, do you feel you   (121)
re not alcoholic, and you can handle drinking OK)   YES NO

o you feel that you have always been a normal drinker?   YES NO   (122)

f YES, skip to the next question.)
    (If NO) Do you feel you were a normal drinker since T5E?   YES   NO   (123)
            In the last year?   YES   NO   (124)
            In the last 1-5 years?   YES   NO   (125)
            More than 5 years ago?   YES   NO   (126)

ve you ever awakened the morning after some drinking
e night before and found that you could not remember
part of the evening?   YES   NO   (127)
    (If YES) Has this occurred since T5E?   YES   NO   (128)
            In the last year?   YES   NO   (129)
            In the last 1-5 years?   YES   NO   (130)
            More than 5 years ago?   YES   NO   (131)

es your wife, parent, or other near relative ever worry
complain about your drinking?   YES   NO   (132)
 the past did any of these people worry or complain
out your drinking?   YES   NO   (133)
    (If YES) Has it occurred since T5E?   YES   NO   (134)
            In the last year?   YES   NO   (135)
            In the last 1-5 years?   YES   NO   (136)
            More than 5 years ago?   YES   NO   (137)

f you now drink, can you stop with no struggle after 1-2 drinks?   YES   NO   (138)
 the past could you stop without a struggle after 1-2 drinks?   YES   NO   (139)
    (If NO) Has the struggle been since T5E?   YES   NO   (140)
            In the last year?   YES   NO   (141)
            In the last 1-5 years?   YES   NO   (142)
            More than 5 years ago?   YES   NO   (143)

o you ever feel guilty about your drinking?   YES   NO   (144)
 the past did you ever feel guilty about your drinking?   YES   NO   (145)
    (If YES) Did you feel guilty about your drinking since T5E?   YES   NO   (146)
            In the last year?   YES   NO   (147)
            In the last 1-5 years?   YES   NO   (148)
            More than 5 years ago?   YES   NO   (149)

o friends or relatives now think you are a normal drinker?   YES   NO   (150)
o friends or relatives think you were always a normal drinker?   YES   NO   (151)
    (If NO) Do they think you were a normal drinker since T5E?   YES   NO   (152)
            In the last year?   YES   NO   (153)
            In the last 1-5 years?   YES   NO   (154)
            More than 5 years ago?   YES   NO   (155)

f you now drink, are you able to stop when you want to?   YES   NO   (156)
ere you always able to stop drinking when you wanted to?   YES   NO   (157)
    (If NO) Were you able to stop when you wanted to since T5E?   YES   NO   (158)
            In the last year?   YES   NO   (159)
            In the last 1-5 years?   YES   NO   (160)
            More than 5 years ago?   YES   NO   (161)

ther than the meetings you attended when on T5E (or T6W, for
former halfway house residents) have you ever attended a
meeting of Alcoholics Anonymous (AA)?   YES   NO   (162)

4a

(If YES) Have you attended a meeting of AA since T5E?	YES	NO	(163)
In the last year?	YES	NO	(164)
In the last 1-5 years?	YES	NO	(165)
More than 5 years ago?	YES	NO	(166)
Have you ever gotten into physical fights when drinking?	YES	NO	(167)
(If YES) Has this occurred since T5E?	YES	NO	(168)
In the last year?	YES	NO	(169)
In the last 1-5 years?	YES	NO	(170)
More than 5 years ago?	YES	NO	(171)
Has your drinking ever created problems between you and your wife, a parent or other relative?	YES	NO	(172)
(If YES) Has this occurred since T5E?	YES	NO	(173)
In the last year?	YES	NO	(174)
In the last 1-5 years?	YES	NO	(175)
More than 5 years ago?	YES	NO	(176)
Has your wife or other family member ever gone to anyone other than this program for help about your drinking?	YES	NO	(177)
(If YES) Did this happen since T5E?	YES	NO	(178)
In the last year?	YES	NO	(179)
In the last 1-5 years?	YES	NO	(180)
More than 5 years ago?	YES	NO	(181)
Have you ever lost friends because of your drinking?	YES	NO	(182)
(If YES) Have you lost friends since T5E?	YES	NO	(183)
In the last year?	YES	NO	(184)
In the last 1-5 years?	YES	NO	(185)
More than 5 years ago?	YES	NO	(186)
Have you ever gotten into trouble at work because of drinking?	YES	NO	(187)
(If YES) Was it since T5E?	YES	NO	(188)
In the last year?	YES	NO	(189)
In the last 1-5 years?	YES	NO	(190)
More than 5 years ago?	YES	NO	(191)
Have you ever lost a job because of drinking?	YES	NO	(192)
(If YES) Has it been since T5E?	YES	NO	(193)
In the last year?	YES	NO	(194)
In the last 1-5 years?	YES	NO	(195)
More than 5 years ago?	YES	NO	(196)
Have you ever neglected your obligations, your family or your work for 2 or more days in a row because you were drinking?	YES	NO	(197)
(If YES) Has it been since T5E?	YES	NO	(198)
In the last year?	YES	NO	(199)
In the last 1-5 years?	YES	NO	(200)
More than 5 years ago?	YES	NO	(201)
If you now drink, do you drink before noon fairly often?	YES	NO	(202)
In the past did you ever drink before noon fairly often?	YES	NO	(203)
(If YES) Has it been since T5E?	YES	NO	(204)
In the last year?	YES	NO	(205)

5a

In the last 1-5 years?	YES NO	(206)
More than 5 years ago?	YES NO	(207)
ave you ever been told you have liver trouble or cirrhosis?	YES NO	(208)
(If YES) Were you told since T5E?	YES NO	(209)
In the last year?	YES NO	(210)
In the last 1-5 years?	YES NO	(211)
More than 5 years ago?	YES NO	(212)

After heavy drinking, have you ever had Delerium Tremens (DTs) r severe shaking, or heard voices or seen things that really ren't there? (Put 2 circles if DT's)

	YES NO	(213)
(If YES) Did this occur since T5E?	YES NO	(214)
In the last year?	YES NO	(215)
In the last 1-5 years?	YES NO	(216)
More than 5 years ago?	YES NO	(217)

ave you ever gone to anyone (outside this program) for help bout your drinking?

	YES NO	(218)
(If YES) Did this occur since T5E?	YES NO	(219)
In the last year?	YES NO	(220)
In the last 1-5 years?	YES NO	(221)
More than 5 years ago?	YES NO	(222)

ther than T5E (or T6W), have you ever been in a hospital ecause of drinking?

	YES NO	(223)
(If YES) Did this occur since T5E?	YES NO	(224)
In the last year?	YES NO	(225)
In the last 1-5 years?	YES NO	(226)
More than 5 years ago?	YES NO	(227)

ther than T5E (or T6W) have you ever been a patient in a sychiatric hospital or on a psychiatric ward of a general ospital where drinking was a part of the problem that caused our hospitalization?

	YES NO	(228)
(If YES) Did this take place since T5E?	YES NO	(229)
In the last year?	YES NO	(230)
In the last 1-5 years?	YES NO	(231)
More than 5 years ago?	YES NO	(232)

Outside of this program, have you ever been seen at a sychiatric or mental health clinic or gone to any doctor, social worker or clergyman for help with any emotional roblem, where drinking was part of the problem?

	YES NO	(233)
(If YES) Did this occur since T5E?	YES NO	(234)
In the last year?	YES NO	(235)
In the last 1-5 years?	YES NO	(236)
More than 5 years ago?	YES NO	(237)

Have you ever been arrested (whether or not convicted) for drunk driving, driving while intoxicated, or driving under the influence of alcoholic beverages?

	YES NO	(238)
(If YES) How many times? _____ (239-240)		
Since T5E?	YES NO	(241)

How many times? _____ (242)
  In the last year?   YES NO (243)
How many times? _____ (244)
  In the last 1-5 years?   YES NO (245)
How many times? _____ (246)
  More than 5 years ago?   YES NO (247)
How many times? _____ (248)

ave you ever been arrested or taken into custody, even for
few hours, because of drunken behavior?   YES NO (249)
       (If YES)   How many times? _____ (250-251)
              Since T5E?   YES NO (252)
             How many times? _____ (253)
              In the last year?   YES NO (254)
             How many times? _____ (255)
              In the last 1-5 years?   YES NO (256)
             How many times? _____ (257)
              More than 5 years ago?   YES NO (258)
             How many times? _____ (259-260)

o you feel that you have ever had a drinking problem?   YES NO (261)
   (If YES) Was this since T5E?   YES NO (262)
          In the last year?   YES NO (263)
          In the last 1-5 years?   YES NO (264)
          More than 5 years ago?   YES NO (265)

o you feel that you have ever been an alcoholic?   YES NO (266)
   (If YES) Were you/have you been alcoholic since T5E? YES NO (267)
          In the last year?   YES NO (268)
          In the last 1-5 years?   YES NO (269)
          More than 5 years ago?   YES NO (270)

ow long did it take you to complete this questionnaire?_____

THANK YOU FOR YOUR PARTICIPATION!

PLEASE RETURN TO THE SECRETARY'S OFFICE, ALCOHOLISM AMBULATORY SERVICE (TGE)
r put in envelope and mail to
J.M.SCHNITT, M.D.
116A4--TGE
VA MEDICAL CENTER
WEST HAVEN, CT 06516

following questions apply only to the LAST 3 DAYS.   DO NOT GIVE INFORMATION from before 3 AGO.

ve you had any alcohol in the last 3 days?
 NO, PLEASE PROCEED TO QUESTION #   .
 YES, please answer the following questions.

w much did you drink on each day?

day:_____

sterday:_____

y before yesterday:_____

at type of alcohol did you have?
er/ale,   Wine/Fortified Wine,   Liquor,   Alcoholic medicines,   Non-beverage alcohol

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