

LIVER DISEASE AMONG POLYVINYL
CHLORIDE PRODUCTION WORKERS

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ABSTRACT

A protocol for systematic testing of all employees of a chemical plant is presented. This factory manufactures polyvinyl chloride compounds and resins, Abson compounds and resins, and synthetic rubber. The results have been reviewed, leading to the discovery of two additional cases of angiosarcoma and 11 cases of portal fibrosis. Two of the 11 cases were found to have developed in other than polyvinyl chloride production employees.

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The B.F. Goodrich chemical plant in Louisville, Kentucky, manufactures polyvinyl chloride resins and compounds, ABS resins and compounds, and specialty synthetic rubber. Although there are over 200 chemicals used in these manufacturing processes, the principal chemicals used in the production of the polyvinyl chloride are the monomers vinyl chloride, vinyl acetate, and vinylidene chloride, whereas those used for the ABS and rubber production are butadiene, styrene, and acrylonitrile.

These processes are housed in different parts of the factory complex, thus making cross exposure very slight or nonexistent. However, work histories of all employees show that many of the rubber and ABS people have been involved in or worked in the polyvinyl chloride production area at some time or other. Also, the areas of production, other than the polyvinyl chloride production area, may have some very slight exposure to vinyl chloride as in the general plant environment.

In an attempt to relate liver abnormality to the degree of vinyl chloride exposure, five categories of work areas have been determined: The higher exposure is in the area of (1) polyvinyl chloride production. This is followed in order by (2) other areas of production, including the rubber plant, (3) maintenance personnel for the polyvinyl chloride production, (4) all other maintenance employees, and (5) all other employees - including administration, plant protection, secretarial services etc.

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In 1973 a series of events resulted in a need to review the death certificates of all former B.F. Goodrich employees¹. This resulted in the discovery of five deaths due to angiosarcoma of the liver. A review of past illnesses of current workers revealed that three employees had had splenectomy and/or a shunt procedure for hypersplenism or portal hypertension. This resulted in the initiation of a series of tests to determine the extent of liver disease in vinyl chloride workers.

As Figure #1 will show, the testing was started with a standard SMA-12, which included the SGOT, LDH, alkaline phosphatase, total bilirubin, albumin, total protein, cholesterol, uric acid, BUN, glucose, phosphorus, and calcium. The blood was drawn from fasting employees, then transported immediately to a local laboratory, where the testing was performed.

As can be seen, if the SMA-12 was reported as normal, the test was repeated in six months. If only one liver function test (SGOT, LDH, alkaline phosphatase, or total bilirubin) was elevated, the test was repeated in three weeks. Should this elevation persist, a battery of liver function tests was then requested. If two or more tests were elevated on the original examination, the battery was requested without delay. In those cases where the battery showed major abnormality, the special procedures and treatment as indicated were carried out. The battery of tests is listed in Table #1.

These included (in addition to the repeat SMA-12) the fractionation of LDH, alkaline phosphatase, and total bilirubin - SGPT, gamma GT, alpha feto protein, ICD, protein electrophoresis; and a CBC with platelet count.

X-rays consisted of chest X-ray and liver-spleen scan using Technetium 99M sulfur colloid.

The special procedures consisted of selective hepatic and splenic angiograms, as described by Viamonte et al in 1970, including free hepatic vein pressure studies and wedge hepatic vein pressure studies, and hepatic vein flow studies². A liver biopsy was performed when indicated. The first eight cases requiring biopsies were done at laporatomy. All remaining cases have been done through the internal jugular vein at the time of the hepatic vein catheterization, using a method first described by Hanafee in 1967 and more recently by Rosch et al in 1973^{3,4}.

In referring back to Figure #1, testing now continues in those cases showing improvement. If the no. 1 battery is found to be normal, the SMA-12 tests are repeated in six months. If there is questionable or only mild abnormality, then the chemical portion of the battery is repeated in three weeks.

If the no. 2 battery is normal, then a routine SMA-12 is done in three months. But if the no. 2 battery is found to persist or increase in degree of abnormality, then the special procedures and biopsy are scheduled.

Figure #2 will indicate the percentage of abnormalities found on the original examination of 1183 employees by using the SMA-12 tests.

315 individuals had one abnormal test - 26.6%.

41 individuals had two or more abnormal tests - 3.5%.

75 individuals out of the 315 tested for the second time were found to persist in the abnormality. This represented 6.3% of the plant population, or 24% of the second SMA-12 group.

A total of 116 cases had batteries run, or approximately 10% of the total plant population. Fifty-seven of the 116 cases were found to have normal batteries; seven cases were found to have major abnormality, requiring special procedures.

Fifty-two cases had minor or questionable abnormalities; ten of these 52 later showed persistent or increased degree of abnormality, leading to special procedures examination.

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The scans which were reported on 116 employees were broken down into five groups:

1. Patchy uptake - indicating cirrhosis or fibrosis.
2. Enlarged liver - which is of doubtful value.
3. Enlarged spleen - over 14-cm as described by Siegel⁵.
4. Cold spot - indicating tumor.
5. Normal liver-spleen scan.

The arterial and venous studies were reported as:

1. Corkscrewing of vessels - indicating cirrhosis or fibrosis.
2. Tumor blush - indicating tumor. (In angiosarcoma the blush persists for 20 seconds.)
3. Reversed portal flow - indicating portal hypertension with collateral circulation.
4. Portal or splenic vein thrombosis.
5. Level of free hepatic vein pressure.
6. Level of wedge hepatic vein pressure.
7. Corrected sinusoidal pressure (#6 minus #5).
8. Normal arterial and venous studies.

To date we have had 17 cases require special procedures, 16 of whom were biopsied. The nonbiopsied case had no abnormal liver tests but showed a defect on the scan which turned out to be a normal functioning displaced gall bladder.

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Table #2 will indicate the location of workers having abnormal SMA-12 examinations. It is seen that there was a greater percentage of abnormalities seen in the areas of production other than PVC. This, however, was of borderline statistical significance. The maintenance and other workers area also showed about the same degree of abnormality.

Table #3 shows the location of abnormal batteries. Here the statistical significance is valid, with 10% for PVC production as opposed to 4.1% abnormal for other areas of production.

Table #4 shows the percentage of individual abnormal tests of the SMA-12 with regard to location. The alkaline phosphatase was seen to be the most frequently elevated test. This could be due to the number of young workers scattered throughout the plant. Fractionation of the alkaline phosphatase elevations shows that only 54% had elevations of the heated fraction of 25% or over. This implies that liver caused the elevation in only 54% of the elevated cases.

Table #5 shows the percentage of abnormal individual battery tests with regard to location. There is no outstanding single test in this group.

Table #6 shows the results of the scan, the special procedures, and of the liver biopsy in 17 cases. Two of the 17 had angiosarcoma. Both are receiving chemotherapy. These two patients also demonstrated periportal fibrosis on the microscopic study of the liver biopsy.

As can be seen, there were five liver biopsies reported as normal - out of a total of 16 biopsies. Three of these five were anticipated, as neither battery, scan, nor special procedures showed any abnormality. The fourth case had minor liver function abnormalities with a cirrhotic scan. The fifth had an elevated liver function test.

Two of the remaining ten abnormal liver biopsies were found in patients who had worked only in other production areas. Both of these patients showed periportal fibrosis, as did the polyvinyl chloride worker. Periportal fibrosis was the most common diagnosis according to biopsy. Two of the eight remaining had splenic vein thrombosis by special procedures tests, including portal venogram at time of surgery. Both had esophageal varices; both had large spleens. Biopsy of both livers showed mild fibrosis.

The findings have resulted in the removal of 59 employees to areas of no exposure to hepatic toxins.

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There may be some significance to the results of the fractionation of LDH. Isolated factor no. 4 elevations were seen in 66% of B.F.Goodrich employees, whereas there was an isolated factor no. 4 elevation in the hospitalized patients (other than B.F.Goodrich employees) of only .02%. The reason for this is unknown.

Another finding was the very high incidence of elevation of CPK found in the black worker (75) of B.F.Goodrich as opposed to the white (12). I know of no reason for this.

Of the seven cases of acroosteolysis tested, only one had an abnormal battery. When asked to stop drinking, his battery returned to normal in three weeks.

In conclusion, a protocol for testing has been presented. The results of these tests have been reviewed. It seems that no one isolated test - be it SMA-12, battery, or special procedures - is adequate for a thorough work-up. It is certain that the SMA-12 or batteries without scan will not predict a cold spot in the liver. It is also true that a scan will not always predict fibrosis. The special procedures seem quite accurate in detecting abnormal pressure studies in the liver, indicating fibrosis or cirrhosis, and may be useful in diagnosing angiosarcoma of the liver (due to the persistent tumor blush).

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It further seems that the battery of more sophisticated tests will need be run on some of the normal SMA-12 group to see if the SMA-12 is a reliable tool in discovering liver abnormalities or in screening out normal cases.

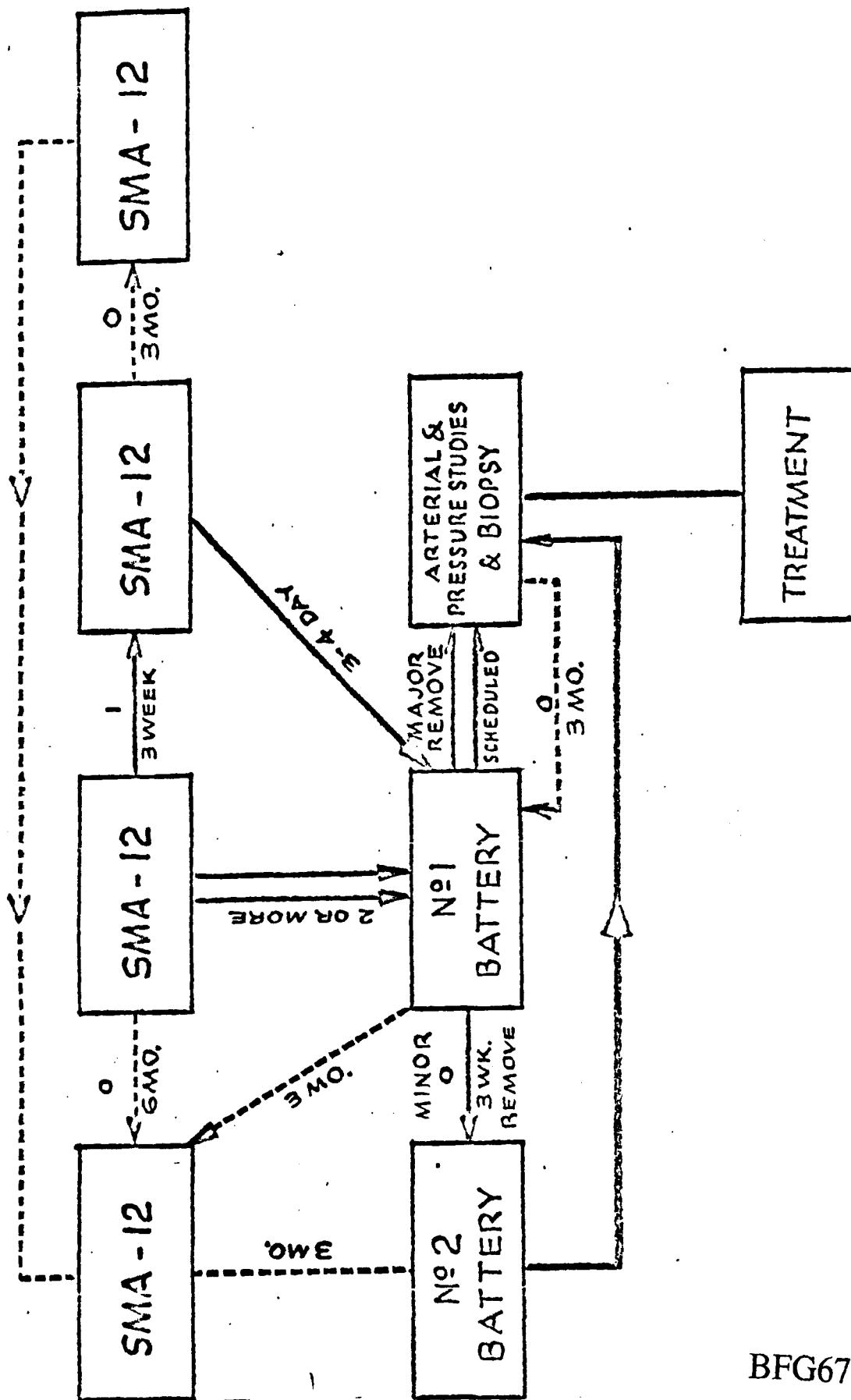
These studies will be continued through the working years of the employee and probably even after his retirement. Undoubtedly the protocol will change as more information is gathered and as research shows a better method for detecting disease, whether it be angiosarcoma, fibrosis, or portal vessel thrombosis with splenomegalia.

I'm sure that everyone in this room hopes that manufacturing procedures have been or will be developed to such an degree that these abnormalities will not occur and thus will require no detection.

REFERENCES

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2. Viamonte MJ, Warren WD, Formon JJ: Liver panangiography in the assessment of portal hypertension in liver cirrhosis. Radiol Clin North Am 8:147-167, 1970.
3. Hanafee WN, Weiner M: Transjugular percutaneous cholangiography. Radiology 88:35-39, 1967.
4. Rosch J, Lakin PC, Antonovic R, Dotter C: Transjugular approach to liver biopsy and transhepatic cholangiography. New Engl J Med 289:227-231, 1973.
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FIGURE 1

WOMAN

SMA

SMA-12

BUN

LDH

SGOT

SGPT

GGT

CEA

ICD

CBC

XFP

NOTIFICATION

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X-RAY-X

SEQUENTIAL MULTIPLE ANALYSIS

CALCIUM, TOTAL BILIRUBIN, ALBUMIN, CHOLESTEROL, TOTAL
PROTEIN, ALKALINE PHOSPHATASE, LDH, SGOT, GLUCOSE, CU
URIC ACID, INORGANIC PHOSPHORUS.

BLOOD UREA NITROGEN

LACTATE DEHYDROGENASE

SERUM GLUTAMIC OXALACETIC TRANSAMINASE

SERUM GLUTAMIC PYRUVIC TRANSAMINASE

GAMMA GLUTAMYL TRANSPEPTIDASE

CARCINO EMBRYONIC ANTIGEN

ISO CITRATE DEHYDROGENASE

COMPLETE BLOOD COUNT (WITH PLATELET)

ALPHA FETO GLOBULIN

PROTEIN ELECTROPHORESIS

LDH

ALKALINE PHOSPHATASE

TOTAL BILIRUBIN

CHEST

LIVER - SPLEEN SCAN

LOCATION OF ABNORMAL SMA-12

AREA	NUMBER EMPLOYEES SEEN	NUMBER COUNTED	% ELEVATED
DOC PRODUCTION	274	59	21.5
OTHER PRODUCTION	411	132	32.2
DOC MAINTENANCE	35	10	28.6
OTHER MAINTENANCE	216	58	26.8
ALL OTHER	247	56	22.6
TOTAL	1183	315	26.6

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LOCATION OF ABNORMAL BATTERIES

AREA	NUMBER EMPLOYEES ABNORMAL		PERCENT
PVC PRODUCTION	274	30	10.9
OTHER PRODUCTION	411	17	4.1
PVC MAINTENANCE	35	0	0
OTHER MAINTENANCE	216	9	4.2
ALL OTHER	247	3	1.2
TOTAL	1183	59	5.0

ABNORMAL SUM-12 BY TEST

AREA	% TOTAL BILIRUBIN	% ALKALINE PHOSPHATASE	% LDH	% SGOT
PVC PRODUCTION	35.6	47.5	3.4	33.9
OTHER PRODUCTION	29.6	50.7	8.3	28.8
PVC MAINTENANCE	10.0	50.0	0	50.0
OTHER MAINTENANCE	17.2	46.5	5.2	51.7
ALL OTHER	33.9	42.8	14.3	41.1

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ABNORMAL DATA BY TEST

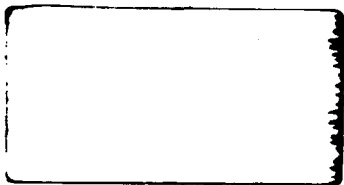
AREA	SGOT	SGPT	ALBUMIN	LDH	TOTAL	PROTEIN	PROTEINASE	CHLORIDE
	%	%	%	%	%	%	%	%
PVC PRODUCTION	46.9	50.0	34.4	59.4	9.4	43.8		
OTHER PRODUCTION	46.2	33.3	20.5	51.9	28.2	41.0		
PVC MAINTENANCE	50.0	0	0	50.0	50.0	0		
OTHER MAINTENANCE	50.0	44.4	38.9	61.1	16.7	50.0		
ALL OTHER	46.7	13.3	6.7	46.7	26.6	40.4		

NAME	WORK AREA	SCAN	HEPATIC ARTERIOGRAM	MICROSCOPY
REDACTED	Maint.	Normal	Normal	Metamorphosis moderate Portal Fibrosis slight
	PVC	Large spleen mild Cirrhosis	Aneurysm S.P.T & Hypersplenism	Slight Metamorphosis
	PVC	Cirrhosis	Hepatomegaly	Metamorphosis, Early Cirrhosis
	PVC	Defect, Cirrhosis	Defect	rosis & Angiocarcinoma
	PVC	Large spleen Cirrhosis	Enlarge spleen Aneurysms	Normal liver, sh.
	PVC	Possible defect	Displaced G.B.	rosis Hypersplenism
	OP	Cirrhosis	Normal	—
	PVC	Defect	Defect	Slight Portal Fibrosis
	PVC	Normal	Normal	Angiocarcinoma Fibrosis
	PVC	Normal	Normal	Normal
	OP	Normal	Normal	Normal
	PVC	Normal	Normal	Portal Fibrosis
	OM	Cirrhosis	Normal	Normal
	PVC	Defect or Patch	Cirrhosis with reverse flow	Fibrosis 6 yrs ago
	PVC-Gyrs	Normal	Normal	Hepatitis Cirrhosis
	PVC	Normal	Normal	Slight Metamorphosis
	PVC	Normal	Normal	Normal

* Done at patient's request.
 * 1950 had PR. shunt - Non-Alcoholic Cirrhosis.
 * ** Worked 6 yrs. Has worked elsewhere for past 6 yrs.

TABLE 6

This is the
Original



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