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STATISTICAL PROCESS CONTROL AND MEDICAL SURVEILLANCE
AN APPLICATION WITH LIVER FUNCTION TESTS

THESIS

Bryan D. Richardson, Second Lieutenant, USAF

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THESIS

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Bryan D. Richardson, B.S.

Second Lieutenant, USAF

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STUDENT:	2Lt Bryan D. Richardson	CLASS:	GOR96-M

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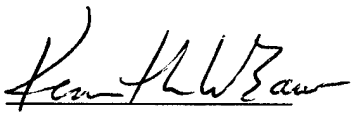
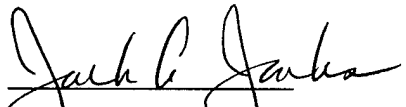
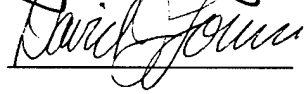
Advisor	Lt Col Kenneth Bauer/ENS	
Reader	Lt Col Jack Jackson/ENS	
Reader	Lt Col Dave Louis/SGPO	

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Bryan D. Richardson

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Abstract

Traditionally, medical surveillance of liver disease generally involves a battery of tests. This research used multivariate analysis techniques to reduce the number of measures required to identify liver dysfunction and found using a Transferase Index (a combination of three tests; ALT, AST, and GGT) provided the most satisfying assessment, but the single best indicator, ALT, may be sufficient. Transferase Index and ALT criterion were both applied to SPC control charts. Through the use of statistical process control (SPC), this research identified work zones possessing signs of adverse effects to an individual's liver as a possible result of their work environment and demonstrated SPC as an excellent way to conduct medical surveillance. Industry has embraced SPC, and control charts, this research extended their scope and demonstrated their effective use in medical surveillance of the liver. This research showed they provide easy, efficient ways to monitor work environments.

STATISTICAL PROCESS CONTROL AND MEDICAL SURVEILLANCE

AN APPLICATION WITH LIVER FUNCTION TESTS

I. INTRODUCTION

Background

Of all the organs in our bodies, the liver is one of the most susceptible to injury from drugs and environmental toxins (Douidar, 1992; 109). The liver plays a central role in the detoxification and elimination of foreign compounds, known as xenobiotics, we encounter every day. Some of these xenobiotics enter our bodies intentionally through inhalation, ingestion, and skin absorption (such as alcohol consumption and smoking), while others enter without our awareness. By virtue of its role in the metabolism of xenobiotics, the liver is especially vulnerable to chemical injury and is thus of central clinical interest (Harrison, 1990a; 247).

The Medical Group's Occupational Medicine Element (74th SGPO) at Wright-Patterson Air Force Base (WPAFB) is one organization with a keen interest in xenobiotic exposures. The mission of the 74th SGPO is to optimize worker health for all civilian and military employees at WPAFB; achieved through monitoring the working environment. Of all occupational related disease, damage to the liver is second most common, only after lung disease (Harrison, 1990a; 247).

To facilitate monitoring WPAFB personnel, the 74th SGPO maintains a health database, called the PHOENIX system, which contains information dating back to 1989. For each individual monitored, there is a record of their work areas which include zones (areas of common exposures within a specific building or organization) and the dates of service in each zone. There is also information on their personal health history, family health history, liver function test results, and personal habits which may contribute to liver disease, such as alcohol consumption. The PHOENIX system is able to monitor personnel, but is not useful in an analytic sense. However, through the use of various software packages, the data in PHOENIX can be extracted and analyzed to provide the 74th SGPO with answers to questions related to occupational liver disease among different work zones.

Employees in particular work zones are logical targets for the screening of occupational disease for two reasons. They have at least some risk factors in common (their workplace exposures) and they have a clear opportunity for prevention, reduction or elimination of those exposures (Levy, 1988; 75). Typical liver disease development is found in Figure 1-1.

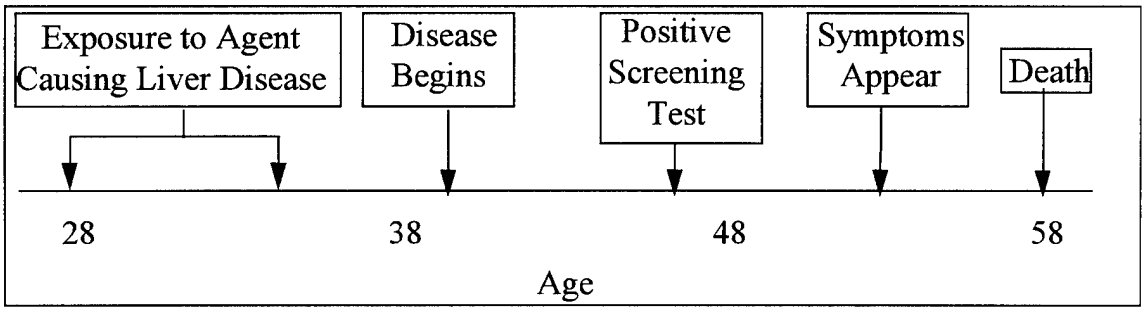

Figure 1-1. Phases of liver disease development (Levy, 1988; 77).

The data extracted from the database for use in this study includes an identifier, social security number, as well as applicable personal history variables and liver related data elements, including liver function tests (see Table 1-1). Most individuals have multiple liver function tests results since surveillance began in 1989. For example, someone may have four different ALT results, a liver function test, each one recorded in a separate year. At most, an individual may have seven test result observations. A summary of data collected for this study is indicated in Table 1-2..

Data Contained in Variable	Variable Used
Social Security Number	SSAN
gender	SEX
work zone when a test was administered	ZONE
date of test	DATE
history of blood disease (0 -1 variable)	BLDDIS
history of liver disease (0 -1 variable)	LIVERBAD
history of hepatitis (0 -1 variable)	HEP
history of jaundice (0 -1 variable)	JAUNDICE
ounces of liquor consumed per week	D1
bottles of beer consumed per week	D2
glasses of wine consumed per week	D3
serum glutamic-pyruvic transaminase or alanine aminotransferase - a liver test	SGPT or ALT
serum glutamic-oxaloacetic transaminase or aspartate aminotransferase - a liver test	SGOT or AST
γ-glutamyl transferase - a liver test	GGT
bilirubin - a liver test	BILIRUBIN
albumin - a liver test	ALBUMIN
alkaline phosphatase - a liver test	AP
white blood count	WBC
level of hematocrit - percent of blood volume occupied by cells	HEMATOCRIT

Table 1-1. Variables collected for the study.

Statement of the Problem

Using the information extracted from the Occupational Health PHOENIX Database, an analysis to determine any signs of possible adverse effects to an individual's liver which may be a result of their work environment is accomplished.

Number of Observations	ALT	AST	GGT	Bilirubin	Albumin	AP
1	453	415	423	377	368	386
2	127	118	104	107	118	123
3	76	88	29	61	56	61
4	51	60	0	19	32	33
5	54	50	2	25	34	33
6	32	19	0	5	18	23
7	11	4	0	0	5	6
TOTAL	804	754	558	624	631	665

Table 1-2. Summary of data for each liver test.

Research Objective

Results from liver function tests are analyzed to identify any trends the 74th SGPO should take action on. This effort is intended to be used as a screening tool for the 74th SGPO. The purpose of screening is early identification of conditions which already exist so their progression can be slowed, halted, or even reversed. Through screening and surveillance, hepatotoxicity can be minimized and hopefully prevented (Douidar, 1992; 118). Therefore, screening is a secondary preventive measure (Levy, 1988; 75). If the results identify individuals or zones with abnormal data, it is the responsibility of the 74th SGPO to determine if liver disease is occupationally related and to take the appropriate corrective action.

II. MEDICAL LITERATURE REVIEW

Medical Surveillance for Occupational Hepatotoxins

The objective of medical surveillance in a workplace is to identify workers with subclinical diseases so that preventive and/or therapeutic interventions can be implemented. Medical surveillance can be done through a variety of screening methods such as questionnaires (which seek suggestive symptoms or exposures), clinical examinations (physicals), and laboratory tests. In order to be used efficiently, the methods must be simple, noninvasive, safe, rapid, inexpensive, and widely available for routine use (Levy, 1988; 75, Harrison, 1990a; 255, and Harrison, 1990b; 516). The "gold standard" for liver testing is liver biopsies where a small piece of the liver is removed. This procedure is the most accurate method, but is morbid and expensive, making other alternatives desirable. The primary alternative is a variety of "liver function tests," serum measurements of liver enzymes, that are used to characterize liver health (Neuschwander-Tetri, 1995; 49). Various enzymes, present in large concentrations in liver cells, are released into the blood stream when the liver is dysfunctional (damaged or destroyed). Through common blood tests, the levels of these enzymes are measured from the serum to provide biochemical evidence of cell death, hepatic synthesis, and the efficiency of common liver processes. These biochemical tests and tests of synthetic function are common for routine use. Another form of testing is clearance tests. Although clearance tests are used in some research settings, they are not widely available and not suggested for routine use (Harrison, 1990a; 255). Tests for evaluation of liver disease can be found in Table 2-1.

Biochemical tests - levels of chemicals (enzymes)
Serum enzyme activity
Serum alkaline phosphatase
Serum lactate dehydrogenase
Serum bilirubin
Urine bilirubin
Test of synthetic liver function - protein production
Serum albumin
Prothrombin time
Alpha-fetoprotein
Serum ferritin
Clearance tests - test of functional ability
Exogenous clearance tests
Sulfobromophthalein
Indocyanine green
Antipyrine test
Aminopyrine breath test
Caffeine breath test
Endogenous clearance tests
Serum bile acid

Table 2-1. Tests for evaluation of liver disease (Harrison 1990a; 255).

Assessing Test Validity

The ideal screening tests for liver problems should correctly identify people with an abnormal test who truly have occupation-associated liver disease. The common way of describing a test's characteristics is through sensitivity (how sensitive the test is at detecting disease) and specificity (how good the test is at rejecting samples that are not diseased) (Streiner, 1989; 81). Sensitivity is a measure of the test's ability to detect people with disease and is measured by:

$$\text{Sensitivity} = \frac{\text{Number with disease who have a positive test}}{\text{Number with disease}}$$

Conversely, specificity measures the ability of the test to correctly identify those who do not have disease and is measured as follows:

$$\text{Specificity} = \frac{\text{Number without disease who have a negative test}}{\text{Number without disease}}$$

However, both of these measures require some knowledge of the true state of affairs (in their denominators) since they are based on people who do or do not have disease. Knowledge about the true state of the liver requires a liver biopsy which is undesirable due to the morbidity of the procedure. Another way to assess the accuracy of the tests is to calculate the probability someone actually has (or does not have) disease when they test positive. Similarly, we can calculate the probability someone who tests negative does or does not have disease. These probabilities are called positive predictive value and negative predictive value. Positive predictive value (PPV) is the ratio of people with positive tests who actually have disease to all positive tests. Negative predictive value (NPV) is the ratio of people with negative tests who do not have disease to all negative tests. A high positive predictive value is desired in screening tests. For an illustration of test measures, see Figure 2-1.

$$\text{Positive Predicative Value} = \frac{\text{People with positive test and disease}}{\text{All people with positive test}}$$

$$\text{Negative Predictive Value} = \frac{\text{People with negative test and no disease}}{\text{All people with negative test}}$$

The predictive value of a test depends upon its reliability (ability of the test to be reproduced), validity (sensitivity and specificity), as well as the prevalence of dysfunction (how common the disease is within the population sampled). When prevalence of liver disease is low (rare within the population), the positive predictive value of the test is low

and negative predictive value is high. Conversely, if the prevalence is very high, the negative predictive value is low, but the positive predictive value is high (Douidar, 1992; 120).

		True State of Nature	
		Have Disease	No Disease
Test Result	Positive	P	E1
	Negative	E2	N

Sensitivity = $\frac{P}{P + E2}$ PPV = $\frac{P}{P + E1}$ E1 = False Positives Type I Error

Specificity = $\frac{N}{N + E1}$ NPV = $\frac{N}{N + E2}$ E2 = False Negatives Type II Error

Figure 2-1. Illustration of accuracy measures and characteristics for liver tests.

Test errors can be made in two ways, false positives and false negatives. False positives, positive tests in the absence of disease, are typically elevated enzyme levels due to nonoccupational causes. They must be minimized to avoid costly and unnecessary clinical and/or worksite intervention. The medical, social, and economic costs of incorrectly identifying a worker as having a disease can have enormous effects (Harrison, 1990b; 516). False negatives (normal values despite the presence of liver dysfunction) renders preventive medicine ineffective and allows workers to return to a dangerous environment (Douidar, 1992; 120).

Screening Enzyme Tests

An ideal test for detection of liver dysfunction would be sensitive enough to detect minimal liver disease, specific enough to exclude normal livers, and capable of reflecting the severity of the underlying problem. The choice of tests used are based on practical criteria such as noninvasiveness, simplicity of test performance, availability of resources, adequacy of test analysis, and cost to ensure efficiency (Harrison, 1990a; 255). The use of these criteria eliminates liver biopsies as a useful surveillance tool despite the fact they are the "gold standard." The two most important criteria for this study are accurate tests and availability of data (data that has already been collected). Therefore, the next best alternative is liver function tests since they have proven to be reliable indicators of many common forms of liver disease (Neuschwander-Tetri, 1995; 49). Further, presence of hepatic disease is usually first identified by these tests (Harrison, 1990a; 247 and Harrison, 1990b; 515). Results from six common liver function tests are in PHOENIX Database System: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), bilirubin (BR), albumin, and alkaline phosphatase (AP).

Performance measures on the tests, sensitivity and specificity, assess the adequacy of these six tests. The most common and useful serum enzymes in screening are the aminotransferases: alanine aminotransferase (ALT), previously known as serum glutamic-pyruvic transaminase (SGPT), and aspartate aminotransferase (AST), previously called serum glutamic-oxaloacetic transaminase (SGOT) (Harrison, 1990a; 255 and Leevy, 1980; 499). Transferase levels are due to release of enzyme protein from liver cells as a result of cell turnover or injury. Elevations of serum aminotransferase activity can occur with

minor cell injury, making such determinations useful in the early detection and monitoring of liver disease of drug or chemical origin. Serum transferases have a relatively high sensitivity for detection of liver disease and remain the test of choice for routine surveillance (Harrison 1990a; 255). However, a serious drawback in using transferases is the lack of specificity in that they may be elevated due to other mechanisms which may or may not be identifiable in a clinical context (Leevy, 1980; 499).

Serum gamma-glutamyl transferase (GGT) is considered a more sensitive indicator than aminotransferase of drug-, virus-, chemical-, and alcohol- induced hepatocellular damage (Leevy, 1980; 501). However, because of its severe lack of specificity, one must interpret abnormalities in conjunction with other tests making GGT alone an incomplete battery in screening for hepatotoxicity (Harrison, 1990a; 255 and Leevy, 1980; 501). Serum bilirubin is of some value in detecting toxic cholestatic liver injury but is frequently normal in the presence of mild and common cellular damage (Harrison, 1990a; 256). Serum albumin concentration maybe a useful index of cellular dysfunction in liver disease. It is of little value in differentiating type of liver dysfunction (Harrison, 1990a; 256). Serum alkaline phosphatase (AP) activity may originate from the liver, bone, intestine, or placenta (Harrison, 1990a; 256). The normal function of AP is not fully understood (Neuschwander-Tetri, 1995; 53). For a more complete discussion on specific tests, see Appendix A.

There is some mixed opinions on the adequacy of the different liver function tests within the medical community. Most physicians recommend workplace screening for hepatotoxicity with the standard serum transferases; that is ALT and AST (Harrison, 1990a; 255). Some others recommend initial screening with AP followed by confirmation

with GGT. The federal government has recommended large batteries of tests. This study explores the adequacy of these tests and demonstrates they are the primary indicators of liver dysfunction in a screening application.

Limitations of Detecting Occupational Liver Disease

There are a number of ways to detect liver dysfunction. However, difficulty arises in isolating the causes of liver disease since exposure to liver disease causing agents is not limited to the workplace. Exposure, whether from the home, environment, or the workplace, has the same damaging effects on the liver. With the exception of a few chemicals that cause specific lesions, hepatic injury due to workplace exposure does not differ clinically, morphologically, or structurally, from most drug-induced damage. Thus, it may be difficult to differentiate between occupational and nonoccupational causes on the basis of screening tests discussed above (Harrison, 1990a; 247). A partial list of specific compounds, the resulting injury, and typical uses are found in Table 2-2.

Further difficulty arises since liver enzyme tests, while moderately sensitive, may not be specific and have poor positive predictive value in identifying true occupational liver disease. In addition, little is known about the synergistic effects of multiple hepatotoxic exposures common to many occupations. This study is limited to identifying clusters in liver disease and does not address specific exposures or potential synergistic effects. It should also be recognized that these screening tests only presumptively identify individuals who are likely, or unlikely, to have liver disease. Further tests are necessary to diagnosis and assess the severity of an individual's condition, which is left to the 74th SGPO (Levy, 1988; 75).

Compound	Type of Injury	Occupation or Use
Arsenic	Cirrhosis, hepatocellular carcinoma, angiosarcoma	Pesticides
Beryllium	Granulomatous	Ceramics workers
Carbon tetrachloride	Acute hepatocellular injury, cirrhosis	Dry cleaning
Dimethylformamide	Acute hepatocellular injury	Solvent, chemical mfg.
Dimethylnitrosamine	Hepatocellular carcinoma	Rocket mfg.
Dioxin	Porphyria cutanea tarda	Pesticides
Halothane	Acute hepatocellular injury	Anesthesiology
Hydrazine	Steatosis	Rocket mfg.
Methylene dianiline	Cholestasis	MDA production workers
2-Nitropropane	Acute hepatocellular injury	Painters
Phosphorus	Acute hepatocellular injury	Munitions workers
Polychlorinated biphenyl	Subacute liver injury	Production, electrical utility
Tetrachloroethane	Acute or subacute hepatocellular injury	Aircraft mfg.
Trichloroethylene	Acute or subacute hepatocellular injury	Leaning solvent sniffing
Trinitotolulene	Acute or subacute hepatocellular injury	Munitions workers
Vinyl chloride	Angiosarcoma	Vinyl chloride workers

Table 2-2: Chemical agents associated with occupational liver disease.

Normal Values

In terms of liver function tests, it is difficult to know what represents normal and abnormal values (Douidar, 1992; 118). Discrepancies arise because normal values for aminotransferase activities depend on technique and conditions as well as the composition of normal control populations (Leevy, 1980; 499). In order to tailor this investigation to the personnel at WPAFB, the normal values used for this study correspond to standards established by a August 1994 study done by the laboratories at the 74th SGPO (see Table

2-3). In doing so, the composition of the control population and technique used to obtain the data conform to the entire study group.

	ALT	AST	GGT	BILIRUBIN	ALBUMIN	AP
Lab AUG87	14-75	14-40	5-85	0.4-1.4	3.9-5.1	12-37
Lab DEC90 male	0-40	0-37	11-50	0-1	3.4-5.0	39-117
female	0-31	0-31	7-32	0-1	3.4-5.0	39-117
Lab AUG94 male	**0-40**	**0-37**	**11-50**	**0-1**	**3.4-5.0**	**39-117**
female	**0-31**	**0-31**	**7-32**	**0-1**	**3.4-5.0**	**39-117**
Lab Software male	0-40	0-37	1-44	0.2-1.2	3.2-4.7	50-136
female	0-40	0-37	3-24	0.2-1.2	3.2-4.7	50-136

Table 2-3. Normal values for liver function tests.

III. METHODOLOGY

Methodology Overview

A brief discussion on aspects of medical surveillance and screening tests are important to understanding the direction of this study. This chapter provides the methodology used for the remainder of the study. It outlines the steps in transferring the database from PHOENIX to the SAS System, the steps used in creating a workable database, the programs used for the analysis, and a brief discussion on techniques used for the analysis. This thesis effort was accomplished in conjunction with similar research done on pulmonary function tests. Therefore, some lung information may be found in the programs used to develop the database for this research. Figure 3-1 depicts the flow of this process.

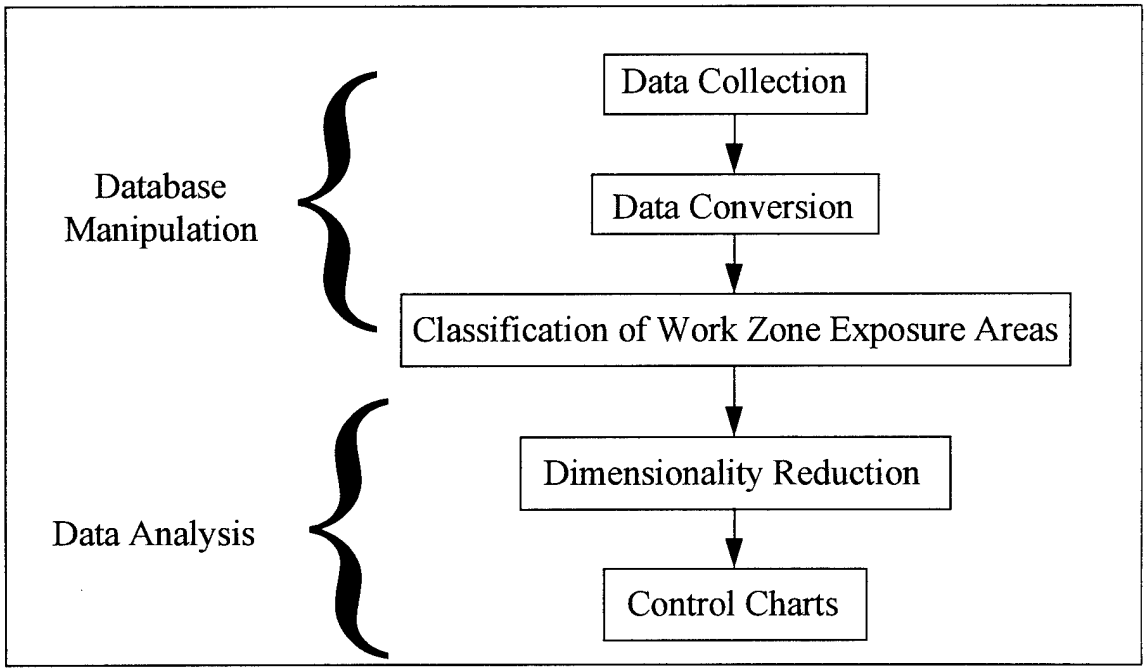

Figure 3-1. Database and analysis development.

Data Collection

The 74th SGPO has maintained their health database, called PHOENIX, on WPAFB personnel since 1989. The liver function tests are performed at the base hospital with the results initially hand-written on lab test result forms. From there, personnel manually transfer the information from test result forms to data entry sheets and finally into the database, all with no error checking procedures. The multiple opportunities for error may be a cause for concern.

Performing simple queries under the Data Base Reporting option isolates and stores each query in a separate file; seven separate files were extracted from PHOENIX. Downloading the files to floppy disk as flat ASCII files allowed them to be transferred to the UNIX mainframe system at AFIT via the WS-FTP protocol.

Data Conversion

The first step in the data conversion process is to convert the seven ASCII files into a SAS compatible database, done via the program CONVERT.SAS (see Appendix B for all SAS programs). This program also eliminates two problems in the database. First, the value 4303 is a code to identify "no data" and does not represent a numerical value. CONVERT.SAS replaces all these entries with a value of 0. Second, some test dates have no corresponding liver function test results. CONVERT.SAS deletes these entries.

In PHOENIX, administering each new test results in a new entry in the system. As a result, a single SSAN may have multiple entries, each corresponding to a different testing date. A series of programs, called *RAW.SAS (* replaces each liver function test variable), eliminates the multiple observations of each SSAN by putting every test result

and the respective test date on a single line. This is done for each liver function test variable. The maximum number of observations for any test is seven, which is hard coded in the programs, the variables are *1, *2, *3, . . ., *7. The output of these programs are designated *.RAW files.

The final step is to convert the *.RAW files into SAS files which is done by MERGEALL.SAS. This program also combines all the *.RAW files into a single database called HEALTH.WPAFB2. This workable database contains 174 variables and 2312 subjects (unique SSANs).

Classification of Work Zone Exposure Areas

In order to monitor common exposures, each subject is assigned a work zone. PHOENIX tracks these work zones and the dates in which a subject works in a particular zone. Work zones are based on the area of WPAFB in which a person works, either A, B, C, or K (Kittyhawk), the building number, a letter for identifying common exposures, and a number for further breakdown of the exact common exposures. For purposes of this analysis, common exposure areas for work zones are based on the area, building number, and 1st letter of exposure. This decision is made under the advisement of the 74th SGPO. LUNGALL.SAS classifies the zones for this analysis. This study uses 115 zones.

Dimensionality Reduction

Analysis begins after the creation of a workable database. The medical literature review suggests ALT and AST as the primary tests of interest in medical surveillance of the liver. By applying multivariate data reduction techniques, this claim may be supported. Two multivariate data analysis techniques applied in this study are principal components analysis and factor analysis. Both data reduction techniques study, explore, and hopefully simplify the interrelationships among the set of variables. Principal components analysis transforms the original set into new variables, called components, which are uncorrelated linear combinations of the original variables. The eigenvalues of the correlation matrix of original variables determine the number of components to include in the analysis. In this study, we employ Kaiser's Criterion; all components with eigenvalues greater than 1.0 will be considered significant. The number of significant principal components will determine the number of factors that will be used in the factor analysis.

Factor analysis is very similar to principal components analysis. Principal components analysis, explains as much of the total variation as possible with the number of components selected, while factor analysis explains the interrelationships (common variation) among the original variables and hopefully reduce the number of variables used through the factors.

Control Charts

After employing multivariate techniques and determing the final data, investigation turns to actually identifying the zones with high proportions of liver disease. The technique used is a form of statistical process control (SPC). SPC quickly detects occurrences (zones) with assignable variability (occupational cause of liver disease). SPC relies heavily on the control chart; a graphical display of a quality characteristic that has been measured or computed from a sample versus the sample number (Montgomery, 1991; 103). This application uses the liver function test results as the quality characteristic and the work zone for the sample number. The chart contains a center line representing the average value of the liver test and another horizontal line called an upper control limit (UCL). A zone in control plots below the UCL, for all but a preselected percentage. Liver test results from in control zones report either normal or abnormal values by chance alone. On the other hand, if a zone has an unexpectingly common occurrence of high test results, it will plot above the UCL. Any zone outside the UCL does not necessarily indicate occupational liver disease, but signals an investigation may be necessary.

In developing control charts, a number of their attributes must be addressed. First, they are generally based on a $\pm 3\sigma$ away from the mean (3 standard deviations in either direction from the average). This accounts for 99.73% of the observations (under the normal distribution). Although this is a standard practice, we used the established lab normals which account from anywhere between almost 90% and over 99% of the observations depending on the test (see Table 4-2). Secondly, we were confronted with varying sample sizes. We accounted for the variation by standardizing the results and plotting:

$$Z_i = \frac{\hat{p}_i - p}{\sqrt{\frac{p(1-p)}{n_i}}}$$

where Z_i = the plotted statistic (in standard deviation units)
$\hat{p}_i$ = (abnormal people in zone i)/sample size
p = probability of being abnormal (0.05)
n_i = sample size for zone i

Once these issues have been addressed, the control chart proves to be an excellent tool in identifying the work zones where occupational liver disease may be a problem.

IV. RESULTS

Overview

This chapter reports all the findings from this analysis. First, we approximated the liver function test empirical distributions. From these distributions, we established upper control limits from the population and compared them to those established by the 74th SGPO. Next, we reduced the data set using multivariate data analysis techniques (principal component analysis and factor analysis). Using those results, we subjected the reduced data set to process control methods where we identified the abnormal zones using three different criterion. This chapter concludes with a brief summary of those findings.

Liver Function Test Distributions

This analysis produced the desired product of the empirical distributions for each liver function tests on WPAFB personnel. To achieve this, the liver test scores for each SSAN, between one and seven observations, were averaged to ensure independence between data points. BestFit software, tested each set of outcomes against 18 families of distributions and the optimal parameters were approximated. To prevent biasing the fit to the distributions, data points outside the expected ranges were eliminated (they are considered erroneous data). A number of the liver function tests were well approximated by normal distributions. All those not well approximated by normal distributions were positively skewed. By transforming them to natural logarithms, their empirical distributions were approximately normal. Figure 4-1 contains the empirical distributions of the tests and the transformations. These transformations enable us to apply later

statistical methods requiring normally distributed data. After transformations, all tests are well approximated by normal distributions, based on Wilk-Shapiro criteria listed in Table 4-1.

Analysis	Eliminated Outliers	Number of Workers	Sample Mean	Sample Std Deviation	Wilk-Shapiro
ALT	none	804	26.10	13.11	0.8400
AST	514	753	23.08	10.06	0.6210
GGT	1601.7, 258	555	27.02	18.97	0.7000
Bilirubin	51.2	620	0.57	0.30	0.8433
Albumin	none	622	4.13	0.32	0.9203
AP	4725, 4266, 893.8, 793.7, 1	656	77.57	21.08	0.9523
ln ALT	none	804	3.16	0.46	0.9717
ln AST	6.24	753	3.08	0.31	0.9237
ln GGT	7.3788, 5.553	555	3.14	0.53	0.9743
ln Bilirubin	3.9357	618	-0.66	0.47	0.9809

Table 4-1. Liver function test applied to normal distributions.

Upper Control Limits

From the empirical distributions of each test, we determined the upper end percentiles for the population used for study and related them to the established upper control limits. To do so, we rank-ordered the observed values from smallest to largest and picked the desired percentile directly from the rank-ordered list. Table 4-2 gives the relevant percentiles of the population studied.

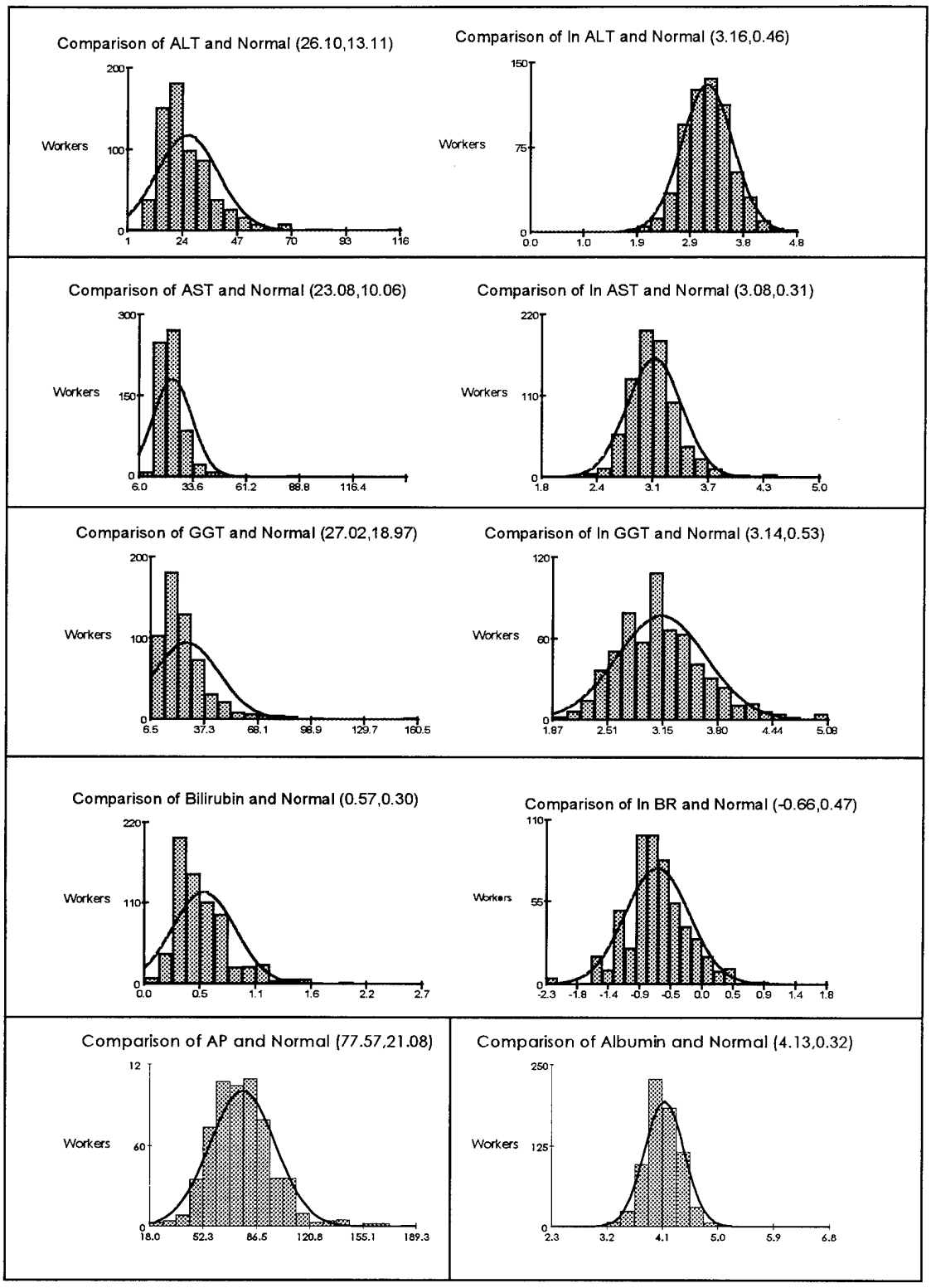

Figure 4-1. Distributions of liver function tests.

Test	Lab Upper Limit	Percentiles			
		90th	95th	97.5th	99th
ALT	40	42	49	59	70
AST	37	31	36	44	68
GGT	50	47	63	79	132
BR	1	1	1.1	1.4	1.6
Albumin	5.0	4.5	4.6	4.7	4.9
AP	117	88	92	94	96

Table 4-2. 90th through 99th percentiles of workers.

Table 4-2, demonstrates the normal limits used and established by the 74th SGPO vary from somewhere below the 90th percentile (ALT) to above the 99th percentile (Albumin and AP) based on the population for this study. Ideally, all tests should use the same percentile, say 95th, for classifying as a normal or abnormal reading. We used the hospital lab upper limits requested by the 74th SGPO.

Multivariate Analysis

The medical literature review suggested ALT and AST as the primary tests of interest in medical surveillance of the liver. By applying multivariate data reduction techniques, this claim may be supported. Two multivariate data analysis techniques applied in this study were principal components analysis and factor analysis.

For this portion of the study, we only used an observation if all six variables were recorded on the date the liver test was administered. Principal components analysis and factor analysis require the same number of observations for each variable. As a result, 424 individuals with all six liver function test results are used in the multivariate portion of the analysis.

The main objective of this analysis was to reduce the dimensionality of the six liver tests to two or three dimensions which can help explain the underlying communality (how each variable covaries with the factors) of the tests. It is hoped factor score plots will reveal regions of normal and abnormal scores. The six variables; ALT, AST, GGT, bilirubin, albumin, and AP determine the six dimensions of the data set. Table 4-3 is a summary of our normality tests using the 424 observation subset on these variables using the Wilk-Shapiro statistic.

Variable	Wilk-Shapiro Statistic of Variable	Wilk-Shapiro Statistic of Natural Log (Variable)
ALT	0.8817	**0.9887**
AST	0.7349	**0.9538**
GGT	0.6830	**0.9686**
Bilirubin	0.8491	**0.9652**
Albumin	**0.9062**	0.9565
AP	**0.9483**	0.9739

Table 4-3. Wilk-Shapiro statistics.

For this study, a Wilk-Shapiro value of 0.9 or higher was considered acceptable for an approximation of normally distributed data. Even though the log transformations for albumin and AP improve the normality, the improvement appears nominal. Therefore, we used the ln(ALT), ln(AST), ln(GGT), ln(BR), albumin, and AP for the principal components analysis. By using these transformations in place of the original variables (using data with approximately normal distributions), the first two eigenvalues explain about three percent more of the variance.

Using the ln(ALT), ln(AST), ln(GGT), ln(BR), albumin, and AP values we obtained the correlation matrix used for the principal components analysis (see Table 4-4).

Three data points had a bilirubin value equal to zero; they were deleted from the data set since the ln(0) does not exist.

	Ln ALT	Ln AST	Ln GGT	Ln BR	AP	Albumin
Ln ALT	1.0000	0.6495	0.5027	-.0204	0.1131	0.2494
Ln AST	0.6495	1.0000	0.2516	-.0038	0.0807	0.1526
Ln GGT	0.5027	0.2516	1.0000	-.0968	0.2337	0.1748
Ln BR	-.0204	-.0038	-.0968	1.0000	-.1342	0.0695
AP	0.1131	0.0807	0.2337	-.1342	1.0000	0.0177
Albumin	0.2494	0.1526	0.1748	0.0695	0.0177	1.0000

Table 4-4. Correlation matrix.

From the correlation matrix, we obtained the eigenvalues which can be used to calculate the amount of variance each of the components explain; the more variance explained, the better (Table 4-5). Using Kaiser's criterion, only two principal components were suggested to be used in this analysis. Although the third principal component has an eigenvalue close to 1.0, but adhered to the criterion of only accepting value above 1.0 established before the study began. The first two components explain about 55% of the total variation in the data.

	Eigenvalue	Difference	Proportion	Cumulative
PRIN1	**2.11392**	0.938320	0.352320	0.35232
PRIN2	**1.17560**	0.270290	0.195933	**0.54825**
PRIN3	0.90531	0.065253	0.150885	0.69914
PRIN4	0.84005	0.157905	0.140009	0.83915
PRIN5	0.68215	0.399177	0.113692	0.95284
PRIN6	0.28297		0.047162	1.00000

Table 4-5. Eigenvalues of the correlation matrix.

	PRIN1	PRIN2	PRIN3	PRIN4	PRIN5	PRIN6
Ln ALT	**0.606582**	0.123107	-.216586	0.026185	-.024660	-.754122
Ln AST	**0.517509**	0.180599	-.428703	0.097185	0.441817	0.557795
Ln GGT	**0.485061**	-.200184	0.165009	0.050529	-.762522	0.336780
Ln BR	-.063085	**0.673889**	0.262303	0.678808	-.110395	0.011112
AP	0.212882	**-.585046**	0.462072	0.487615	0.397880	-.053061
Albumin	0.282242	0.340220	**0.678058**	-.537372	0.228591	0.061688

Table 4-6. Matrix of eigenvectors.

By Kaiser's criterion, the data is reduced to two dimensions with the first dimension (PRIN1) being characterized by ln(ALT), ln(AST), and ln(GGT) and the second dimension (PRIN2) being characterized by AP and ln(bilirubin). Albumin dominates PRIN3 with a corresponding eigenvalue of 0.9. Adding this dimension would then explain over 70% of the total variation. Although this is a valid case for including the third component, the albumin test has a different clinical interpretation than the other five variables. Plus, from an analytical view point, it is better to use the single variable albumin (independently) instead of the third principal component. Since the component is less than 1.0 and only heavily influenced by the single variable, the variable should be used if the information in protrays is important enough. At this point, we kept albumin in the data set, but adhered to Kaiser's criterion and examined only the first two dimensions in the factor analysis. Later, the effects of removing albumin were also examined. The factor pattern of the initial factor analysis using the principal components procedure above is in Table 4-7.

The factors appear interpretable; Factor 1 deals primarily with tests measuring the direct health of the liver (how many liver cells are damaged or dying) while factor 2 deals with the congestion within the liver function. This supports the distinctions made by

	Factor 1	Factor 2	Communality
Ln ALT	**0.88193**	0.13348	0.795616
Ln AST	**0.75242**	0.19581	0.604483
Ln GGT	**0.70525**	-0.21705	0.544481
Ln BR	-0.09172	**0.73066**	0.542284
AP	0.30952	**-0.63434**	0.498182
Albumin	0.41036	0.36888	0.304471
Variance Explained	2.113918	1.175598	
Final Communality Estimate: Total = 3.289517			

Table 4-7. Factor pattern.

Douidar, 1992, who stated ALT, AST, and GGT all represent loss of hepatocyte cellular integrity and BR and AP measure cholestatic functioning. Although the factors are interpretable, a varimax rotation was applied to make these loadings easier to interpret and more clear. This transformation is used to find new axes in the two dimensional space to represent the factors. The new axes we determined by maximizing the sum of the variances of the squared factor loadings within each factor and adjusting them by dividing by the communalities which correspond of these variables. The orthogonal transformation matrix which accomplished this rotation is in Table 4-8.

	1	2
1	0.96476	-0.26135
2	0.26315	0.96476

Table 4-8. Orthogonal transformation matrix for varimax rotation.

We get the factor pattern in Table 4-9 after the varimax rotation which gives us the same interpretation as before with slightly more distinction between the factors. One point of interest is the sign difference between ln(BR) and AP in factor 2. This contrast stems

from the nature of the tests and what they measure; a rise in bilirubin results when there is excessive red blood cell destruction in the liver while AP (a protein) production is decreased in a dysfunctional liver. The negative correlation is expected since bilirubin increases and albumin decreases with liver damage.

	Factor 1	Factor 2	Communality
Ln ALT	**0.88597**	-0.10330	0.795616
Ln AST	**0.77743**	-0.00908	0.604483
Ln GGT	**0.62327**	-0.39498	0.544481
Ln BR	0.10378	**0.72905**	0.542284
AP	0.13168	**-0.69343**	0.498182
Albumin	0.49297	0.24790	0.304471
Variance Explained	2.048943	1.240573	

Table 4-9. Factor pattern after varimax rotation.

Each factor score was estimated by a linear combination of standardized values of the six variables. The standardized scoring coefficients are in Table 4-10. Using these coeffiecients, each observation was given a factor 1 and factor 2 score. Utilizing the normal values for liver function tests established by the 74th SGPO (Table 2-3), individuals were classified as normal or abnormal. For plotting purposes, those with abnormal readings were put into one of two categories. Abnormal results in any of the tests primarily contributing to factor 1 (ALT, AST, and GGT) were combined as were the individuals with abnormal results in tests primarily contributing to factor 2 (BR and AP).

	Factor 1	Factor 2
Ln ALT	0.43238	-0.00025
Ln AST	0.38722	0.06703
Ln GGT	0.27328	-0.26591
Ln BR	0.12169	0.61104
AP	-0.00073	-0.55910
Albumin	0.26985	0.25164

Table 4-10. Standardized scoring coefficients.

Since albumin did not factor heavily in the scores, an abnormal albumin reading was not plotted. The factor scores for normal and abnormal individuals are plotted in Figure 4-2.

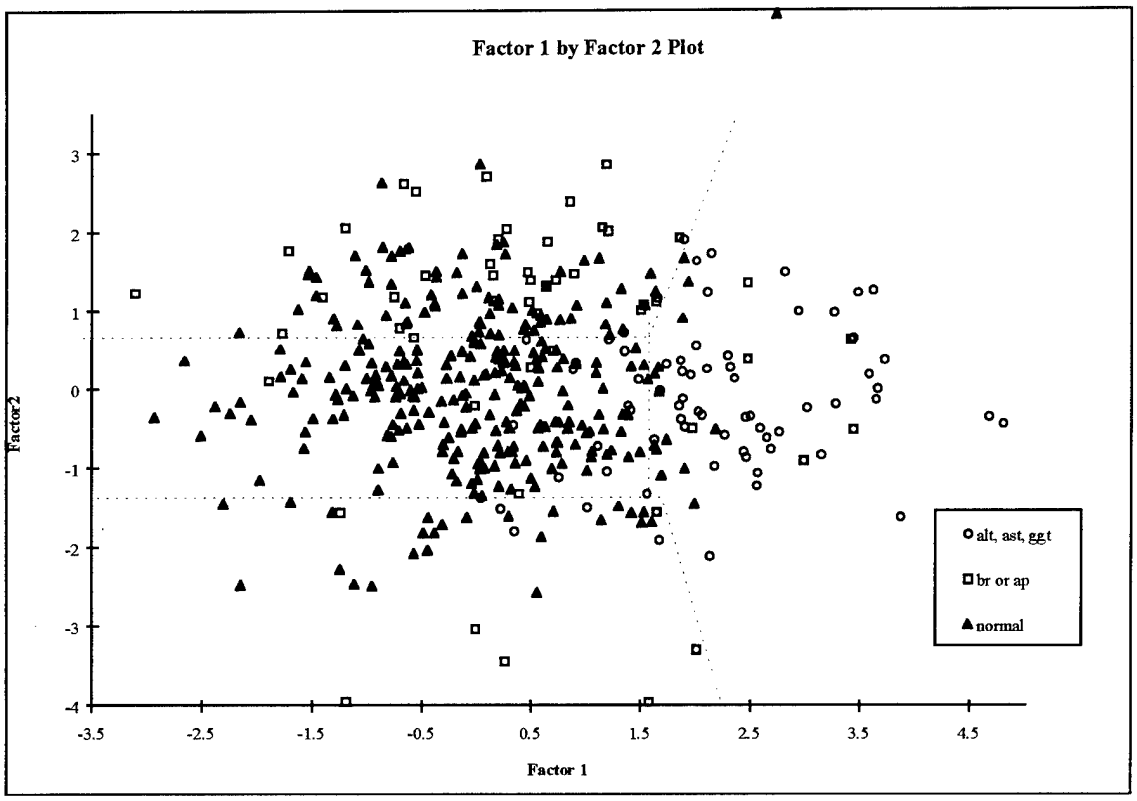

Figure 4-2. Plot of factor 1 scores and factor 2 scores.

Figure 4-2 shows four regions; normal subjects, abnormalities corresponding to component 1, and two regions of abnormalities corresponding to component 2. Component 1 is predominately associated with high factor 1 scores (> 1.1) and nearly uniform with respect to factor 2 scores. On the other hand, component 2 is predominately in the region of high or low factor 2 scores and uniform with respect to factor 1. Those low factor 2 scores are not a concern because they do not represent liver dysfunction. Figure 4-2 not only illustrates the regions of normality and abnormality, but also

demonstrates the distinction between the two factors and their respective components (ALT, AST, and GGT are associated with quality of the cellular function while BR and AP are associated with congestion in the liver). Since albumin measures something independent, it was not included in Figure 4-2. However, keeping albumin in the data set may have caused a confounding effect and had undue influence on the scores. One of the reasons for accomplishing factor analysis is to determine what variables are important and albumin did not appear important for what we wanted to measure. Independent studies by Kremer, 1994, Lundberg, 1994, and Tamburro, 1981, support using ALT, AST, GGT, BR, and AP (eliminating albumin). Therefore, we considered the contribution from albumin to be irrelevant information for this study and dropped it from the original data set and performed the analysis again. The results using the remaining five variables are found in Tables 4-11 through 4-14 and Figure 4-3.

The analysis for the five variable case paralleled the six variable case, but with stronger evidence that ALT, AST, and GGT are interrelated and separate from

	Eigenvalue	Difference	Proportion	Cumulative
Prin 1	**2.0187**	0.8817	0.4037	0.4037
Prin 2	**1.1370**	0.2719	0.2274	0.6311
Prin 3	0.8650	0.1711	0.1730	0.8041
Prin 4	0.6939	0.4085	0.1388	0.9429
Prin 5	0.2854		0.0571	1.0000

Table 4-11. Eigenvalues of the correlation matrix with five input variables.

interrelated BR and AP. Figure 4-3 shows similar results to Figure 4-2, but the regions are more pronounced. There appears to be a fairly good distinction in the factor 1 scores in measuring the health of the liver as abnormal or normal. A similar break exists with respect to the congestion measure on the factor 2 score scale. However, this distinction is

not as clear as in factor 1. The conclusions drawn from the factor analysis allowed us to classify the factors based on what their respective function: factor 1 can be called a Transferase Index and factor 2 is a Liver Congestion Index.

	Before Rotation		After Varimax Rotation		
	Factor 1	Factor 2	Factor 1	Factor 2	Communality
Ln ALT	0.88382	0.22600	**0.91172**	0.03129	0.832215
Ln AST	0.76797	0.32739	**0.82901**	-0.09855	0.696972
Ln GGT	0.71672	-0.18362	**0.63555**	0.38009	0.548399
Ln BR	-0.13360	0.72395	0.07508	**-0.73234**	0.541952
AP	0.34093	-0.64998	0.14524	**0.71764**	0.536105
Var Explained	2.018690	1.136953	1.949155	1.206489	

Table 4-12. Factor patterns before and after rotation for five variable case.

	1	2
1	0.95976	0.28082
2	0.28082	-0.95976

Table 4-13. Orthogonal transformation matrix for five variable case.

	Factor 1	Factor 2
Ln ALT	0.47602	-0.06783
Ln AST	0.44599	-0.16954
Ln GGT	0.29473	0.25699
Ln BR	0.11529	-0.62971
AP	0.00204	0.59442

Table 4-14. Standardized scoring coefficients for five variable case.

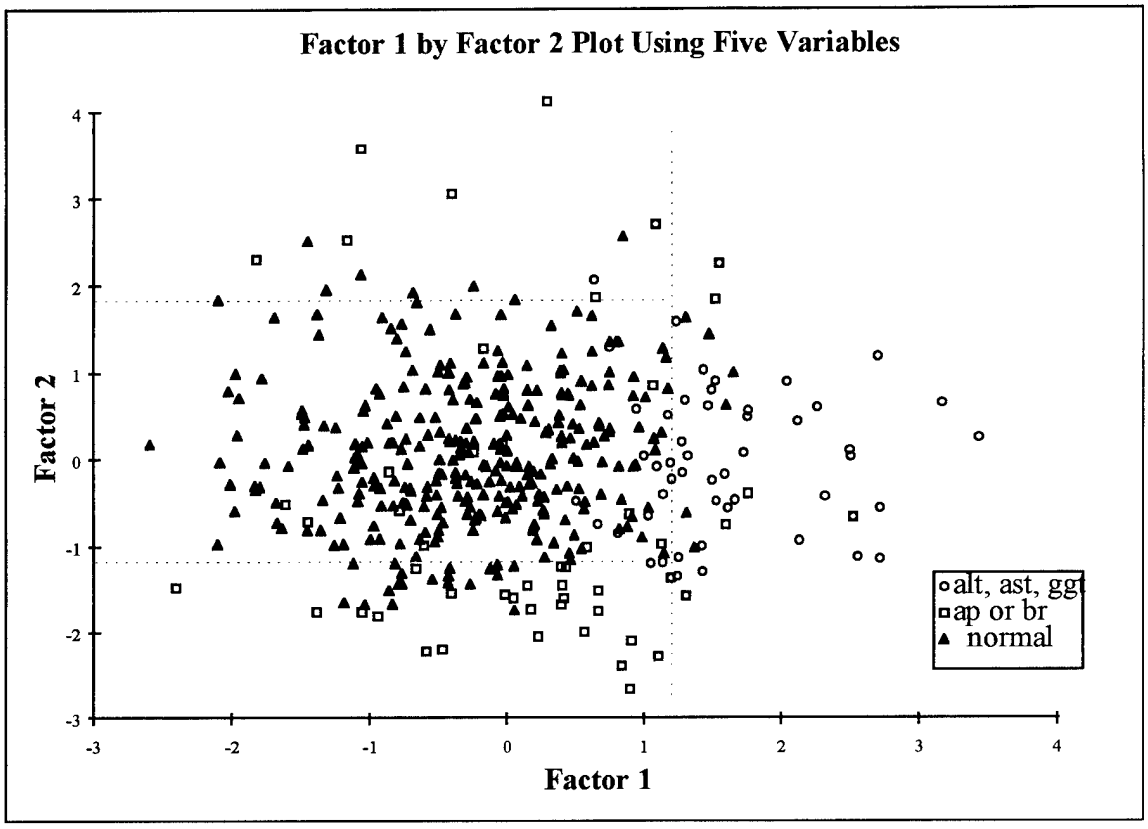

Figure 4-3. Factor 1 by Factor 2 plot using five variables.

The use of these indicies as screening metrics had promising potential. However, the 74th SGPO desired a single easy measure for the screening of liver disease. Therefore, we pursued further data reduction. Occupational exposures causing liver disease primarily impact the inputs to the Transferase Index, made up of the natural logs of ALT, AST, and GGT. Therefore, we emphasized these tests for further examination and eliminated BR and AP from consideration as screening tools for liver disease. Although eliminating data has potential adverse consequences, our goal was to find the easiest efficient metric possible and eliminating data that is not is as meaningful helped accomplish this end. To further understand the relationships between ALT, AST, and GGT, we performed another factor analysis on just these three variables to determine the

underlying communality of these tests (an attempt to reduce three dimensional data to one dimension); 1 factor was retained by Kaiser's criterion. The results are summarized in Tables 4-15, 4-16, and Figure 4-4.

	Eigenvalue	Difference	Proportion	Cumulative
Prin 1	**1.9424**	1.1744	0.6475	**0.6475**
Prin 2	0.7680	0.4783	0.2560	0.9034
Prin 3	0.2897		0.0966	1.0000

Table 4-15. Eigenvalues of the correlation matrix using ALT, AST, and GGT.

	Factor 1	Communality	Scoring Coefficient
Ln ALT	0.91085	0.829652	0.46894
Ln AST	0.80399	0.646400	0.41392
Ln GGT	0.68287	0.466316	0.35157
Variance Explained	1.942368		
Final Communality Estimates: Total = 1.942368			

Table 4-16. Results from factor analysis on ALT, AST, and GGT.

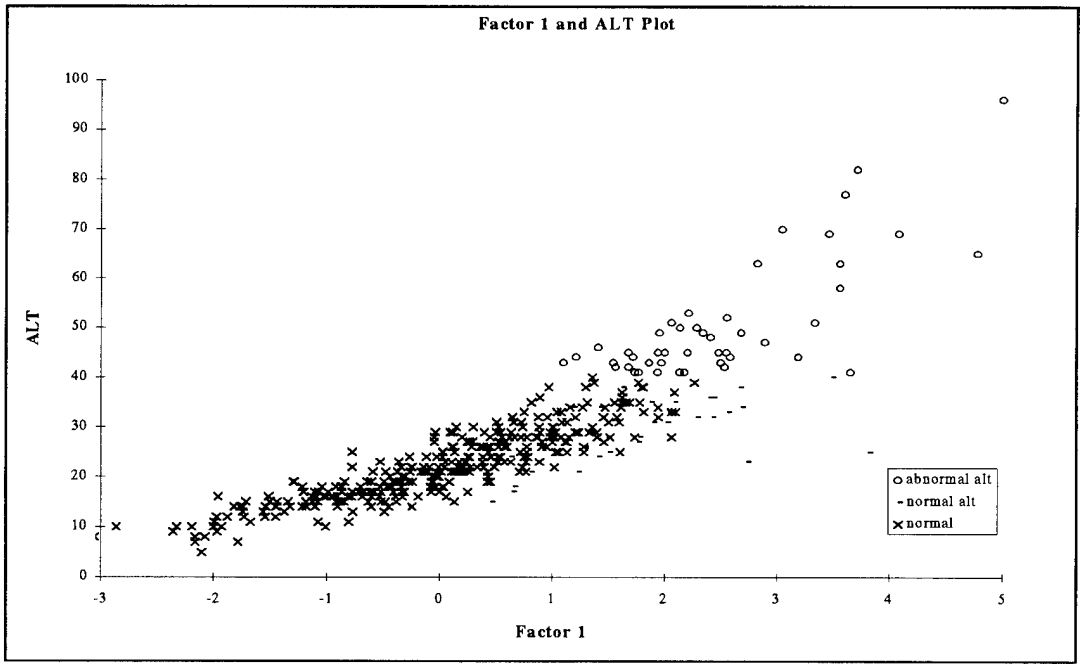

Figure 4-4. Plot of Factor 1 and ALT

The natural log of ALT is highly correlated with the resulting factor score at 0.91 which, not surprisingly, is seen in Figure 4-4. Figure 4-4 shows if the ALT reading is abnormal, we should also have an abnormal Transferase Index. Although there are some missed observations (where the Transferase Index indicates abnormality but there is a normal ALT reading), the overall trend is convincing. This supports the literature which states the ALT measurement is the most useful tool in screening for occupational health hazards. Abnormal factor 1 socres with normal ALT scores appear to be related to the lack of specificity found in the GGT test. Therefore, ALT is a reasonable sole indicator of the liver disease the 74th SGPO is trying to identify.

Control Charts

Multivariate analysis, indicated a combination of ALT, AST, and GGT were the optimal liver function test battery. Further, ALT by itself is a respectable indicator as a screening test for liver disease. These liver tests were applied to statistical process control (SPC) techniques and resulting control charts (graphical displays of liver test results versus work zones) were constructed. Due to the nature of the data set, separate control charts were made for each year.

Three sets of control charts were developed. The first set used all the inputs in the Transferase Index. Due to inconsistant data collection from year to year , the actual Transferase Index could not be applied. Therefore, if an individual had at least one test (ALT, AST, or GGT) above the established upper limits (see Table 2-3), they were classified as abnormal for that year. Every person was then put in their respective work

zone and the zones were standardized based on sample size. To standardize, the variable plotted is:

$$Z_i = \frac{\hat{p}_i - p}{\sqrt{\frac{p(1-p)}{n_i}}}$$

where Z_i = the plotted statistic (in standard deviation units)
$\hat{p}_i$ = (abnormal people in zone i)/sample size
p = probability of being abnormal (0.05)
n_i = sample size for zone i

The observations were arranged in descending order by standardized score to avoid any sense of time series from one observation (zone) to the next. An example of a control chart is in Figure 4-5.

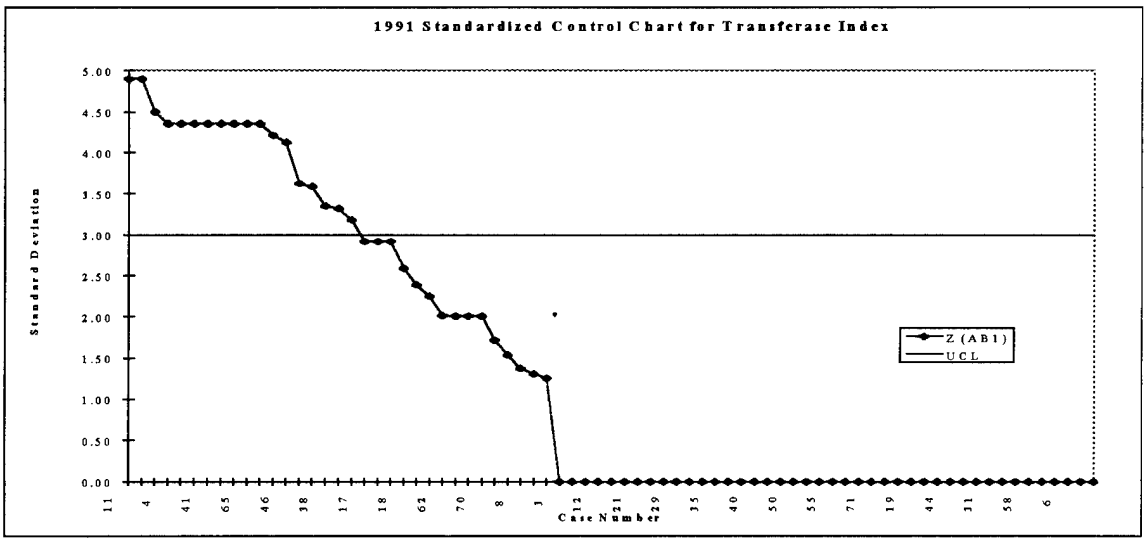

Figure 4-5. 1991 standardized control chart for Transferase Index inputs.

Figure 4-5 shows 18 zones above the UCL of 3.0 standard deviations in 1991. The case numbers which plot above the acceptable limits correspond to specific zones (which can be read off a chart); using case numbers simplified the chart. 1991 was chosen because

the data in that year was the most extensive. Control charts were made for each year and a summary table for this set of control charts is in Table 4-17. The summary table is used to eliminate looking up case numbers in a table. We also examined the effects of multiple abnormal scores for the same individual and no conclusive findings were made.

The second set of control charts used a different criterion for abnormality. At the request of the 74th SGPO (and supported by the multivariate analysis), only ALT was considered. If an individual had an abnormal test result in a given year, they were classified as abnormal. The remainder of the procedure followed that of the first set of control charts. A summary table for this set of control charts is found in Table 4-18.

The natural question becomes "which criterion is the better alternative?" Table 4-19 shows a comparison between the two alternatives. Every shaded area is year when the respective zone was identified as out of control by the Transferase Index inputs criterion. A "hit" signifies where the ALT criterion also found that zone to be out of control and a "miss" indicates in control by the ALT criterion. It should also be noted that the data for 1994 and 1995 rely heavily on ALT; AST and GGT results are scarce which may skew the comparison of the two criterion.

Lastly, a series of demerit charts were produced. A demerit system was employed to account for varying degrees of abnormality. Not all abnormal test results are equally important since a zone with three or four individuals moderately above normal is not as great of a concern as a zone with two or three severe cases. Therefore, each abnormal test was assigned to a class according to severity. Each class represents a standard deviation further away from the mean. For the men, the standard deviation ($\sigma = 13.11$)

Zone	Occupational Group	1990	1991	1992	1993	1994	1995
A278A	Pest Management		3.63		3.39		
A830J	Hospital - Hyperbarics		4.36				
A830Q	Hospital - Hematology/Oncology			4.13			
A878A	Golf Course			3.59			
A894A	Golf Course (Twin Base)		4.36				
B18B	WL - Experimental Research	4.36					
B18C	WL - Experimental Research		4.90				
B33A1	Accel Eff		4.90				
B36D	Heat Distribution		4.36				
B433A	Navy Toxicology				4.07		
B4D	WL - Electro-Optics Warfare				4.36		
B490A	WL - Experimental Support		4.50				
B5G1	ASC - Production Control	4.36					
B6000	Fire Department (Page Manor)	5.13	3.35	4.77	6.33		7.55
B620C	WL - Systems Integration		4.36				
B620N	WL - Electronic Warfare		4.36				
B640B	AFIT/ENP Physics		4.13				
B652B	WL - Materials & Surf Interaction	3.59					
B654B	WL - Polymer Branch		3.18				
B655C	WL - Nondestructive Eval		4.36				
B743A	DRMO					4.36	
B76A1	Fire Departments #3 & #6	3.63			4.05		4.50
B79C	AL - Hazard Assessment		3.59				
B79E	AL - Hazard Assessment		4.36				
B824B	Machine Shop	4.36					
B838A	Occ. Env. Vet Medicine				4.36		
C13R	Aircraft Structural Maintenance			3.18			
C163A	Fire Departments #1, #2, & #5		3.32	3.80	8.04	5.91	6.27
C206E	Aircraft Modification				3.59	4.36	6.16
C70A	AFOSI Tech Svcs			4.36			
C71A1	Packing and Crating		4.36				
C89B	Environmental Management		4.22				
C91B1	Fuel Systems					3.59	
Number of Zones		62	75	38	31	23	24
Abnormal Count		6	18	6	8	4	4
Percent Abnormal		9.68	24.00	15.79	25.81	12.50	16.67

Table 4-17. Standardized scores of zones above upper control limits based on abnormal ALT, AST, or GGT tests (WL = Wright Labs, AL = Armstrong Labs).

Zone	Occupational Group	1990	1991	1992	1993	1994	1995
A830Q	Hospital - Hematology/Oncology			4.13			
A894A	Golf Course (Twin Base)		4.36				
B18B	WL - Experimental Research	4.36					
B18C	WL - Experimental Research		4.90				
B36D	Heat Distribution		4.36				
B433A	Navy Toxicology				3.30		
B490A	WL - Experimental Support		4.50				
B4D	WL - Electro-Optics Warefare				4.36		
B6000	Fire Department (Page Manor)		3.35	4.77	6.33		7.55
B620C	WL - Systems Integration		4.36				
B654B	WL - Polymer Branch		3.18				
B655C	WL - Nondestructive Eval		4.36				
B743A	DRMO					4.36	
B76A1	Fire Departments #3 & #6				4.05		4.50
B79C	AL - Hazard Assessment		3.59				
B79E	AL - Hazard Assessment		4.36				
B838A	Occ Env Vet Medicine				4.36		
C163A	Fire Departments #1, #2, & #5		3.32	3.80	8.04	3.71	6.27
C70A	AFOSI Tech Svcs			4.36			
C71A1	Packing and Crating		4.36				
C89B	Environmental Management		4.22				
C91B1	Fuel Systems					3.59	
C206E	Aircraft Modification				3.59		6.16
Number of Zones		62	75	38	31	23	24
Abnormal Count		1	13	4	7	3	4
Percent Abnormal		1.61	17.33	10.53	22.58	13.04	16.67

Table 4-18. Standardized scores of zones above upper control limits using abnormal ALT criterion (WL = Wright Labs, AL = Armstrong Labs).

was rounded up to 14 since all the ALT readings were integers. Further, the mean (26.096) plus 1σ (14) coincided with the upper control limit established by the 74th SGPO. A similar situation occurred with the female's ranges. The scheme we used was the following (female values in parentheses):

Zone	Occupational Group	1990	1991	1992	1993	1994	1995
A278A	Pest Management		miss		miss		
A830J	Hospital - Hyperbarics		miss				
A830Q	Hospital - Hematology/Oncology			hit			
A878A	Golf Course			miss			
A894A	Golf Course (Twin Base)		hit				
B18B	WL - Experimental Research	hit					
B18C	WL - Experimental Research		hit				
B33A1	Accel Eff		miss				
B36D	Heat Distribution		hit				
B433A	Navy Toxicology				hit		
B4D	WL - Electro-Optics Warfare				hit		
B490A	WL - Experimental Support		hit				
B5G1	ASC - Production Control	miss					
B6000	Fire Department (Page Manor)	miss	hit	hit	hit		hit
B620C	WL - Systems Integration		hit				
B620N	WL - Electronic Warfare		miss				
B640B	AFIT/ENP Physics		miss				
B652B	WL - Materials & Surf Interaction	miss					
B654B	WL - Polymer Branch		hit				
B655C	WL - Nondestructive Eval		hit				
B743A	DRMO					hit	
B76A1	Fire Departments #3 & #6	miss			hit		hit
B79C	AL - Hazard Assessment		hit				
B79E	AL - Hazard Assessment		hit				
B824B	Machine Shop	miss					
B838A	Occ. Env. Vet Medicine				hit		
C13R	Aircraft Structural Maintenance			miss			
C163A	Fire Departments #1, #2, & #5		hit	hit	hit	hit	hit
C206E	Aircraft Modification				hit	miss	hit
C70A	AFOSI Tech Svcs			hit			
C71A1	Packing and Crating		hit				
C89B	Environmental Management		hit				
C91B1	Fuel Systems					hit	
TOTAL HITS = 31							
TOTAL MISSES = 14							
PERCENT HITS = 69%							

Table 4-19. Comparison of ALT, AST, GGT criterion and ALT criterion (WL = Wright Labs, AL = Armstrong Labs).

Class	Test Range	Approximate Standard Deviation Range
Class A Abnormalities	82 or > (69 or >)	> 4σ
Class B Abnormalities	68 - 81 (56 - 68)	3σ - 4σ
Class C Abnormalities	54 - 67 (43 - 55)	2σ - 3σ
Class D Abnormalities	41 - 53 (32 - 42)	1σ - 2σ

Let c_A, c_B, c_C, and c_D represent the number of Class A, Class B, Class C, and Class D abnormalities, respectively, in a particular zone. We assumed each class of defects was independent, and the occurrences in each class were well modeled by a Poisson distribution. Then we defined the number of demerits in that zone as

$$D = 100c_A + 50c_B + 10c_C + c_D$$

The demerit weights of Class A - 100, Class B - 50, Class C - 10, and Class D - 1 are used fairly widely in practice (Montgomery, 1991; 186).

Suppose a zone had n individuals it. Then the number of demerits per individual, u, is:

$$u = \frac{D}{n}$$

where D is the total number of demerits in the entire zone. Since u is a linear combination of independent Poisson random variables, Montgomery suggests plotting statistics u on control charts with the following parameters:

$$\text{UCL} = u + 3\hat{\sigma}_u$$

$$\text{Center line} = \overline{u}$$

where

$$\overline{u} = 100\overline{u}_A + 50\overline{u}_B + 10\overline{u}_C + \overline{u}_D$$

and

$$\hat{\sigma}_u = \left[\frac{(100)^2 \bar{u}_A + (50)^2 \bar{u}_B + (10)^2 \bar{u}_C + \bar{u}_D}{n} \right]^{1/2}$$

$\bar{u}_A, \bar{u}_B, \bar{u}_C, \bar{u}_D$ represent the average number of Class A, Class B, Class C, and Class D abnormalities per individual. From these calculations, control charts were made for each year. The 1991 Demerit Control Chart is in Figure 4-6 and a summary chart is in Table 4-20.

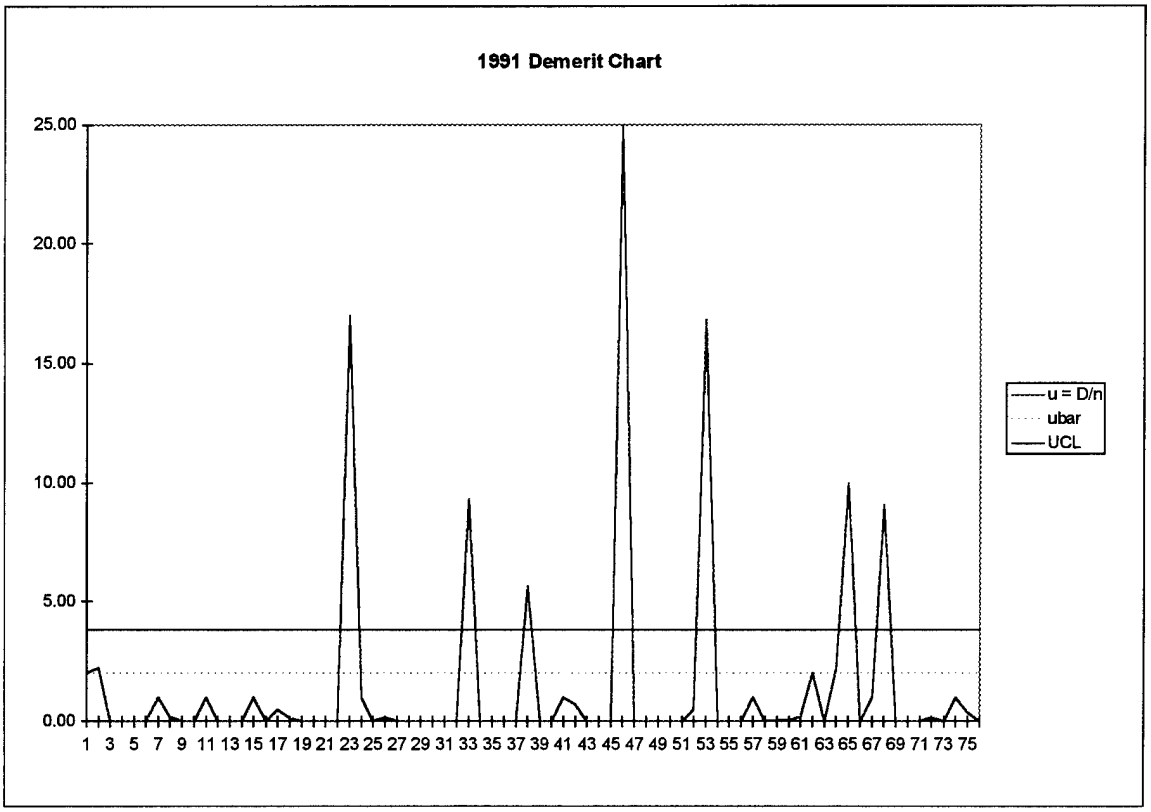

Figure 4-6. 1991 demerit control chart.

Summary

This study answered the questions initially posed by the 74th SGPO. It first looked into the distributions of the tests they use for monitoring occupational liver disease.

Zone	Occupational Group	1990	1991	1992	1993	1994	1995	Zone Sum
A278A	Pest Management		20		51	51	51	173
A830A	Hospital				1	1	1	3
A830Q	Hospital - Hematology	1		200				201
A878A	Golf Course			1	1	1	1	4
A894A	Golf Course (Twin Base)	1	1		50	10	100	162
B145A	Control Instrum & Assess		3					3
B33A	Accel Eff		51					51
B433	Navy Toxicology		2		261	1		264
B450D	WL - Aero & Airframes	50						50
B490A	WL - Experiment Support		112					112
B6000	Fire Dept (Page Manor)	12	102	111	161	1	3	390
B620F	Solid State Electronics		12					12
B640B	AFIT/ENP Physics		100					100
B652D	WL - Material & Surfaces	10						10
B654B	WL - Polymer Branch	100	101	100				301
B65A		10						10
B682A	Lib Cong - Mot Pic						11	11
B76A1	Fire Departments #3 & #6	64	2	102	103		4	275
B76A2	Fire Departments #3 & #6	1	1	1				3
B79A	AL - Hazard Assessment		62	100	50			212
B79C	AL - Hazard Assessment		11					11
B79E	AL - Hazard Assessment		10			10		20
C13R	Aircraft Stuctural MX			2	2	1		5
C148A	Aircraft Generation Branch	10						10
C163A	Fire Dept #1, #2, & #5	63	43	127	301	263	348	1145
C206E	Aircraft Modification	200	100	10	11		2	323
C4020A	Fuel Systems		1	1	51			53
C4021E	AGE				10			10
C89B	Environmental Mgt		3	11		50		64
C91B	Fuel Systems			10		111		121
Total		528	748	777	1057	501	522	

Table 4-20. Summary of demerit control charts.

All six test, either in their original form or through a log transformation, can be approximated using the normal distribution. We also examined the upper control limits they established and found some inconsistencies where the limits were set based on

percentiles of the population. Through multivariate analysis, we were able to eliminate some of the tests used in the past for screening. We found that ALT, AST, and GGT (Transferase Index) are sufficient in examining liver disease for their application and BR, AP, and albumin need not be used. Support was also found for the 74th's decision to use just ALT as the primary liver function screening test. Based on three different criterion, including a demerit system to weight severity, we identified five work zones on WPAFB where liver disease appears to have been a severe problem over the past six years (summary in Table 4-21). With this knowledge in hand, the 74th SGPO is equipped to concentrate efforts in the diminution or possible elimination of occupational liver disease at WPAFB.

Zone	Occupational Group	Transferase Criterion Average	ALT Criterion Average	Demerit Score
C163A	Fire Departments #1, #2, & #5	5.47	5.03	1145
B6000	Fire Department (Page Manor)	5.43	5.5	390
C206E	Aircraft Modification	4.7	4.88	323
B654B	WL - Polymer Branch	3.18	3.18	301
B76A1	Fire Departments #3 & #6	4.06	4.28	275
B433A	Navy Toxicology	4.07	3.3	264
A830Q	Hospital - Hematology/Oncology	4.13	4.13	201
A894A	Golf Course (Twin Base)	4.36	4.36	162
C91B1	Fuel Systems	3.59	3.59	121
B490A	WL - Experimental Support	4.5	4.5	112
C89B	Environmental Management	4.22	4.22	64
B79E	AL - Hazard Assessment	4.36	4.36	20
B79C	AL - Hazard Assessment	3.59	3.59	11

Table 4-21. Summary of liver disease "hot-spots." Zones identified by all three criterion (listed by demerit scores).

V. FINAL REMARKS AND FOLLOW-ON WORK

Final Remarks

The analysis conducted in this study was designed to be a screening tool for the 74th SGPO and help them identify zones with abnormal occurrences of liver disease. Based on the data and information available we developed a method to help detect abnormal zones enabling them concentrate efforts in the removal of occupational toxins causing liver disease. However, the study was not without areas of concern and possible improvement.

First, the PHOENIX database was extremely difficult to work with and produce meaningful results. At the time of this study, a new system was in the process of coming on-line. Hopefully, it will provide better access to the information collected and more reasonable means for future investigations. Secondly, the data itself is poorly entered and managed. There were numerous errors and inconsistencies. The database, whether with PHOENIX or some new system, must be properly maintained. The data must be put in accurately and consistently in order to obtain meaningful results from future studies.

Another area of concern was the current practices of the 74th SGPO; namely the established normals and the use of just ALT. The population used in this study does not correspond to consistent cut-offs for determining the normality of an individual's test result when compared to the established normals. Considering a change in the established normals may be appropriate unless proper justification exists for the current ones. In regard to primarily monitoring ALT since 1994, the multivariate analysis did show it is the single most important liver function test. However, the use of the Transferase Index

(or at least the tests used as inputs to the index) may provide more accurate assessments of the prevalence of liver disease.

Regardless of the specific values or criterion used to classify an individual as normal or abnormal, SPC, namely control charts, provide a ready means for monitoring worker health. The control charts present information in a meaningful and easy to understand manner which requires minimal understanding of statistics to the medical practitioner. Further, the use of a demerit system better captures the severity of abnormality, an important issue in medical surveillance.

Follow-On Work

While this research fully accomplished the set objectives, there exists areas for possible future research.

Criterion. A study could be done to find the most accurate criterion for identifying liver disease. Possible criterion include those used in this study, the Transferase Index, and a combination of other liver function tests.

Demerit System. An exploration into a demerit system to find optimal classifications and weights may provide better results. A study of this nature could be applied to the results from this research or many other areas of interest.

Body Systems. While this research was done in conjunction with a similar study on pulmonary functions, other body systems could be studied. Comparing results may add further insight into occupational exposures.

Common Exposures. This research only identified abnormal zones and did not investigate the actual causes of liver disease. Identifying common exposures is a logical next step in preventing workplace exposures.

Composite Health Index. This study only examined liver functions. Ideally, an overall composite health index to measure worker health, can be developed. Such an index would greatly assist medical surveillance efforts.

APPENDIX A
SCREENING ENZYME TESTS
Adopted from Fischbach, 1992

ALT (SGPT)

This test of enzyme levels is done primarily to diagnose liver disease. High concentration of the enzyme occur in the liver, and relatively low concentrations are found in the heart, muscle, and kidney. These enzymes are also used to monitor the course of treatment for hepatitis, active postnecrotic cirrhosis, or the effects of drug treatment that might be toxic to the liver. This test is also used to differentiate between hemolytic jaundice and jaundice due to liver disease. In comparison to AST, the ALT test is more specific for liver malfunction.

AST (SGOT)

AST is an enzyme present in tissues of high metabolic activity. It occurs in decreasing concentration in the heart, liver, skeletal muscle, kidney, brain, pancreas, spleen, and lungs. The enzyme is released into the circulation following the injury or death of cells. Any disease that causes change in these highly metabolic tissues will result in a rise in AST. The amount of AST in the blood is directly related to the number of damaged cells and the amount of time that passes between injury to the tissue and the test. In liver disease, the level may be 10 to 100 times the normal. Also, liver disease occasionally may cause a decrease instead of the expected increase.

GGT

The enzyme γ-glutamyl transferase is present mainly in the liver, kidney, prostate, and spleen. The liver is considered the source of normal serum activity, despite the fact that the kidney has the highest level of the enzyme. This enzyme is believed to function in the transport of amino acids and peptides into cells across the cell membranes and to be involved in glutathione metabolism. Men will have higher normal levels because of the large amounts found in the prostate. This test is used to determine liver cell dysfunction and to detect alcohol-induced liver disease. It is also an efficient way to screen for consequences of chronic alcoholism. The GGT is very sensitive to the amount of alcohol consumed by chronic drinkers. It can be used to monitor the cessation or reduction alcohol consumption. GGT activity is elevated in all forms of liver disease.

Bilirubin

Bilirubin, resulting from the breakdown of hemoglobin in the red blood cells, is a by-product of hemolysis (red blood cell destruction). A rise in serum levels will occur if there is an excessive destruction of red blood cells or if the liver is unable to excrete the normal amounts of bilirubin produced. A normal level of total bilirubin rules out any significant impairment of the excretory function of the liver or excessive hemolysis or red blood cells.

Albumin

Proteins and nucleic acids, the structural component of a cell, serve as biocatalysts (enzymes), regulators of metabolism (hormones), and preservers of genetic makeup (chromosomes). Amino acids are the building blocks of proteins. Albumin is a protein that is formed in the liver and that helps to maintain normal distribution of water in the body (colloidal osmotic pressure). It also helps in the transport of blood constituents such as ions, pigments, bilirubin, hormones, fatty acids, enzymes, and certain drugs. Approximately 53% to 60% of total protein is albumin. Decreased albumin levels are caused by many different conditions. Increased albumin levels are generally not observed.

AP

Alkaline phosphatase is an enzyme originating mainly in the bone, liver, and placenta, with some activity in the kidney and intestines. It is called alkaline because it functions best at a pH of 9. This enzyme test is used as a tumor marker and an index of liver and bone disease, when correlated with other clinical findings. In liver disease, the blood level rises when excretion of this enzyme is impaired as a result of obstruction in the biliary tract.

APPENDIX B
SAS PROGRAMS

The essential components of the three SAS programs used to develop a SAS compatible database are included in Appendix B. They are CONVERT.SAS which converts the ASCII files to SAS compatible files, SGPTRAW.SAS which eliminates multiple SSANs (similar programs were developed for each fiver function test variable), and MERGEALL.SAS which merges all *.RAW files into the HEALTH.WPAFB2 database we developed. A number of other programs were developed for data exploration, zone classification, factor analysis (through the use of PROC FACTOR), and extracting counts abnormalities based on varying criteria for each of the zones. Additional program templates can be found in the thesis completed by Cpt Paul McAree, GOR-96M.

APPENDIX B.1
CONVERT.SAS

```
libname health 'user2';
/*  Similar sections were done for each of
    the seven extracted files.  Those
    essential to the liver data are inclued
    here.*/
data health.chem;
    infile 'bryan1.';
    input first $ 1 ssan $ 1-9 sgpt 11-14
       sgot 16-19 yr 23-24 mo 26-27 dy
       29-30  ap 32-35 ggt 37-40 bili 42-
       45 albumin 47-50;
    if index('0123456789',first)>0;
    if ap = 4303 then delete;
    if sgpt = . & sgot = . & ap = . & ggt
       = . & bili = . & albumin = . then
       delete;
    format chemdate yymmdd6.;
    chemdate = mdy(mo,dy,yr);
    drop mo dy yr;
run;
data health.blood;
    infile 'thesis4.';
    input first $ 1 ssan $ 1-9 wbc $ 11-14
       yr 20-21 mo 23-24 dy 26-27
         hemcrit 29-33;
    if index('0123456789',first)>0;
    format blddate yymmdd6.;
    blddate = mdy(mo,dy,yr);
    drop mo dy yr;
run;
data health.zone;
  infile 'thesis5.';
     input first $ 1 ssan $ 1-9 zone $ 11-
       18 syr 22-23 smo 25-26 sdy 28-29
       eyr 33-34 emo 36-37 edy 39-40;
    if index('0123456789',first)>0;
    format stdate yymmdd6. enddate
       yymmdd6.;
    stdate = mdy(smo,sdy,syr);
    enddate = mdy(emo,edy,eyr);
   drop smo sdy syr emo edy eyr;
run;
```

APPENDIX B.2
SGPTRAW.SAS

```
libname health 'user3';
run;
options ls = 75 ;
proc sort data = health.chem;
        by ssan;
run;
data _null_;
 set health.chem;
 by ssan;
 file print notitles;
if first.ssan then do;
        put @1 ssan @11 sgpt @;
                n = 15;
end;
if first.ssan = 0 and last.ssan = 0 then do;
        put @n sgpt @ ;
        n = n+4;
        retain n;
end;
if last.ssan then do;
        put @n sgpt     @75 first;
end;
run;
```

APPENDIX B.3
MERGEALL.SAS

```
/* Similar components were done for all
*RAW files (including those for the
pulmonary research; data sets a through
h). Only those applicable to this effort
are included here.*/

data i;
   infile 'sgpt.raw';
   input ssan $ 1-9 sgpt1  11-14 sgpt2
      15-18 sgpt3  19-22 sgpt4  23-26
      sgpt5  27-30 sgpt6 31-34 sgpt7
      35-38 sgpt8  39-42;
   run;
   proc sort data = i; by ssan ; run;
data j;
   infile 'sgot.raw';
   input ssan $ 1-9 sgot1  11-14 sgot2
      15-18 sgot3  19-22 sgot4  23-26
      sgot5  27-30 sgot6  31-34 sgot7
      35-38 sgot8  39-42;
   run;
   proc sort data = j; by ssan ; run;
data k;
infile 'ap.raw'  ;
   input ssan $ 1-9 ap1    11-14 ap2
      15-18 ap3    19-22 ap4    23-26
      ap5    27-30 ap6    31-34 ap7    35-
      38 ap8    39-42;
   run;
   proc sort data = k; by ssan ; run;
data l;
   infile 'ggt.raw' ;
   input ssan $ 1-9 ggt1   11-14 ggt2
      15-18 ggt3   19-22 ggt4   23-26
      ggt5   27-30 ggt6   31-34 ggt7
      35-38 ggt8   39-42;
   run;
   proc sort data = l; by ssan ; run;
data m;
   infile 'bili.raw';
   input ssan $ 1-9 bili1  11-15 bili2  16-
      20 bili3  21-25 bili4  26-30 bili5
      31-35 bili6  36-40 bili7  41-45 bili8
      46-51;
   run;
   proc sort data = m; by ssan ; run;
data n;
   infile 'albumin.raw' ;
   input ssan $ 1-9 albumin1 11-15
      albumin2 16-20 albumin3 21-25
      albumin4 26-30 albumin5 31-35
      albumin6 36-40 albumin7 41-45
      albumin8 46-50;
   run;
   proc sort data = n; by ssan ; run;
data o;
   infile 'chemdate.raw';
   input ssan $ 1-9 yr1 11-12 mo1 13-14
      dy1 15-16 yr2 20-21 mo2 22-23
      dy2 24-25 yr3 29-30 mo3 31-32
      dy3 33-34 yr4 38-39 mo4 40-41
      dy4 42-43 yr5 47-48 mo5 49-50
      dy5 51-52 yr6 56-57 mo6 58-59
      dy6 60-61 yr7 65-66 mo7 67-68
      dy7 69-70 yr8 74-75 mo8 76-77
      dy8 78-79;
    format cdt1 cdt2 cdt3 cdt4 cdt5 cdt6
      cdt7 cdt8 yymmdd6.;
    cdt1 = mdy(mo1,dy1,yr1);
    cdt2 = mdy(mo2,dy2,yr2);
    cdt3 = mdy(mo3,dy3,yr3);
    cdt4 = mdy(mo4,dy4,yr4);
    cdt5 = mdy(mo5,dy5,yr5);
    cdt6 = mdy(mo6,dy6,yr6);
    cdt7 = mdy(mo7,dy7,yr7);
    cdt8 = mdy(mo8,dy8,yr8);
   drop yr1 mo1 dy1 yr2 mo2 dy2 yr3
      mo3 dy3 yr4 mo4 dy4 yr5 mo5 dy5
      yr6 mo6 dy6 yr7 mo7 dy7 yr8 mo8
      dy8;
   run;
```

```
   proc sort data = o; by ssan ; run;
/* Data sets p,q, and r were for data not
   used in the analysis*/
data s;
   infile 'zone.raw'  ;
   input ssan $ 1-9 zone1 $11-19 zone2
      $20-28 zone3 $29-37 zone4 $38-
      46 zone5 $47-55 zone6 $56-64
      zone7 $65-73 ;
   run;
   proc sort data = s; by ssan ; run;
data t;
   infile 'stdate.raw'  ;
   input ssan $ 1-9 yr1 11-12 mo1 13-14
      dy1 15-16 yr2 20-21 mo2 22-23
      dy2 24-25 yr3 29-30 mo3 31-32
      dy3 33-34 yr4 38-39 mo4 40-41
      dy4 42-43 yr5 47-48 mo5 49-50
      dy5 51-52 yr6 56-57 mo6 58-59
      dy6 60-61 yr7 65-66 mo7 67-68
      dy7 69-70;
   format sdt1 sdt2 sdt3 sdt4 sdt5 sdt6
      sdt7  yymmdd6.;
   sdt1 = mdy(mo1,dy1,yr1);
   sdt2 = mdy(mo2,dy2,yr2);
   sdt3 = mdy(mo3,dy3,yr3);
   sdt4 = mdy(mo4,dy4,yr4);
   sdt5 = mdy(mo5,dy5,yr5);
   sdt6 = mdy(mo6,dy6,yr6);
   sdt7 = mdy(mo7,dy7,yr7);
   drop yr1 mo1 dy1 yr2 mo2 dy2 yr3
      mo3 dy3 yr4 mo4 dy4 yr5 mo5 dy5
      yr6 mo6 dy6 yr7 mo7 dy7;
   run;
   proc sort data = t; by ssan ; run;
data u;
   infile 'enddate.raw' ;
   input ssan $ 1-9 yr1 11-12 mo1 13-14
      dy1 15-16 yr2 20-21 mo2 22-23
      dy2 24-25 yr3 29-30 mo3 31-32
      dy3 33-34 yr4 38-39 mo4 40-41
      dy4 42-43 yr5 47-48 mo5 49-50
      dy5 51-52 yr6 56-57 mo6 58-59
      dy6 60-61 yr7 65-66 mo7 67-68
      dy7 69-70;
   format edt1 edt2 edt3 edt4 edt5 edt6
      edt7  yymmdd6.;
   edt1 = mdy(mo1,dy1,yr1);
   edt2 = mdy(mo2,dy2,yr2);
   edt3 = mdy(mo3,dy3,yr3);
   edt4 = mdy(mo4,dy4,yr4);
   edt5 = mdy(mo5,dy5,yr5);
   edt6 = mdy(mo6,dy6,yr6);
   edt7 = mdy(mo7,dy7,yr7);
   drop yr1 mo1 dy1 yr2 mo2 dy2 yr3
      mo3 dy3 yr4 mo4 dy4 yr5 mo5 dy5
      yr6 mo6 dy6 yr7 mo7 dy7;
   run;
   proc sort data = u; by ssan ; run;
/* Data sets v and w were for data not
   used in the analysis*/
libname health 'user3';
   data health.wpafb2;
   merge a b (in=in1) c d e f g h i
      (in=in2) j k l m n o p q (in=in3) r s
      t u v w;
   by ssan;
   if in1 or in2 or in3;
   if zone1 = '  ' then delete;
   run;
   proc contents;
   run;
```

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VITA

Second Lieutenant Bryan D. Richardson was born on 15 September 1971 in Anchorage, Alaska. He graduated from Evergreen High School, Evergreen, Colorado, in 1990 and entered undergraduate studies at the United States Air Force Academy. After graduating with a Bachelor of Science degree in Operations Research and Economics, he was assigned to the School of Engineering, Air Force Institute of Technology. Following his March, 1996 graduation, Lieutenant Richardson was assigned as an analyst for Air Force Materiel Command, WPAFB.

Permanent Address: 92 Burning Tree Lane
Butte, MT 59701

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13. ABSTRACT *(Maximum 200 words)*

Traditionally, medical surveillance of liver disease generally involves a battery of tests. This research used multivariate analysis techniques to reduce the number of measures required to identify liver dysfunction and found using a Transferase Index (a combination of three tests; ALT, AST, and GGT) provided the most satisfying assessment, but the single best indicator, ALT, may be sufficient. Transferase Index and ALT criterion were both applied to SPC control charts. Through the use of statistical process control (SPC), this research identified work zones possessing signs of adverse effects to an individual's liver as a possible result of their work environment and demonstrated SPC as an excellent way to conduct medical surveillance. Industry has embraced SPC, and control charts, this research extended their scope and demonstrated their effective use in medical surveillance of the liver. This research showed they provide easy, efficient ways to monitor work environments.

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GENERAL INSTRUCTIONS FOR COMPLETING SF 298

The Report Documentation Page (RDP) is used in announcing and cataloging reports. It is important that this information be consistent with the rest of the report, particularly the cover and title page. Instructions for filling in each block of the form follow. It is important to ***stay within the lines*** to meet ***optical scanning requirements***.

Block 1. Agency Use Only *(Leave blank)*.

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Block 3. Type of Report and Dates Covered. State whether report is interim, final, etc. If applicable, enter inclusive report dates (e.g. 10 Jun 87 - 30 Jun 88).

Block 4. Title and Subtitle. A title is taken from the part of the report that provides the most meaningful and complete information. When a report is prepared in more than one volume, repeat the primary title, add volume number, and include subtitle for the specific volume. On classified documents enter the title classification in parentheses.

Block 5. Funding Numbers. To include contract and grant numbers; may include program element number(s), project number(s), task number(s), and work unit number(s). Use the following labels:

C	- Contract	**PR**	- Project
G	- Grant	**TA**	- Task
PE	- Program Element	**WU**	- Work Unit Accession No.

Block 6. Author(s). Name(s) of person(s) responsible for writing the report, performing the research, or credited with the content of the report. If editor or compiler, this should follow the name(s).

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- **DOD** - See DoDD 5230.24, "Distribution Statements on Technical Documents."
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