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Distribution		
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SUBJECT		

Health Records Study -- Louisville Plant
(Liver Function Blood Tests Versus Personal
History, Work History, Chemical Exposure)

GENERAL OBJECTIVE

Use statistical techniques to relate the personal and environmental histories of the Louisville plant employees to their health, especially that of the liver.

SPECIFIC OBJECTIVES

- A. Relate the personal and environmental histories of the Louisville plant employees to six liver function blood tests.
- B. Determine whether vinyl chloride monomer exposure can be directly (or in combination with another factor) related to liver function blood test abnormalities.
- C. Determine which employees may be prone to developing liver disorders, based on their personal histories and work experiences.

INTRODUCTION

In late 1973 Dr. J. Creech, the Louisville plant physician, discovered two cases of angiosarcoma of the liver (a rare form of liver cancer) among the deceased plant employees. Epidemiological studies of the Louisville plant employees followed immediately and by the Spring of 1974, five deaths due to angiosarcoma of the liver had been discovered for Louisville plant employees.¹ Furthermore, it was found that still other cases of angiosarcoma had occurred in vinyl chloride monomer (VCM) or polyvinyl chloride (PVC) producing plants in various parts of the world.^{2,3} Angiosarcoma is an extremely rare form of cancer -- so rare that the incidence, less than 1 per 500 employees at the Louisville plant, is still highly significant.

An in-depth study of angiosarcoma and its causes is underway at the University of Louisville Health Sciences Center. In the meantime, the present study was conceived at BFG in March, 1974, and data compiled through November of that year. The data have been made available to the University of Louisville. In addition, we have attempted to relate the six liver function blood tests to personal histories and worker exposures to 19 hazardous chemicals (including VCM).^{*} It is the first study we know of which has extended the investigation beyond VCM exposure level, age, and length of exposure.^{4,5}

* Table 4 in the Appendix lists the 19 hazardous chemicals which were selected.

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The real reason for a study such as this is to take employee histories and relate them to pathological disorders of the liver. Hopefully, this will some day be successfully accomplished, showing when a particular set of environmental circumstances clearly increases the chances of angiosarcoma. Further, precursors of angiosarcoma should be defined well enough so that an endangered individual can be removed from exposure before the disease is contracted. We could not hope to do this within the confines of the present study. The task will be more in the hands of those such as the Health Sciences Group at the University of Louisville.

Another reason for this study is to set up a medical-work history surveillance system for the B. F. Goodrich Company. A system specific to vinyl chloride workers through June, 1974 has been set up and assembled for seven Chemical Company locations (Avon Lake General Chemical, Avon Lake Technical Center, Calvert City, Henry, Long Beach, Louisville, and Pedricktown). Currently, a corporate team is working on a company-wide system. The information collected by the current study will be compatible with the new system.

The reader is reminded that only one person in 500 has contracted angiosarcoma and that the general pattern of blood test results is close to that usually observed (except SGPT levels seem high). The variation in blood quality among healthy individuals is about the same as the total variation of the blood tests included in this study. Therefore, rather weak correlations should be anticipated, and these may indicate relationships as strongly as will ever be found.

ACKNOWLEDGEMENTS

Early impetus for this study began at Louisville. Dr. J. Creech and J. R. Kute began setting up body function systems and worker job codes. W. J. Wilcox coordinated the planning effort and saw that data assembly was activated in the plants. The Akron Corporate Medical Staff critiqued plans and helped set up the personal history questionnaires. R. L. Bowles lent his assistance at many points and joined with J. P. Sandoz and J. R. Kute in planning the exposure index series. Advice and much chemical information was given by Dr. B. M. G. Zwicker. W. Bachtel and G. D. Schaaf assisted in selecting the hazardous chemicals and helped organize the exposure level series. Both the University of Kentucky and University of Louisville Medical staffs gave useful advice. The seven participating plants spent untold hours putting the best possible data together. Finally, R. Lasch, R. C. Bosshardt, S. Haehn, and L. L. Stephens set up special computer programs for the study, and both the Cleveland and Avon Lake Computer staffs made it possible to get everything together for the analysis.

CONCLUSIONS

1. SGPT level is directly related to an employee's vinyl chloride monomer exposure. None of the other 5 liver function tests were affected by VCM as strongly as SGPT.
2. Factors affecting the liver function tests are shown below. The arrows ($\uparrow$, $\downarrow$) indicate whether the blood test increases or decreases as the corresponding factor increases.

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<u>Tests</u>	<u>Related Factors</u>
SGPT	VCM exposure (↑), alcohol consumption (↓)
GGTP	Alcohol consumption (↑), VCM exposure (↑), liver problems (↑)
SGOT	Race, butadiene exposure (↑), liver problems (↑)
Total Bilirubin	Cigarette consumption (↓), VCM exposure (↑), vinylidene chloride exposure (↑)
Alkaline Phosphatase	Cigarette consumption (↑), sex, VCM exposure (↑), caprylyl peroxide exposure (↑)
LDH	None found

3. Of the 19 "suspect" chemicals evaluated in the form of 266 exposure indices, only the four mentioned above could be associated with any of the six liver function tests evaluated.

RECOMMENDATIONS

1. Given that the liver function blood tests are indicators of liver dysfunction, the results of this study suggest that
 - a. Exposures to high concentrations of vinyl chloride monomer, especially repeated exposures sufficient to produce dizziness or unconsciousness, must be avoided. (The Company has already taken steps to eliminate this as a possibility.)
 - b. High consumption of alcohol or tobacco, especially when combined with prolonged vinyl chloride monomer exposure, is undesirable. If health records studies of the other plants confirm this, it is recommended that vinyl chloride workers be advised of these results.
 - c. High vinylidene chloride and butadiene exposures may have harmful effects. Exposures to these chemicals probably should be minimized.

The above recommendation is based on the statistical results of the Health Records Study. The authors of this report are not qualified to give a medical opinion.

2. A list of those most likely to have blood abnormalities, based on chemical exposure and personal history experience, has been developed and sent to the Louisville plant medical group and University of Louisville Health Sciences Group. This list may be helpful in identifying people likely to develop health disorders.
3. Extend the Health Records analysis to the Avon Lake plant. Compare the conclusions for consistency.

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4. Extend this study to more sophisticated liver tests as soon as possible.
(Presumably this is being done by the University of Louisville Health Sciences Group.)

DATA ASSEMBLY

The data for this study came from four sources: (1) blood test results, (2) personal history questionnaires, (3) employee work histories, and (4) chemical exposure job ratings.

- (1) The blood test data were obtained from screenings carried out at the Louisville plant. Each plant employee was tested at least once.⁶ The following six liver function tests were the only blood tests used in this study:
 - a. Total Bilirubin
 - b. Alkaline Phosphatase
 - c. Lactic Dehydrogenase (LDH)
 - d. Glutamic-oxaloacetic transaminase (SGOT)
 - e. Glutamic pyruvic transaminase (SGPT)
 - f. Gamma glutamyl transpeptidase (GGTP)
- (2) Each plant employee was instructed to fill out a personal history questionnaire listing past history of liver-related diseases, individual VCM exposure information, and personal habits which might influence liver function.⁷
- (3) Each employee's work history was documented. Data available were (a) year started each job, (b) months on each job, and (c) job code. Each job in each building of the plant was assigned a separate job code.⁸
- (4) Each job was rated for exposure to each of the nineteen selected chemicals during each year of plant operation.⁸

Parts (3) and (4) above were then combined to provide fourteen exposure indices per chemical. Each index represents a different viewpoint of the type of exposure that might produce illness. E.g. average exposure, total time exposed, time working at a high level of exposure, etc.⁹

Figure 1 in the Appendix diagrams the steps of the data assembly.

A statistical description of the method of data reduction and analysis is contained in Appendix A.

ANALYSIS

Once the number of indices under consideration had been reduced to practical dimensions, several types of analysis were tried. The results of four approaches are discussed below. It will be seen that the four methods yield the same general conclusions. Of these four approaches, multiple correlation was the most successful in showing interactions and less obvious effects.

1. Automatic Interaction Detector (AID) was used to identify the single most important variable.

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2. AID was also used to develop proportionate abnormality tables for each blood test. These tables contrast the proportions of normal to abnormal liver function test results for each personal history question and principal exposure index.
3. Multiple correlation was used to develop mathematical models and graphs for each blood test.
4. Canonical correlations were used to combine the six liver tests into a single (best) function representing the general (liver) health of the individual.* This "function" was related to the personal history questions and more important exposure indices in a multiple correlation.

DISCUSSION

1. Single Most Significant Variable Affecting an Employee's Blood Tests

- a. Table 1 presents the single most significant variable affecting each of the blood tests. Total Bilirubin (T.B.) and Alkaline Phosphatase (A.P.) are both affected by cigarette consumption -- but in opposite directions. Cigarette smoking raises A.P. but lowers T.B. The groups are well within the norms,** but the differences are still statistically significant.
- b. GGTP is highly affected by alcohol consumption. GGTP tests on 33 employees consuming one or more drinks per day averaged above the upper norm.
- c. The personal history question concerning liver problems was related to SGOT. Those 14 reporting liver problems averaged at the upper norm.
- d. SGPT is affected by exposure to vinyl chloride monomer (VCM). Two variables, number of times dizzy from VCM and months of VCM exposure at levels greater than or equal to the intermediate level of (3), were found to have equal effects on SGPT.
- e. LDH showed no trends.

* The function was developed by the mathematical techniques of canonical correlation. Its medical significance is undefined.

** Norms for a blood test are selected so that approximately 95% of the test results from healthy people will fall within these limits.

2. Proportionate Study of Abnormal Blood Tests

A proportionate study of abnormal blood tests, similar to the Tabershaw/Cooper studies of proportionate mortality, shows additional variables affecting the blood tests (see Table 2).*

- a. Total Bilirubin and Alkaline Phosphatase are again related to cigarette consumption. A.P. also increased when gall bladder trouble was reported. GGTP is affected by alcohol and may be affected by vinylidene chloride ($VC1_2$), but the number of people exposed to $VC1_2$ is small. Liver problems are also related to an increase in GGTP.
- b. SGOT is again related to employees reporting liver problems.
- c. Of those exposed to caprylyl peroxide, 90% had an abnormal SGPT. However, this group of people was also highly exposed to VCM.
- d. As before, higher levels of SGPT are related to dizziness from VCM, and VCM exposure levels greater than or equal to 3.

3. Distribution of SGPT Test Results When Classified by Dizziness from Vinyl Chloride

Dizziness from VCM exposure represents acute exposure levels and VCM is a cancer producing suspect. The sharp differences in average SGPT for people repeatedly dizzy from VCM prompted a closer look at this relationship. Distributions of SGPT results for those employees never dizzy, dizzy one or more times, and dizzy five or more times are shown in Figures 2 and 3.

The median (50% point) for those dizzy one or more times from VCM is about fifteen points higher than for those never exposed. For those exposed five or more times, there is almost a 20 point difference in the median SGPT values.

Similar contrasting distributions were developed for GGTP and A.P. They showed no such separation. Rather, the curves for "dizzy" and "non-dizzy" groups were superimposed.

4. Considering Personal History and Chemical Exposure Variables in Combinations -- Multiple Correlation

The preceding tables were based on considerations of one variable at a time, and as such are useful for discovering variables with large effects and comparing numbers of people affected by the variables (such as the number of employees exposed to VCM).

A more powerful tool for uncovering variables that influence the blood tests is multiple correlation. GGTP and SGPT produced considerably stronger correlations than the other tests. However, none of the correlations explain a major portion of the observed liver function test variation (see Appendix A).

* Example of how to read this table: Under GGTP, of those 33 persons having ≥ 1 drink/day, 12 (36%) had an abnormal GGTP (> 37). Of the 191 consuming less than 1 drink per day, only 11 (6%) had an abnormal GGTP.

a. Total Bilirubin

Figure 4 shows the variables affecting Total Bilirubin. Increased cigarette consumption is again related to lower Total Bilirubin, but the amount of the decrease depends on an employee's VCM exposure.

There is also a synergism between VCM exposure and alcohol consumption -- a combination of both increases Bilirubin. Vinylidene chloride exposure is also related to increased Bilirubin.

b. Alkaline Phosphatase

Variables affecting Alkaline Phosphatase are shown in Figure 5. Males average 14 points higher (54 vs. 40) than females, but neither are above the upper norm of 85. The greater the number of months since an employee's last significant exposure to caprylyl peroxide, the higher the Alkaline Phosphatase.

An interrelationship was found between total tobacco usage (packs of cigarettes plus number of cigars plus frequency of chewing) and average vinyl chloride exposure. At 3 packs per day (or equivalent), employees with higher vinyl chloride exposure averaged 84, right at the upper norm.

c. GGTP

Variables affecting GGTP are shown in Figure 6. Liver problems increase GGTP from 15 to 49 (upper norm 37). Losing consciousness from vinyl chloride three times increased GGTP from 14 to 52, although only 2 employees who had the GGTP blood test reported losing consciousness this often. Alcohol consumption increases GGTP, confirming the results reported above.

d. SGOT

SGOT level is correlated with race (blacks average higher than whites), a history of liver problems, and average butadiene exposure. Employees with liver problems had an average SGOT of 39, which is near the upper norm (Figure 7).

e. SGPT

SGPT is correlated with vinyl chloride exposure and alcohol consumption (Figure 8). This interrelationship suggests that VCM exposure increases SGPT for non-drinkers, but heavy drinkers (4 drinks or more per day) with long VCM exposure exhibited low SGPT. In addition, those employees missing work for 2 or more weeks due to illness had lower SGPT's. These relationships were among the most difficult to rationalize in this investigation.

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5. Relating Combinations of Blood Tests to the Personal History and Chemical Exposure Variables

In the preceding sections, each blood test was correlated individually with the personal history and chemical exposure variables. Another approach is to consider the effects of the independent variables on all of the blood tests as a whole; i.e. finding variables which affect overall blood quality.*

The combination of blood tests which produced the highest possible correlation with personal history and chemical exposure indices varies as follows:

- a. At one extreme, GGTP is high while T.B. and LDH are kept at medium-to-low values.
- b. At the other extreme, T.B. and LDH are high while GGTP is maintained at very low levels.
- c. SGPT and SGOT have minor involvement with this variable.

Table 3 illustrates data for ten people, five at each extreme of the overall quality. It is found that a combination of high vinyl chloride exposure, frequent dizziness from VCM, alcohol consumption, and smoking contrasts very sharply for the two groups.

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* In general, this type of statistical analysis is called Multivariate Analysis. The specific multivariate analysis employed here is canonical correlation in which a linear combination of the blood tests, $a(\text{T.B.}) + b(\text{A.P.}) + c(\text{LDH}) + d(\text{SGOT}) + e(\text{SGPT}) + f(\text{GGTP})$, is correlated with the personal history and chemical exposure variables.