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# Mortality Among Employees of PVC Fabricators

Leonard Chiazze, Jr., Sc.D., William E. Nichols, Ph.D., and Otto Wong

A cross-sectional mortality study of 4,341 deaths occurring among current and former employees of 17 PVC fabricators during 1964-1973 is presented. The objectives were (1) to identify any angiosarcoma deaths among the employees of these fabricators, and (2) to examine the distribution of deaths by cause. No angiosarcoma deaths were found among the study group. Sex-race-cause-specific Proportional Mortality Ratios (PMR's) were computed, using the corresponding U.S. mortality as the standard. Among white employees, there appears to be an excess in total cancer mortality, particularly that of the digestive system. Observed deaths were found to exceed the expected in cancers of the breast and urinary organs among white females. Deficit mortality was observed in cirrhosis of liver among both male and female white employees.

The January 1974 disclosure of three deaths from angiosarcoma of the liver in a single vinyl chloride polymerization plant and the attention focused on this new occupational disease are well known. A significant amount of information from animal experimentation and observation on humans engaged in the production of vinyl chloride followed.<sup>1</sup> However, there was no information regarding the possible adverse effects on employees engaged in polyvinyl chloride (PVC) fabrication, where potential exposures were thought to be low and to result from the release of unreacted monomer trapped in the resin. This issue was considered of great import because of the very large number of workers believed to be engaged in fabrication.

In March 1974, representatives of PVC producers, who are members of the Organization Resources Counselors (ORC), Occupational Safety and Health Standards Group, contacted ORC about the feasibility of a study of health risks to employees working with vinyl chloride and polyvinyl chloride. Since the National Institute for Occupational Safety and Health (NIOSH) was conducting a study of vinyl chloride and resin producing employees, the scope of the proposed ORC study was limited to employees of

companies engaged in the fabrication of PVC resin into finished products. A number of alternative study designs was considered, and it was decided that a proportional mortality study would best meet the urgent need for information. The study concentrated on deaths occurring during the ten-year period 1964-1973 among active fabricating employees plus retirees. Since it was not possible to identify those employees with only vinyl chloride exposure, the study focused on deceased employees who worked anywhere in those plants where PVC fabrication was carried on. The primary objective of the study was to determine whether or not any angiosarcoma deaths had occurred among employees of the fabricators under study. A secondary objective was to examine the distribution of all deaths by cause.

The relatively few producers of vinyl chloride monomer and of PVC resin are generally medium to large companies. PVC fabricators, however, range from large plants of major companies to very small job shops. Even in a large plant, there may be few employees who are in the vicinity of PVC resins. The range of company plant size and number of exposed employees help to explain the wide range of estimates of total employment dependent upon PVC resins. Fabrication is geographically disbursed, with at least some operation in almost every state. Typical fabrication products include coated wire, upholstery fabrics, floor and wall coverings, pipe and other construction materials, toys, recreational equipment, phonograph records, containers and container lining, and a myriad of novelty items. Since the fabrication of PVC resin into finished products is often a part of diversified product lines in a plant, raw materials other than resin are utilized. Thus, employees may be exposed to toxic agents other than vinyl chloride. Consequently, in the current study, it is not possible to isolate only the effect of vinyl chloride. Some departures from expectation may be due to exposures to vinyl chloride, to one or more other agents, to some combination, or to employee characteristics other than occupation.

## Materials and Methods

The decision to focus on a cross-sectional mortality study rather than on an historical cohort study derived from several considerations. First, the primary study objective was to determine relatively quickly whether or not any angiosarcoma deaths could be identified among the study group, and this was best accomplished by examining causes of death among relatively recent

<sup>1</sup>From the Division of Biostatistics and Epidemiology, Department of Community Medicine and International Health, Georgetown University School of Medicine, Washington, DC 20007 (Dr. Chiazze and Wong) and Organization Resources Counselors, Inc., Washington, DC 20006 (Dr. Nichols).

(i.e., past ten years) decedents. The desirability of identifying an historical cohort for follow-up was recognized, but it was determined that it would not be possible to identify clearly and completely the necessary cohort of workers within a reasonable period of time, if at all. As a consequence, this study is based upon 4,341 deaths which occurred during the period 1964-1973 among current or former employees of 17 companies engaged in PVC fabrication. A total of 55 plants supplied data on all identifiable deaths since, as was mentioned earlier, it was not possible to identify those employees with only vinyl chloride exposure for the study.

In order to be included in this study, a deceased employee fell into one of the following categories: (1) employee died while actively employed, (2) employee died after retiring from the company with retirement benefits, and (3) employee died after terminating employment but with vesting in a company-sponsored life insurance plan. Deaths occurring among former employees with less than the number of years necessary for insurance vesting were not included in plant records and were, therefore, not available for this study.

An attempt was made to compensate for at least some of the "leakage" due to employees leaving the industry prior to the time they were vested in any insurance program by using the following procedures. Once death records for a given company were identified, death certificates were obtained and separated into two groups as follows: (1) all deaths with cancer (ICDA 140-205 up to 1967; ICDA 140-209 for 1968 on), or liver disease (ICDA 580-586 up to 1967; ICDA 570-576 for 1968 on), or suspected liver condition mentioned on the death certificate; and (2) all deaths from causes other than cancer or liver disease. Death records mentioning cancer or liver disease and giving a hospital as place of death were segregated and sorted by hospital. Where there were several death records for a single hospital or several hospitals in the same area, arrangements were made for a Registered Records Administrator (IRRA) to visit the hospitals, review medical records, contact the hospital pathologist and review pathology records to determine whether there were any angiosarcoma cases in the hospital's pathology records. If so, an attempt was made to determine whether or not the angiosarcoma possibly could be related to vinyl chloride exposure. This procedure enabled us to identify whether any employees, who had left the industry prior to vesting in an insurance program and remained in the local area, had died from angiosarcoma of the liver. The hospital inquiry procedures turned up five deaths from angiosarcoma of the liver; according to company employment records, none were employed at any time in PVC fabricating plants. These deaths were reported to OSHA, NIOSH, and CDC for inclusion in the nationwide angiosarcoma survey.

Death certificates not mentioning a hospital as a place of death required an additional step to determine whether death occurred in a hospital or if a recent hospitalization had occurred prior to death. The certifying physician was queried by mail for information on recent hospitalization of the decedent and whether there was any indication that he or she had cancer or liver disease. Additionally identified hospitals were contacted as above.

Originally, it was planned that death certificates would be obtained from life insurance carriers. In practice, both company and life insurance records were used because of record retention practices and retrieval problems in the insurance carriers. All available death certificates were examined by a trained nosologist for mention of angiosarcoma anywhere on the certificate, and no angiosarcomas were found on the death certificates. Underlying cause

of death was classified according to the eighth revision of the International Classification of Diseases.<sup>2</sup>

Over the ten-year period under study, plant size was found to have changed drastically in many cases. In one instance, a plant employing 300 employees in 1973 employed fewer than 10 in 1964. At the other extreme, one plant employing 5,000 people in 1964 had only 2,000 in 1973. Some companies had gone out of business. Such developments show not only the rapid changes taking place but also the difficulty of determining average industry employment. The 17 companies covered in this report ranged from single plant, small companies (one with 70 employees) to multiplant large companies (one with over 7,000 employees). Average number of employees clustered between 300 and 500. Although total employment is difficult to determine precisely, it is estimated to have been between 65,000 and 70,000 at the end of 1973.

Since the population at risk could not be determined, mortality rates as measures of risk could not be calculated. Rather, results were summarized in terms of Proportionate Mortality Ratios (PMR) adjusted for the age distribution of the study group. The PMR uses relative frequencies of specific causes of death by age in a comparison population to obtain expected numbers of deaths from that cause in the study population. Selection of an appropriate comparison population poses some difficulties since it would be desirable to have a cause of death distribution for a similar group of workers dying during the same period, but not subjected to the factor under study. But such a comparison population was not available, and the study used mortality for the United States, specific for color and sex, for comparative purposes.<sup>3</sup> Despite recognized deficiencies, the PMR can provide clues on unusual distributions of causes of death where true rates cannot be calculated.

## Results

Table 1 gives the distribution of deaths among the employees of the 17 PVC fabricators within each of the ten years. An increase in the proportion of deaths taking place in later years of the decade may reflect a variety of factors, such as an increasing employee population, less complete availability of records for earlier years (e.g., in one company, there were no records for the first four of the ten years), increase in duration of exposure, etc. However, there is no reason to believe that any unavailable death records for earlier years would be concentrated in a few causes and thereby bias the distribution of deaths for those years.

Table 1. — Distribution of Deaths Among Employees of 17 PVC Fabricators by Year of Death, 1964-1973.

| Year of Death | No.  | %    |
|---------------|------|------|
| 1964          | 325  | 7.5  |
| 1965          | 345  | 8.0  |
| 1966          | 400  | 9.2  |
| 1967          | 429  | 9.9  |
| 1968          | 499  | 11.5 |
| 1969          | 449  | 10.3 |
| 1970          | 465  | 10.7 |
| 1971          | 471  | 10.9 |
| 1972          | 528  | 12.2 |
| 1973          | 430  | 9.9  |
| Total:        | 4341 | 100  |

Table 2. — Distribution of Deaths Among Employees of 17 PVC Fabricators by Color and Sex, 1964-1973.

| Race     | Total | Male | Female | Unknown |
|----------|-------|------|--------|---------|
| Total    | 4341  | 3676 | 663    | 2       |
| White    | 3849  | 3248 | 601    | 0       |
| Nonwhite | 204   | 180  | 24     | 0       |
| Unknown  | 288   | 248  | 38     | 2       |

The distribution of deaths in the study group by race and sex is given in Table 2. Most deaths (84.7%) occurred among males. The vast majority (88.7%) of decedents were white and there were 288 (6.6%) for whom race could not be determined. Table 3 shows this distribution of deaths by age. For both white male and white female employees, more than half of the deaths occurred among those aged 65 and over (58.1% and 51.9% for white men and white women, respectively). The corresponding proportions of deaths which occurred after age 65 in the United States population in 1968 were 59% and 72%, respectively. The higher proportion of deaths among white women over 65 in the U.S. population compared to the employee population may indicate that relatively fewer women work to retirement age than do men. While the numbers of deaths among nonwhite employees are too small for any definite conclusions, the distribution of deaths by age among nonwhite men is roughly comparable to that for the total United States.

Tables 4 and 5 show the distribution of deaths for selected causes by sex for whites and nonwhites, respectively. Among white men, nearly 60% of the deaths are from diseases of the circulatory system (ICDA 390-458) and 20% are deaths from cancer (ICDA 140-209). The corresponding percentages for the total U.S. population of white males in 1968 (midpoint of the study period) were 54% for diseases of the circulatory system and 16% for cancer. Digestive and respiratory cancers account for somewhat less than two-thirds of all cancer deaths among the white males in the study group as compared to about 59% of all cancer deaths among U.S. white males in 1968. For white women, over 46% of the deaths are from diseases of the circulatory system (compared to 57% for all U.S. white women in 1968), and 30% were from cancer (compared to 18% for all U.S. white women in 1968). Somewhat over half of the cancer deaths among white women in the study were from cancers of the breast and digestive system.

about the same proportion as for all U.S. white women in 1968. About two-thirds of the deaths for both nonwhite men and women were from diseases of the circulatory system and from cancer. The numbers of deaths for most causes among nonwhites, however, are quite small making interpretation difficult and are presented mainly for completeness.

Age-adjusted PMRs for white male and white female employees of the 17 PVC fabricators are presented in Table 6 for selected causes of death. There were no similar analyses for nonwhites because for nearly all causes, the numbers of deaths were too small to produce stable PMRs. Expected numbers of deaths have been calculated on the basis of the sex-cause-age specific distribution of deaths among U.S. whites in 1968 applied to the total number of deaths by age among white men or white women in the study group. The midpoint of the study period (1968) was selected for the standard, since it is representative of the study period and provides U.S. mortality data coded according to the eighth revision of the International Classification of Diseases. Expected numbers are deaths for individual causes to be expected in the study group if the proportion of total deaths ascribed to a given cause were the same as for the corresponding U.S. race-sex group, while accounting for differences between the age distributions of deaths in the study groups and deaths for the United States. A PMR larger than unity would indicate that the relative proportion of mortality from that particular cause in the study population is higher than would be expected based on the 1968 U.S. mortality experience.

In addition to the numerical value of the PMR itself, the observed number of deaths is also of interest. The larger the number of deaths observed, the more reliable the PMR. There were two deaths of unknown age among the white males, one a digestive cancer (ICDA 153) and one an unspecified cancer (ICDA 199). These were included in the age groups with the lowest relative frequency for those causes, that is, less than 35 years for total cancer and digestive cancer and 65 and over for other and unspecified cancer. Such an assignment has a trivial effect on the expectation but is the most conservative way of handling these unknowns, since it serves to increase the expectation (and hence lower the PMR) by the least amount.

Based upon both the number of deaths and the value of the PMR, there seems to be an important excess in total cancer mortality among the white males in the study group. The distribution by specific cancer site suggests that any excess appears to be con-

Table 3. — Distribution of Deaths Among Employees of 17 PVC Fabricators by Age, Color, Sex, 1964-1973.

| Color, Sex | All Ages |     | Under 35 |      | 35-44 |      | Age 45-54 |      | 55-64 |      | 65 & over |      | Unknown |      |
|------------|----------|-----|----------|------|-------|------|-----------|------|-------|------|-----------|------|---------|------|
|            | No.      | %   | No.      | %    | No.   | %    | No.       | %    | No.   | %    | No.       | %    | No.     | %    |
| White      |          |     |          |      |       |      |           |      |       |      |           |      |         |      |
| Male       | 3248     | 100 | 107      | 3.3  | 136   | 4.2  | 365       | 11.2 | 752   | 23.2 | 1886      | 58.1 | 2       | 0.1  |
| Female     | 601      | 100 | 24       | 4.0  | 42    | 7.0  | 100       | 16.6 | 123   | 20.5 | 312       | 51.9 | 0       | 0    |
| Nonwhite   |          |     |          |      |       |      |           |      |       |      |           |      |         |      |
| Male       | 180      | 100 | 21       | 11.7 | 24    | 13.3 | 28        | 15.6 | 39    | 21.7 | 68        | 37.8 | 0       | 0    |
| Female     | 24       | 100 | 6        | 25.0 | 2     | 8.3  | 5         | 20.8 | 6     | 25.0 | 5         | 20.8 | 0       | 0    |
| Unknown    |          |     |          |      |       |      |           |      |       |      |           |      |         |      |
| Male       | 248      | 100 | 20       | 8.1  | 5     | 2.0  | 32        | 12.9 | 48    | 19.4 | 131       | 52.8 | 12      | 4.8  |
| Female     | 38       | 100 | 1        | 2.6  | 5     | 13.2 | 4         | 10.5 | 8     | 21.1 | 18        | 47.4 | 2       | 5.3  |
| Unknown    | 2        | 100 | 1        | 50.0 | 0     | 0    | 0         | 0    | 0     | 0    | 0         | 0    | 1       | 50.0 |

Table 4. — Distribution of Deaths from Selected Causes Among Employees of 17 PVC Fabricators by Sex, White Only, 1964-1973.

| Cause of Death                                | ICDA<br>8th Rev. | Male |        | Female |        |
|-----------------------------------------------|------------------|------|--------|--------|--------|
|                                               |                  | No.  | %      | No.    | %      |
| All Causes                                    |                  | 3248 | 100.00 | 601    | 100.00 |
| All Cancers                                   | 140-209          | 666  | 20.50  | 181    | 30.12  |
| Buccal Cavity and Pharynx                     | 140-149          | 15   | 0.46   | 3      | 0.50   |
| Digestive System                              | 150-159          | 209  | 6.43   | 53     | 8.82   |
| Stomach                                       | 151              | 41   | 1.26   | 8      | 1.33   |
| Intestine                                     | 153              | 73   | 2.25   | 24     | 3.99   |
| Rectum                                        | 154              | 25   | 0.77   | 6      | 1.33   |
| Liver                                         | 155              | 6    | 0.18   | 0      | 0      |
| Respiratory System                            | 160-163          | 205  | 6.31   | 12     | 2.00   |
| Lung                                          | 162              | 183  | 5.94   | 12     | 2.00   |
| Bone, Connective Tissue, Skin, Breast         | 170-174          | 24   | 0.74   | 51     | 8.49   |
| Breast                                        | 174              | 0    | —      | 44     | 7.32   |
| Genital Organs                                | 180-187          | 44   | 1.35   | 19     | 3.16   |
| Urinary Organs                                | 188-189          | 36   | 1.11   | 11     | 1.83   |
| Brain & Other Nervous System                  | 191-192          | 16   | 0.49   | 4      | 0.67   |
| Other & Unspecified                           | 190, 193-199     | 56   | 1.72   | 18     | 3.00   |
| Lymphomas                                     | 200-203, 208-209 | 42   | 1.29   | 9      | 1.50   |
| Leukemias                                     | 204-207          | 19   | 0.58   | 1      | 0.17   |
| Diabetes                                      | 250              | 42   | 1.29   | 11     | 1.83   |
| Diseases of the Circulatory System            | 390-458          | 1931 | 59.45  | 281    | 46.76  |
| Cerebrovascular Disease                       | 430-438          | 289  | 8.90   | 66     | 10.98  |
| Cirrhosis of Liver                            | 571              | 42   | 1.29   | 3      | 0.50   |
| Cholelithiasis, Cholecystitis and Cholangitis | 574-575          | 7    | 0.22   | 3      | 0.50   |
| Accidents, Poisoning, and Violence            | E800-E999        | 188  | 5.79   | 48     | 7.99   |
| Accidents                                     | E800-E949        | 134  | 4.13   | 38     | 6.32   |
| Suicide                                       | E950-E959        | 40   | 1.23   | 2      | 0.33   |
| All Other Causes (Residual)                   |                  | 372  | 11.45  | 74     | 12.31  |

centrated in digestive system cancer, given the large number of deaths (31% of all cancer deaths). For each of the sites within the digestive system, observed numbers of deaths are greater than expected. Although, except for intestinal cancer, the observed numbers of deaths are small. The PMR for liver cancer is rather high, but a definite conclusion is difficult with only six observed deaths. On the other hand, the PMR for cirrhosis of the liver suggests a deficit in mortality from that cause.

For white women, the PMR for total cancer appears high as it did for white men, with cancer of the digestive system and perhaps, cancer of the breast contributing a fair amount to the excess. The PMRs for individual sites within the digestive system are based upon small numbers but suggest an increase in intestinal cancer. The PMR for urinary cancer, though based upon only 11 deaths, seems strikingly high and may be an indication for further investigation. On the other hand, in contrast to the observation in white men, the PMR for respiratory cancer among white women is very close to unity. Similar to the observation in white men, mor-

Table 5. — Distribution of Deaths from Selected Causes Among Employees of 17 PVC Fabricators by Sex, Nonwhite Only, 1964-1973.

| Cause of Death                               | ICDA<br>8th Rev. | Male |        | Female |        |
|----------------------------------------------|------------------|------|--------|--------|--------|
|                                              |                  | No.  | %      | No.    | %      |
| All Causes                                   |                  | 180  | 100.00 | 24     | 100.00 |
| All Cancers                                  | 140-209          | 39   | 21.66  | 8      | 33.33  |
| Buccal Cavity and Pharynx                    | 140-149          | 0    | 0      | 0      | 0      |
| Digestive System                             | 150-159          | 13   | 7.22   | 4      | 16.67  |
| Stomach                                      | 151              | 3    | 1.67   | 0      | 0      |
| Intestine                                    | 153              | 2    | 1.11   | 1      | 4.16   |
| Rectum                                       | 154              | 1    | 0.56   | 0      | 0      |
| Liver                                        | 155              | 1    | 0.56   | 0      | 0      |
| Respiratory System                           | 160-163          | 7    | 3.89   | 0      | 0      |
| Lung                                         | 162              | 7    | 3.89   | 0      | 0      |
| Bone, Connective Tissue, Skin, Breast        | 170-174          | 0    | 0      | 3      | 12.50  |
| Breast                                       | 174              | 0    | 0      | 3      | 12.50  |
| Genital Organs                               | 180-187          | 4    | 2.22   | 0      | 0      |
| Urinary Organs                               | 188-189          | 3    | 1.67   | 0      | 0      |
| Brain & Other Nervous System                 | 191-192          | 1    | 0.56   | 0      | 0      |
| Other & Unspecified                          | 190, 193-199     | 6    | 3.33   | 0      | 0      |
| Lymphomas                                    | 200-203, 208-209 | 4    | 2.22   | 0      | 0      |
| Leukemias                                    | 204-207          | 2    | 1.11   | 1      | 4.16   |
| Diabetes                                     | 250              | 2    | 1.11   | 0      | 0      |
| Diseases of the Circulatory System           | 390-458          | 81   | 45.00  | 8      | 33.33  |
| Cerebrovascular Disease                      | 430-438          | 19   | 10.56  | 3      | 12.50  |
| Cirrhosis of Liver                           | 571              | 3    | 1.67   | 1      | 4.16   |
| Cholelithiasis, Cholecystitis, & Cholangitis | 574-575          | 0    | 0      | 0      | 0      |
| Accidents, Poisoning & Violence              | E800-E999        | 33   | 18.33  | 3      | 12.50  |
| Accidents                                    | E800-E949        | 17   | 9.44   | 1      | 4.16   |
| Suicide                                      | E950-E959        | 2    | 1.11   | 0      | 0      |
| All Other Causes (Residual)                  |                  | 22   | 12.22  | 4      | 16.67  |

tality from cirrhosis of the liver seems to be in deficit, but the corresponding observed number of deaths is quite small. Among both white male and female employees, diseases of the circulatory system account for a large percentage of total deaths. In each case, observed numbers of deaths are close to expected. There appears to be a somewhat different pattern among men and women for deaths due to accidents, poisonings, violence with the number of deaths somewhat low among men and high among women.

There were 39 cancer deaths among nonwhite men, somewhat greater than expectation, although the numbers by site are too small for meaningful analysis. Mortality from cerebrovascular disease appeared high (PMR = 2.11) but the finding was based upon only 19 deaths.

## Discussion

The present study was designed with two objectives. The first was to determine whether or not any angiosarcoma deaths had

Table 6. — Observed and Expected Deaths for Selected Causes Among Employees of 17 PVC Fabricators by Sex, White Only, 1964-1973.

| Cause of Death                                       | ICDA<br>8th Rev. | Male     |          |      | Female   |          |      |
|------------------------------------------------------|------------------|----------|----------|------|----------|----------|------|
|                                                      |                  | Observed | Expected | PMR* | Observed | Expected | PMR* |
| All Causes                                           | 140-209          | 666      | 561.997  | 1.19 | 181      | 137.699  | 1.31 |
| Buccal Cavity and<br>Pharynx                         | 140-149          | 15       | 16.875   | 0.89 | 3        | 1.896    | 1.58 |
| Digestive System                                     | 150-159          | 209      | 162.143  | 1.29 | 53       | 35.342   | 1.50 |
| Stomach                                              | 151              | 41       | 31.507   | 1.30 | 8        | 4.981    | 1.61 |
| Intestine                                            | 153              | 73       | 52.528   | 1.39 | 24       | 15.344   | 1.56 |
| Rectum                                               | 154              | 25       | 19.631   | 1.27 | 8        | 3.877    | 2.06 |
| Liver                                                | 155              | 6        | 4.190    | 1.43 | 0        | 0.633    | —    |
| Respiratory System                                   | 160-163          | 205      | 176.657  | 1.16 | 12       | 11.888   | 1.00 |
| Lung                                                 | 162              | 193      | 165.566  | 1.17 | 12       | 11.224   | 1.07 |
| Bone, Connective<br>Tissue, Skin, Breast             | 170-174          | 24       | 15.117   | 1.59 | 51       | 35.661   | 1.43 |
| Breast                                               | 174              | 0        | —        | —    | 44       | 32.397   | 1.36 |
| Genital Organs                                       | 180-187          | 44       | 52.828   | 0.83 | 19       | 23.297   | 0.82 |
| Urinary Organs                                       | 188-189          | 36       | 33.131   | 1.09 | 11       | 4.537    | 2.42 |
| Brain & Other<br>Nervous System                      | 191-192          | 16       | 13.885   | 1.15 | 4        | 3.499    | 1.14 |
| Other & Unspecified                                  | 190, 193-199     | 56       | 34.607   | 1.62 | 18       | 9.622    | 1.87 |
| Lymphomas                                            | 200-203          | 42       | 32.382   | 1.30 | 9        | 7.631    | 1.18 |
| Leukemias                                            | 204-207          | 19       | 23.364   | 0.81 | 1        | 5.005    | 0.20 |
| Diabetes                                             | 250              | 42       | 49.600   | 0.85 | 11       | 15.436   | 0.71 |
| Diseases of the<br>Circulatory System                | 390-458          | 1931     | 1832.515 | 1.05 | 281      | 309.232  | 0.91 |
| Cardiovascular<br>Disease                            | 430-438          | 289      | 292.074  | 0.99 | 66       | 71.965   | 0.92 |
| Coronary of Heart                                    | 571              | 42       | 62.821   | 0.67 | 3        | 12.343   | 0.24 |
| Cholelithiasis,<br>Cholecystitis, and<br>Cholangitis | 574-575          | 7        | 6.349    | 1.10 | 3        | 1.783    | 1.68 |
| Accidents, Poisoning,<br>and Violence                | E800-E999        | 188      | 265.548  | 0.71 | 48       | 40.855   | 1.17 |
| Accidents                                            | E800-E949        | 134      | 189.268  | 0.71 | 38       | 27.931   | 1.36 |
| Suicide                                              | E950-E959        | 40       | 52.325   | 0.76 | 2        | 9.171    | 0.22 |

\*PMR is the ratio of observed to expected where the expected number is calculated on the basis of the distribution of deaths for the total U.S. in 1968 specific for color, sex, cause, and age.

occurred among employees of the PVC fabricators under study. Since no angiosarcoma deaths were found among the employees studied, the first question has an unequivocal answer. A secondary objective was that of examining the distribution of deaths by cause among the employees under study. Implicit in that objective is the question of whether or not that distribution is, in some sense, unusual. There is no unequivocal answer to the latter question. Whether or not an observed distribution of causes of death is unusual clearly relates to the standard or comparison population as well as the analytic methodology.<sup>2</sup>

On the basis of a proportionate mortality analysis, there appear to be excesses in total cancer mortality among both white men and white women in the study, when compared to the distributions of deaths for the total United States specific for color and sex and adjusted for age. Excesses in cancer mortality appear concentrated in cancers of the digestive system and, in particular, in cancers of the intestine for both men and women. In addition, there is a suggestion that mortality from cancer of the breast and urinary organs among white women employees is higher than that for the total U.S. There are, however, several reasons why

definitive interpretation is difficult. It has, for example, been suggested that a Proportionate Mortality Ratio based on an external population may not be sufficiently discriminating in screening for potential hazards.<sup>3</sup> In addition, an analysis using PMRs fails to take account of the absolute risk of dying in the population under study.<sup>4</sup> Further, a number of studies have suggested an overall favorable mortality for industrial working populations, even in those where well-defined hazards increase risk for a specific cause.<sup>5-8</sup> Factors such as these are meant to suggest that proportionate mortality analysis must be interpreted cautiously, with the intention of providing leads for further investigation.

Results consistent with those of previously published studies would be of particular interest. With no comparable working populations in the fabrication industry, potential contrasts may be found in studies of vinyl chloride workers. Monson, et al. provided a proportionate mortality analysis of 161 deceased workers (all presumably white males) in two plants, one where vinyl chloride monomer is produced and one where it is polymerized into polyvinyl chloride.<sup>9</sup> Results of that study suggest a possible excess in total cancer mortality, primarily cancer of the

liver. However, there was a suggestion that cancers of the lung and brain also appeared with excess frequency. The current study, while suggesting an excess in total cancer, particularly digestive cancer, does not clearly point to marked excesses for cancers of the liver, lung, and brain among white men, although the PMRs for these cancers are greater than one. The observed-to-expected PMRs reported by Monson for vascular lesions affecting the central nervous system, circulatory diseases, and external causes are similar to those reported here.

Tabershaw and Gaffey, in a study of workers engaged in the manufacture of vinyl chloride and its polymers, conclude that no specific cause of death was statistically significantly greater than expectations based upon Standardized Mortality Ratios (SMRs) using the U.S. male population as the standard.\* By other criteria, however, the authors conclude there may be an excess risk for mortality from digestive cancer, respiratory cancer, cancer of other and unspecified sites, and lymphomas. At lower exposure levels, they suggest some excess for cancers of the buccal cavity and cancers of the other and unspecified sites.

The current study would seem to indicate that excesses of mortality from cancer of the digestive system are not sex-specific and are not limited to liver cancer. The majority of the PMRs for cancer among both white men and white women are in excess of unity. Such results must be interpreted with caution but, since they appear to be consistent with previously studied workers, they suggest the need for continued investigation.

#### Summary

Results of a study of 4,341 deaths occurring among current and former employees of 17 PVC fabricators during the period 1964-1973 are presented. The study was carried out to determine whether any angiosarcoma deaths had occurred among employees of these fabricators and to examine the distribution of deaths by cause. **No angiosarcoma deaths were found among the study population.** Distributions by cause of death among white male and white female employees were compared with those for

the entire U.S., specific for color and sex and adjusted for age by means of Proportionate Mortality Ratios. **There appears to be an excess of mortality among both white men and white women for digestive cancer, particularly for cancer of the liver, which is attributed to the excess among the white men. Cancers of the breast and urinary organs were not in excess.** No excesses were found for diseases of the circulatory system. There were deficits in mortality from cirrhosis of the liver among both male and female employees and a deficit in accidents, poisonings, and violence among men. The use of the Proportionate Mortality Ratio based on an external standard requires caution in interpreting these results, but the need for further investigations is indicated.

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## Discussion

We infer that hyperexcitability of the nervous system can be associated with hypomagnesaemia without concomitant hypocalcaemia. This observation accords with the findings of Vallee et al. (1960) but not with those of other workers (Hanna et al. 1960, Zimmet et al. 1968) who have claimed that a low serum-calcium arising from the hypomagnesaemia is necessary to produce the signs seen in the hypomagnesaemic syndrome.

One should not conclude from this association that the hypomagnesaemia caused the tremors or convulsions, although this seems likely in view of the fact that magnesium levels returned to normal on recovery. Furthermore, the dose of magnesium in six of the cases was not large enough to cause drowsiness yet the tremors were quickly controlled.

The cause of the low serum-magnesium is unknown. Since some of the cases recovered spontaneously within a day or two, it is possible, at least in some of the patients, that the hypomagnesaemia was due to a transient shift of the mineral from the extracellular to the intracellular compartment. The feasibility of such shifts has been mentioned by Martin et al. (1952), and Hasselman and Van Kampen (1958). It is possible that because of metabolic alterations in the neonatal period and in children who are ill, the magnesium homeostatic mechanism might not be functioning efficiently.

A decreased serum-magnesium could, in turn, stimulate the parathyroids to release parathormone in an attempt to conserve magnesium (MacIntyre et al. 1963). At the same time the excess parathormone would raise blood-calcium, thus accounting for the elevated ultrafiltrable calcium level.

The combination of hypomagnesaemia and hypercalcaemia is not incompatible with the production of hyperexcitability of the nervous system. In magnesium-deprivation studies in rats, the animals demonstrate hyperirritability, hypomagnesaemia, and hypercalcaemia (Whang and Welt 1963). Furthermore, there is evidence to suggest that calcium specifically facilitates the release of acetylcholine by a nerve impulse (Fatt 1959) and that the action of excess magnesium is to cause a block in neuromuscular transmission by decreasing the amount of transmitter substance released at nerve terminals (del Castillo and Engbaek 1954). Hence a combination of hypomagnesaemia and an elevated calcium concentration may act synergistically in facilitating acetylcholine release, thus accounting for the neuromuscular irritability seen in our patients. This antagonistic action of magnesium and calcium at nerve-endings contrasts with their common action in raising the threshold depolarisation for the initiation of an action potential in a nerve or muscle fibre (Fatt 1959).

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# AN ADVERSE EFFECT OF POLYVINYLCHLORIDE TUBING USED IN EXTRACORPOREAL CIRCULATION

HELEN N. DUKE  
M.B., Ph.D. Edin.

SENIOR LECTURER IN PHYSIOLOGY, MIDDLESEX HOSPITAL MEDICAL SCHOOL, LONDON W.1

J. R. VANE

B.Sc. Birm., B.Sc., D.Phil. Oxon.

PROFESSOR OF EXPERIMENTAL PHARMACOLOGY, INSTITUTE OF BASIC MEDICAL SCIENCES, ROYAL COLLEGE OF SURGEONS OF ENGLAND, LONDON W.C.2

**Summary** The pulmonary vascular resistance is increased by ventilation hypoxia both in isolated perfused lungs from cats and in anaesthetised cats under conditions of circulatory control. This effect of hypoxia also occurs in man and dog. The pulmonary blood-vessels of isolated perfused cats' lungs do not respond to hypoxia when the perfusion circuit is partly made from polyvinylchloride (P.V.C.) tubing. Normal pulmonary vascular responses to noradrenaline, 5-hydroxytryptamine, and prostaglandin  $F_{2\alpha}$  are still obtainable when the response to hypoxia is abolished. It is suggested that a new British Standard should be devised to cover the acute effects produced by injection into the body of fluids which have been in contact with P.V.C. tubing.

## Introduction

ADVERSE effects have been shown to follow the use of polyvinylchloride (P.V.C.) tubing in normal laboratory procedures. Stewart and Sturridge (1959) found, for instance, that some types of tubing caused haemolysis of the blood perfused through them. Meigler and Durrer (1959) and Meyler et al. (1960) found that isolated rats' hearts were killed within 15 minutes when perfused with fluid delivered through some types of P.V.C. tubing, whereas when the same fluid traversed glass tubing the isolated heart preparations survived many hours; they ascribed the toxicity to the presence of organic tin compounds in certain kinds of P.V.C. tubing. Haberman et al. (1968) described harmful effects of plastics and their component materials on reactions involving human and rabbit antibodies, guineapig complement, and serum-proteins. Few, if any, of the commonly used components of plastic tubing were without effect on their test systems. Bowery and Lewis (1968) found that substances were leached out of P.V.C. tubing which contracted guineapig isolated ileum and inhibited the contractions of the rat uterus induced by many substances. Considerable amounts of activity were added to plasma after 10 minutes' contact and these reached a maximum after 60 minutes. The leaching process occurred again and again each time fresh plasma was added. The amount of activity leached out was directly dependent on the protein concentration in the plasma, and this dependence was also demonstrated with purified bovine albumin solutions.

## Methods

Isolated lungs of cats anaesthetised with chloralose (80 mg. per kg. intraperitoneally) were perfused by the method of Duke (1951). A Dale-Shuster pump was used to perfuse the lungs through the pulmonary artery (fig. 1). The perfusion was maintained at constant minute volume inflow with the animal's own heparinised blood (10 I.U. heparin per ml.) at a temperature of 37–39°C. The volume of blood in the apparatus was approximately 120 ml. The venous outflow from the lungs was led through a left-atrial cannula into a venous reservoir which

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The pressor response to anoxia was also abolished when the P.V.C. (10 H.E.) tubing added to the venous reservoir had been previously boiled in 2% sodium-bicarbonate solution.

Some P.V.C. tubing contains different chemical additives from those in 10 H.E. The experiments were therefore repeated using one of these—N.T. 14 SH 80, which is said to be more suitable for perfusion work (Vincent 1968). In one experiment 60 cm. of this tubing abolished the pulmonary pressor response to anoxia, and in another experiment the pressor response was reduced. In both experiments there was a partial recovery of the anoxic pressor response 5 minutes after the tubing was withdrawn from the venous reservoir.

#### Discussion

Hypoxia causes an almost immediate increase of pulmonary arterial pressure in anaesthetised cats (von Euler and Liljestrand 1946, Logaras 1947) and also in anaesthetised cats with left-lung perfusion (Duke 1957). In isolated lungs from cats perfused with blood at a constant minute volume, hypoxia causes a similar increase of pulmonary vascular resistance with similar time relationships to that in the anaesthetised animal. The pulmonary pressor response to hypoxia is not accompanied by changes in bronchial resistance to airflow or left atrial pressure (Duke 1951, see also Duke and Lee 1963, Daly and Hebb 1966) and is therefore probably due to pulmonary vasoconstriction. In isolated perfused lungs from cats the pressor response to hypoxia of 3–15 minutes' duration is inversely related to the tension of oxygen in the ventilating gas mixture for gas mixtures containing less than 15% oxygen in nitrogen; equivalent effects are produced by ventilation of isolated perfused lungs with neon, hydrogen, or nitrogen (Duke 1951). It appears therefore that the pressor effect of ventilation hypoxia that has been studied in the present series of experiments is a physiological response in the cat, and that the response obtained when the gas mixture is changed from air to nitrogen varies only in degree to the effects produced by changing the ventilating gas mixture from air to 15% or less oxygen in nitrogen. Evidence that pulmonary vasoconstriction to hypoxia is found in man and other species as well as cats was discussed by Duke and Lee (1963) and Daly and Hebb (1966).

The present experiments show that the pulmonary pressor response to hypoxia is abolished by P.V.C. tubing. It is therefore possible that procedures involving the use of plastic tubing in man may be attended by hitherto-unsuspected harmful effects. Such procedures include extracorporeal circulation, renal dialysis, and even blood-transfusion.

In the present experiments two different types of tubes were used, both of which are listed in the current manufacturer's catalogues as of "surgical non-toxic quality". The plasticiser was acetyl-tri-n-butyl citrate in epoxy soya-bean oil. The stabiliser in the H.E. tubing was of an octyltin type, whereas the stabiliser in NT 14 SH 80 was a calcium-zinc compound. The latter type of tubing had a less harmful effect in our preparation.

The manufacturers of the tubing state (Vincent 1968) that acetyl-tri-n-butyl citrate and small amounts of epoxy soya-bean oil are listed under the U.S. Food and Drug regulations as suitable for food packaging, as is also the calcium-zinc stabiliser. Both types of tubing used in the present experiments comply with the requirements of B.S. 2571: 1963 which specifies maximum

permitted weight changes when a plastic disc is immersed in distilled water for 48 hours. The tubing also conforms with the rabbit implantation test laid down in MIL-C-36145A (BuMed.) Oct. 16, 1963. In addition, the NT tubing complies with B.S. 2463 (specification for transfusion equipment) appendix F which uses a toxicity test in mice injected with eluates from tubing heated at 85°C for 1 hour. Mouse fibroblast and 10-day chick-embryo tests are performed by the factory. These tests of biocompatibility are designed to establish the safety of P.V.C. either as a chronic implant or in a simple transfusion apparatus and may be completely unsuitable for testing the potential toxicity of the large amounts of plastic tubing used acutely in an extracorporeal circulation. British Standard 2571: 1963 allows a loss in weight in 48 hours of 20 mg. from a disc weighing about 4.4 g. In our apparatus, which might be regarded as a small-scale cardiac bypass circuit, 60–120 g. of P.V.C. tubing was used; the British Standard would have allowed the leaching out of between 1 and 3 g. of material into the circuit, to reach a concentration of 20 mg. per ml. (2%) in 48 hours. Assuming steady leaching over 48 hours, the allowable concentration of material in the circulating blood could attain at least 0.4 mg. per ml. in 1 hour.

Our results suggest that the toxicity of substances associated with the manufacture of P.V.C. tubing should be further investigated. They also suggest that a new British Standard should be devised to cover the use of such tubing in extracorporeal circulations.

Requests for reprints should be addressed to J. R. V., Department of Pharmacology, Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2.

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### OXIDIZED GLUTATHIONE LEVELS IN ERYTHROCYTES OF GLUCOSE-6-PHOSPHATE-DEHYDROGENASE-DEFICIENT SUBJECTS

SATISH K. SRIVASTAVA

Ph.D. Lucknow

RESEARCH SCIENTIST

ERNEST BEUTLER

M.D. Chicago

CHAIRMAN

DIVISION OF MEDICINE, CITY OF HOPE MEDICAL CENTER,  
DUARTE, CALIFORNIA 91010

**Summary** Oxidized glutathione (G.S.S.G.) was estimated in normal erythrocytes and in erythrocytes deficient in glucose-6-phosphate dehydrogenase (G-6-P.D.) using an improved method in which the oxidation of glutathione was prevented by prior alkylation with N-ethyl-maleimide. The content of G.S.S.G. in the erythrocytes deficient in G-6-P.D. was about 3 times that in normal erythrocytes.



## Annotations

### WHAT'S IN P.V.C.?

LAST year,<sup>1</sup> discussing situations which may arise after prolonged endotracheal intubation or tracheostomy, we remarked particularly on the excoriation of the mucous membrane of the trachea, which, it was suggested, resulted from pressure necrosis, very much as in a bedsore. Since red mineralised rubber had been suspected of causing chemical irritation of the lining of the trachea, the increasing use of polyvinylchloride (P.V.C.) in the manufacture of endotracheal equipment was welcomed, for this plastic was generally held to be inert. Guess and Stetson<sup>2</sup> now emphasise, however, that P.V.C. can contain agents (such as organic compounds containing tin, added to improve flexibility and stability) which may leach out and damage tissues with which they are in contact for a long time. In experiments with plastics Guess and Autian<sup>3</sup> observed tissue reactions which closely resembled the changes seen in the region of the glottis after prolonged endotracheal intubation; and these findings stimulated Guess and his colleagues to study the possible hazards of plastic in endotracheal equipment. After these investigations a committee met in New York last December to discuss a formulation of P.V.C. suitable for endotracheal use, and the American and European manufacturers present agreed that, in the absence of a relevant specification of the British Standards Institute or of the U.S.A. Standards Institute, they would adopt, as an interim measure, the U.S. military specification for plastic used in endotracheal tubes,<sup>4</sup> which is based on freedom from toxicity when implanted in rabbit muscle. As Rendell-Baker<sup>5</sup> points out, anyone about to use plastic endotracheal apparatus for long-term care should verify that the P.V.C. is of the new formula. A large manufacturer in the U.K., Portland Plastics, is now making such equipment from plastic which meets the recommended U.S. military specification.

As a result of their observations recorded on p. 21 Dr. Duke and Professor Vane suggest that a new British Standard should also be devised to cover the use of P.V.C. tubing in extracorporeal circulations. They found that the pulmonary blood-vessels of isolated perfused cats' lungs did not respond in the normal way to hypoxia when the perfusion circuit was partly made from P.V.C. tubing. In their experiments two different types of tubing were used: the plasticiser in both was acetyl-tri-*n*-butyl citrate in epoxy soya-bean oil<sup>6</sup>; and in one the stabiliser was of an octyltin type and in the other it was a calcium-zinc compound. The second type had a less harmful effect on the cat-lung preparation.

The adsorptive property of plastic introduces another possible hazard, for traces of toxic substances used in sterilisation processes may linger, despite all efforts to remove them. Cunliffe and Wesley<sup>7</sup> have shown that P.V.C. sterilised with ethylene oxide always retains traces of this toxic gas and they recommend the utmost care in removing all traces by long-continued extraction. The very toxic substance, ethylene chlorohydrin, is formed

when ethylene oxide reacts with saline, and this substance can be expected to be present when material contaminated by ethylene oxide is in contact with tissues. Irradiation (another means of sterilisation) can render P.V.C. toxic by the formation of hydrochloric acid. Materials other than plastic can adsorb ethylene oxide—for example, rubber, polyethylene, and soft nylon—and all traces of the gas must also be extracted from these substances. Smith<sup>8</sup> reported skin reaction in wearers of rubber surgical gloves sterilised with ethylene oxide by a manufacturer.

Over five years have passed since Little and Parkhouse<sup>9</sup> recognised the potential hazard of inflammation caused by chemical additives in plastics and drew attention to the need for a standard specification for plastics used medically.

### THE FAMILY PLANNING ACT

AT the national conference of the Family Planning Association in Leicester last week, Mr. Edwin Brooks, the M.P. who sponsored the Family Planning Act, looked back on what had happened (or not happened) in the year since the Act was passed. It had never been his expectation that the Act would automatically eradicate the effects of forty years' delay and timidity on the part of society in general, and many local authorities in particular, towards family planning. The very success of the campaign would have lulled many local authorities into believing that the only change brought about by the Act was one of nomenclature and formal responsibility. Moreover, local government committees dealing with the welfare services had become accustomed to see their activities as essentially a matter of spending, of outlay, or of entries in the debit account: benefits were usually intangible—a sort of social wellbeing to be measured and vindicated by largely subjective criteria, such as the relief of suffering or worry. This produced a dichotomy of approach, in which we were always conscious of the financial outlay, but rarely of the financial reward. Those who had come to think of themselves as charities for the deserving poor were in danger of forgetting that they too were getting a return on their efforts. Society as a whole—not just the woman helped, say, by a domiciliary family-planning service—was the beneficiary of planned parenthood.

In Mr. Brooks' view cost-benefit realism was generally absent from the day-to-day thinking of those who planned and controlled local-authority expenditure. A common argument about family planning was the one recently deployed in the *County Councils Gazette*: "Quite apart from widely held religious beliefs and long established standards of morality, as Education, Children and Health authorities they (county councils) will wish to take into account mental and physical health hazards. Rightly they will tend to proceed with caution and the Government's curbs on public expenditure will re-inforce this tendency." Justifiably, Mr. Brooks lashed into this "depressing and dated" outlook. At a time when the vast majority of educated families, of all religious persuasions, accepted contraception as one of the boons of civilisation, it was time to be a bit less timorous about the "widely held religious beliefs". With the human species on the edge of demographic disaster, with world over-population an overriding menace, it was time

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2. Guess, W. L., Stetson, B. J. *Am. med. Ass.* 1968, 204, 580.

3. Guess, W. L., Autian, J. *Am. J. Hosp. Pharm.* 1964, 21, 260.

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5. *J. Am. med. Ass.* 1968, 204, 624.

6. Cunliffe, A. C., Wesley, F. *Br. med. J.* 1967, i, 575.

7. Smith, E. A. U.S. Bureau of Science, 1968, no. 679 (Drugs).

8. Little, K., Parkhouse, J. *Lancet*, 1962, ii, 857.

9. *County Councils Gazette*, May, 1968.



H. Wallnöfer, N. Zinnagl

Medizinische Abteilung des Landeskrankenhauses  
Vöcklabruck (Vorstand: Primarius Dr. H. Wallnöfer) und  
Konservativ-Angiologische Station  
(Leiter: Oberarzt Dr. N. Zinnagl)  
der Dermatologischen Abteilung  
(Vorstand: Primarius Prof. Dr. J. Zelger)  
der Landeskrankenanstalten Salzburg

## Hämangiosarkomatose nach Polyvinylchloridexposition

### Zusammenfassung

Nach kurzer Übersicht über neoplastische Entwicklungen nach beruflicher Exposition mit Vinylchlorid und Polyvinylchlorid wird über einen Fall berichtet, bei dem eine multilokuläre Hämangiosarkomatose nach relativ kurzdauernder und nur intermittierender Exposition mit Polyvinylchlorid auftrat. Das Latenzstadium betrug etwa 15 Jahre. Betroffene Gefäßbereiche waren die Aorta abdominalis, intrarenale Nierengefäße und intrazerebrale Gefäßsysteme. Symptomatisch trat das Krankheitsgeschehen unter dem Bilde progredient fortschreitender peripherer Durchblutungsstörungen in Erscheinung. Die Möglichkeit eines sklerotischen Vorschadens, gefördert durch Schwefelkohlenstoff wird diskutiert.

### Summary: Haemangiosarcomatosis after professional exposure to polyvinylchloride

After taking a cursory look at neoplastic developments particularly at professional exposure to vinylchloride and polyvinylchloride, one case is reported in which a multilocal haemangiosarcomatosis occurred after a relatively short and only intermittent exposure to polyvinylchloride. The latent stage lasted 15 years. The vessel areas affected were the aorta abdominalis, the intrarenal kidney vessels, and the intracerebral vessel-systems. Symptomatically, the disease presented the picture of a progrediently advancing peripheral circulatory disturbance. The possibility of previous sclerotic damage caused by carbon sulphide is discussed.

Vor rund 200 Jahren (1775) hat Sir Percivall Pott [35] über die berufsbedingte Karzinogenese des Skrotalkarzinoms bei Londoner Rauchfangkehrern berichtet, doch erst in den letzten Jahrzehnten ist der Exposition durch kanzerogene Stoffe in Industrie und Umwelt mehr Beachtung beigemessen worden [12, 30, 31]. Von klinischen Beobachtungen geleitet, haben sich zahlreiche Ergebnisse experimentell beweisen lassen [14]. Es sei in diesem Zusammenhang an das gehäufte Auftreten des Lungenkrebses bei Erzarbeitern [11, 21] und Rauchern, von Blasenkrebs, Lungenkrebs, Karzinomen des Gastrointestinaltrakts sowie malignen Mesotheliomen [1], Pleura- und Peritonealtumoren unter Exposition von Asbest [21, 32], Benzidin [44], Anilin [36], Arsen [17, 28, 31, 34] und aromatischen Aminen und an den gesicherten Zusammenhang von Leberkrebs und Aflatoxin erinnert. Heute wissen wir, daß viele der kanzerogenen Substanzen selbst in unserem Wasser anzutreffen sind [39] als Resultate gesteigerter Agrikultur, industrieller Technologie und letztlich unkontrollierter Umweltverschmutzung durch eine fast in Exponentialfunktion übersteigerten Industrieleistung. Epidemiologische Studien zeigen zudem, daß es sich bei der Karzinomentwicklung um ein kompliziertes multifaktorielles Komplexgeschehen handelt, wobei selbst negative

Resultate nicht notwendigerweise die Inaktivität eines Agens beweisen müssen, daß neben Risikofaktoren letztlich auch dispositionelle Komponenten für die Karzinogenese einer Substanz verantwortlich sein können.

Erst in den letzten Jahren wurde bekannt, daß Vinylchlorid als potentes karzinogenes Agens für die Entstehung von Leberkrebs und Karzinomen anderer Organe anzusprechen ist [2, 4, 10, 14, 15, 18, 22-25, 40, 43]. Ursprünglich war man der Meinung, daß der karzinogene Effekt vorwiegend oder ausschließlich dem Monomer Vinylchlorid zukame, in der Zwischenzeit hat sich aber erwiesen, daß auch die Polymere (Polyvinylchlorid) praktisch dieselbe Kanzerogenität besitzen [3, 6, 9, 13, 16, 20, 33, 37, 38]. Dabei handelt es sich vorwiegend um Entstehung von Angiosarkomen der Leber, des zentralen Nervensystems, der Lunge, der Niere, aber auch der Fingerknochen. Viola et al. [41] konnten experimentell bei Ratten Haut-, Lungen- und Knochenkrebs durch Inhalationsexposition innerhalb von zwölf Monaten erzeugen. Maltoni [22-24] berichtete über dieselbe hepatische Neoplasmaentwicklung im experimentellen Tierversuch nach Vinylchlorid-inhalation. Seither lassen ausgedehntere experimentelle Untersuchungen in Bezug auf die Kanzerogenität von Vinylchlorid-Polymeren erwarten, daß diese ebenfalls als Kanzerogene anzusprechen sind.



sammenhang des Angiosarkoms oder der Angiosarkomatose mit Vinylchlorid oder Polyvinylchlorid.

Interessant dabei ist die Feststellung, daß nach entsprechender Exposition unter Umständen eine bis zu 15jährige Latenzzeit bis zum Auftreten des Angiosarkoms bestehen kann. Waxweiler et al. [42] haben die experimentellen Inhalationsstudien von Viola et al. [41], Malroni [22] sowie Keplinger [14] mit Induktion von hepatischen Angiosarkomen, Adenomen, Adenokarzinomen der Lunge, Neuroblastomen des Gehirns, Lymphomen und verschiedenen anderen Tumoren in einer ganzen Reihe verschiedener Tierspezies anhand einer sorgfältig geführten Studie mit Erzeugung von Krebs der Leber, Lunge, des lymphatischen und zentralnervösen Systems erweitert. Der ätiologische Nachweis des exzessiven Krebsrisikos durch Vinylchlorid wurde zudem epidemiologisch und histopathologisch geführt. Infante [13] kommt aufgrund seiner Untersuchungen bei Polyvinylchlorid zum Ergebnis, daß Mütter, die in Siedlungen in unmittelbarer Nachbarschaft von PVC-Produktionsstätten leben, zu einem hohen Grad Kinder mit kongenitalen Fehlbildungen gebären, unabhängig von Dauer der Ehe, Rasse und anderen Faktoren. Dabei scheinen Anomalien des zentralen Nervensystems am häufigsten aufzutreten. Da neben Fehlbildungen zweifelsohne auch andere Faktoren [7, 8] für mutagene und/oder teratogene Mechanismen der Karzinogenese verantwortlich sind, muß dem Polyvinylchlorid nicht allein die Ursache kongenitaler Mißbildungen zukommen.

Die Angiosarkomentstehung der Leber durch Vinylchlorid und seine Polymere wird durch Fallberichte aus der letzten Zeit belegt [2, 10, 25]. Dabei zeigt sich, daß die Latenzzeit für sklerodermieartige Veränderungen der Haut, der Hände, Unterarme und Wangen, das Raynaud-Syndrom, Uhrglasnägel, periphere Gefäß- und Knochenveränderungen mit Akroosteolysen, restriktive Lungenveränderungen bis zur Lungenfibrose [29, 41], Milzvergrößerung, Leberschäden [25] bis zu Hämangioendotheliomen, Thrombo- und Leukopenien im Durchschnitt 2 bis 5 Jahre [11, 29], für das Auftreten des Angiosarkoms der Leber 10 bis 20 Jahre beträgt. Oft läßt sich laparoskopisch eine netzförmige Kapselfibrose mit einem Art Banti-Syndrom vorzeitig erkennen [5, 26, 27], und in der Leberbiopsie sieht man toxische Schäden [39] der Leberepithelien, dilatierte Sinusoide, perisinusoidale Kollagenisierungs- und Proliferationsvorgänge [9, 27, 43].

#### Fallbericht

59-jähriger Mann, der seit 1973 wiederholt in stationärer Behandlung steht. Leitsymptom sind periphere Durchblutungsstörungen der beiden unteren Extremitäten, die als Bürger-Wimwarner-Syndrom angesprochen wurden. Dazu Kopfschmerz, Schwindel, gehäufte abendliche Schweißbrüche.

Angiographisch fand sich eine hochgradige Sklerose der Aorta descen-

der Oberschenkelhauptäste. Auffallend war die starke Progredienz des Prozesses. Eine chirurgische Intervention mit plastischem Ersatz der distalen Aorta, der Aortengabel und der beiden Femoralarterien bei postoperativer Antikoagulation brachte nur kurzfristig leichte objektive (palpatorisch, rheographisch usw.) Besserung, die aber subjektiv nicht in Erscheinung trat.

Im Blutbild bestand eine mäßige Anämie, eine Leukozytose (zwischen 10000 bis 20000) und eine beträchtliche Senkungserhöhung. Konstante Albuminurie (bis 1 g%), grenzwertige Harnstoff- und Kreatininwerte. Zeichen eines Leberschadens waren durch geringe Transaminasenerhöhung, in späterer Folge deutliche Erniedrigung der Cholinesterase sowie eine Gammaglobulinämie (30%) nachweisbar. Die Leberbiopsie erbrachte histologisch eine häufig portale (reaktive) Hepatitis mit deutlicher epithelialer Schädigung im Sinne eines „toxisch-metabolischen Leberschadens“. Elektronenoptisch war eine beträchtliche Erweiterung des endoplasmatischen Retikulums mit Veränderung der Mitochondrien im Sinne der toxischen Schädigung zu beobachten, wobei zudem besonders auffallend die beachtliche Bindegewebsproliferation mit starker Kollagenisierung des Gitterfasernetzes in Erscheinung trat.

Da gleichzeitig immunologische Parameter vorlagen (positives C-reaktives Protein, Rheumafaktor, Waaler-Rose, erhöhte Titerstufen auf Humankollagen, antinukleäre Faktoren und DNS-Benrohnung sowie eine Erhöhung der IgG- und in geringem Ausmaß der IgA-Fraktion der Immunglobuline), wurde die Möglichkeit immunologischer Phänomene im Sinne einer Vasculitis allergica diskutiert und als Ultima ratio eine Immunsuppressionsbehandlung mit Azathioprin (Imurek®) und Glucocorticoiden eingeleitet. Eine nur kurzzeitige Besserung des Befundes – diesmal vorwiegend subjektiv und weniger objektiv – wurde gefolgt von einer weiteren hochgradigen Beschwerdeprogredienz, die letztlich in ein hepatorenales Syndrom mündete. Auch eine vorgenommene Arwin®-Behandlung brachte nur kurzfristige subjektive Besserung.

Der Patient kam rund drei Jahre nach Auftreten der ersten Symptome durch Ruptur eines Aneurysmas der Bifurkationsaorta ad exitum. Der Obduktionsbefund (Prof. Dr. J. Thurner, Salzburg) deckte nun eine Hämangioendothelkarkomatose mehrfacher Gefäßbereiche auf (im Gehirn, Niere, Leber sowie im Bereich der verschlossenen Extremitätengefäße und der Aorta).

Obduktionsprotokoll: Hämangioendothelkarkomatose mit nachgewiesenen, weitgehend nekrotischem Sarkomthrombus in der Bauchaorta (Aorta abdominalis im Bereich eines Bifurkations-Bypass vollständig verschlossen) mit Befall zahlreicher intrarenaler Nierengefäße, auch uteroveneraler Gefäße (mehrere bis erbsengroße Blutungen in der Rinde und im Mark beider Großhirnhemisphären – kein Hirndruck), Allgemeinen hochgradigen Arteriosklerose und „Athrombose“ mit verschiedenen sekundären Folgezuständen.

1. Zustand nach Anlegung eines aorto-femoralen Bifurkations-Bypass: Gefäßprothese von sarkomatösem, weitgehend nekrotischem Gewebe verlegt. Aorta oberhalb der Anastomose sowie beide Ilakalarterien ebenfalls mit sarkomatösen thrombotischen Abscheidungen.

2. Walnußgroßes, rupturiertes Anastomosenaneurysma an der oberen Anschlußstelle der Gefäßprothese mit 2 cm langer Ruptur der Aneurysmawand, mit retroperitonealer Wühlblutung und sekundärem Einbruch der Blutung in die freie Bauchhöhle (Hämoperitoneum: 2500 ml flüssiges Blut). Sogenannte Eigenfarbe parenchymatoser Organe.

3. Alte Thrombose der Arteria renalis dextra ohne nachweisbare Auswirkung auf die rechte Niere (rechte Niere 140 g, linke Niere 150 g).

4. Mäßiggradige exzentrische Linksberzhyperthrophie (linke Kammerwand 16 mm, rechte Kammerwand 4 mm, Herzgewicht 390 g, keine Myocardschwelen).

#### Diskussion

Trotz wiederholter stationärer Aufnahmen und überaus



eines überaus reichhaltigen Untersuchungsprogrammes war die Diagnose intra vitam nicht zu stellen. Sie wurde zunächst nicht einmal in die differentialdiagnostische Erwägung eingeschlossen. Erst durch die Kenntnis des Obduktionsbefundes wurden weitere Nachforschungen und Erhebungen betrieben. Der Patient lebt seit mehr als 20 Jahren in der unmittelbaren Umgebung einer Faserstoff- und Zellwollefabrik, wo er auch beschäftigt war. In den letzten 15 Jahren war er allerdings nur mehr zur Büroarbeit eingesetzt. Die Exposition durch Schwefelstoffe, vorwiegend Schwefelkohlenstoff ( $CS_2$ ) ist erhöht und war in den letzten Jahren zum Teil für die Anrainer und Bevölkerung der unmittelbaren Umgebung belästigend. Eine Großzahl aus dieser Bevölkerungsgruppe ließ im Zuge durchgeführter biopischer Untersuchungen der Leber deutliche Hinweise auf eine Leberzellschädigung, besonders elektronenoptisch, erkennen. Die Erweiterung des rauhwandigen endoplasmatischen Retikulums und letztlich Veränderungen der Mitochondrien, gelegentlich begleitet von leichten biochemischen Reaktionen, wie geringe Elevation von SGPT, manchmal auch SGOT und GDH, selten eine leichte Verminderung der Cholinesterase standen im Vordergrund. Diese überzufällige Häufung derartiger – vorwiegend elektronenoptischer – Leberbefunde betraf auch jenen Patientenkreis, der aus ganz anderen Ursachen ins Krankenhaus aufgenommen war.

Bekannt bei höhergradiger Exposition schwefelhaltiger Substanzen, vorwiegend Schwefelkohlenstoff, ist das erhöhte Risiko von Gefäßatherogenität. Mit Polyvinylchlorid ist der Patient 15 Jahre zuvor, wenn auch nicht häufig, so doch in einem gewissen Ausmaß konfrontiert worden, so daß die Expositionsrate an sich als gering und durchaus nicht permanent anzusprechen ist. Folgt man aber der Inzidenzrate auch bei relativ geringer Exposition nach den Literaturhinweisen, so würde auch das Latenzstadium von etwa 15 Jahren die hochgradige Wahrscheinlichkeit eines Zusammenhanges ergeben. Bei einer

heute angenommenen Morbiditätsrate von 10% [20, 33, 38], zeigt sich, daß neben der Exposition auch andere Faktoren für die Entwicklung des Angiosarkoms entscheidend sein müssen, da selbst bei dauernder Exposition rund 90% eine neoplastische Entwicklung vermissen lassen.

Im vorliegenden Fall läßt sich mit hoher Wahrscheinlichkeit folgender pathogenetischer Zusammenhang vermuten: In Analogie zur zunehmenden Häufung des primären Leberkarzinoms bei Leberzirrhosen und der hohen Inzidenzrate durch Aflatoxin (fast 70%!), wo der gestörten Biotransformation der kranken Leber die fehlende Metabolisierung kanzerogener Stoffe zugeschrieben wird, die dann als Mutationskarzinogene unabgebaut liegenbleiben und zur Entwicklung des Heparoms führen, könnte im vorliegenden Fall an sich schon die Prädisposition zur prämaternen Sklerose und Atheromatose vorgelegen haben. Die Atherogenität und die Progredienz der prämaternen Gefäßsklerose könnte durch Schwefelkohlenstoffexposition durchaus gefördert worden sein. Möglicherweise liegen auch immunphänomenologische Faktoren einer Art Bürger-Winiwarter-Syndrom zugrunde. Auf diesem mehr oder minder ubiquitär gefäßsklerotischen Schaden würde eine – unter Umständen auch kurze und intermittierende – Exposition mit Polyvinylchlorid ausreichen, um diese toxische und kanzerogene Substanz in die Gefäßwand unabgebaut einzulagern, da eine Metabolisierung infolge des gestörten Biotransformationsvermögens zumindest vielerorts unmöglich ist. Damit wäre ein Kreislauf geschlossen, der einen pathogenetischen Mechanismus kennzeichnet, in welchem der multifaktoriellen Genese der Entstehung von Angiosarkomen Rechnung getragen wird, wobei dem Polyvinylchlorid als kanzerogene Substanz aber letztlich die Schlüsselstellung der neoplastischen Entstehung zukommt.

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