CORRESPONDENCE

A potential cause of bladder cancer

Sir,—The connection of bladder cancer with exposure to certain aromatic amines was first noticed in workers in the magenta dye industry in 1895.1 Since that time, prime agents have been identified among groups of polycyclic aromatic amines that have been used particularly in the manufacture of synthetic dyes. One of these groups is based on biphenyl; an example is benzidine (4,4' diamino-biphenyl).

\[
\text{H}_3\text{N} - \begin{array}{c}
\text{C} \\
\text{H} \\
\text{B} \\
\text{H} \\
\end{array} - \begin{array}{c}
\text{B} \\
\text{H} \\
\text{C} \\
\text{H} \\
\end{array} - \begin{array}{c}
\text{N} \\
\text{H} \\
\end{array}
\]

The manufacture and use of these compounds was placed under strict control by the Carcinogenic Substances Regulations 1967, yet the incidence of bladder cancer has continued to rise—in Wales it has doubled from 0.126 per 1000 in 1974 to 0.252 per 1000 in 1985, and the incidences are remarkably uniform across the country, ranging from 0.21 in Powys and in South Glamorgan, to 0.27 per 1000 in Clwyd (1985 figures). If these occurrences are caused in part by exposure to such chemicals, they are clearly not confined to workers in the chemical industry. In recognition of this, the Health and Safety Executive has recently set up a register2 to help trace unknown factors.

Smoking has been established as a major cause,3 but surveys designed to separate the smoking factor from others have identified certain occupations as having increased risk factors, for reasons not yet understood. Cole et al.4 found statistically significant risks among cooks, kitchen workers, and clerical workers, and commented that none of these groups is exposed to any known carcinogen in their work. Howe et al.3 noted that a substantial proportion of bladder cancers cannot be accounted for by smoking and hazardous occupational exposures alone, particularly in women (who are generally less likely to work in environments associated with bladder carcinogens). Their data show increased risks for female clerical workers. They concluded that "...more is known about the etiology of bladder cancer in males than in females. Thus, although we have confidence in the importance of tobacco use in the etiology of female bladder cancer, further study of other potential associations is required." Increased risk of bladder cancer among male clerical workers was also reported as long ago as 1950.5

Whereas statistically valid data can only be obtained by properly conducted surveys, there is much to learn from individual case studies. I recently had the opportunity to examine the occupational background of a woman with bladder cancer in an attempt to trace a cause. Suspicion had been aroused by the fact that she had at one time been employed in a "chemical works", but this turned out to be a pharmaceutical firm and there was no evidence that aromatic amines were involved. Furthermore, she was a clerical worker who had virtually no contact with production.

She had, however, spent much time making copies of documents by means of a process that she described as smelling of ammonia. This was subsequently identified as dyeline copying, otherwise known as whiteprinting, and used the diazo process.8 It was first demonstrated in 1917 and was in use in offices in the 1960s and 1970s until it was largely superseded by the electronic photocopier, although its ability to make multiple copies from large transparencies relatively cheaply still finds some applications.

In the diazo process, a sheet of paper impregnated with a diazo compound is placed beneath a transparency to be copied and ultraviolet light is directed through it. In the areas exposed to the light, the diazo compound is decomposed; beneath dark areas of the transparency the compound survives and is subsequently developed into a visible colour by reaction with another compound in the paper to form an azo dye. This reaction is initiated by passing ammonia through the paper—hence the smell associated with the process.

Over the years, many types of diazo compound were used, but most were based on the framework (with various additional groupings):

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\end{array} - \begin{array}{c}
\text{C} \\
\text{H} \\
\text{B} \\
\text{H} \\
\end{array} - \begin{array}{c}
\text{N} \\
\text{H} \\
\end{array}
\]

Of interest here is the fate of the diazo molecules bleached by the ultraviolet light. When diazo compounds decompose, they do so by a free radical mechanism. Exposure to ultraviolet light of a suitable wavelength will encourage this process of homolytic fission. The first stage can be written as:

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\end{array} - \begin{array}{c}
\text{C} \\
\text{H} \\
\text{B} \\
\text{H} \\
\end{array} - \begin{array}{c}
\text{N} \\
\text{H} \\
\end{array} \rightarrow \begin{array}{c}
\text{N} \\
\end{array} + \begin{array}{c}
\text{B} \\
\text{C} \\
\text{H} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{C} \\
\text{H} \\
\text{B} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{N} \\
\text{H} \\
\end{array}
\]

Free radicals are very reactive and various subsequent reaction pathways are possible, many leading directly to diphenyls. These reactions were extensively studied in the 1930s and one—the Gomberg reaction—is particularly well known to organic chemists. One of the obvious possibilities is the chain termination process whereby two free radicals combine thus:

\[
\begin{array}{c}
\text{N} \\
\end{array} + \begin{array}{c}
\text{B} \\
\text{C} \\
\text{H} \\
\text{H} \\
\end{array} \rightarrow \begin{array}{c}
\text{N} \\
\end{array} + \begin{array}{c}
\text{B} \\
\text{C} \\
\text{H} \\
\text{H} \\
\end{array}
\]

Depending on the exact nature of the original diazo compound, what has been produced is a substituted benzidine. Other probable reaction pathways will result in similar products being formed. The nitrogen atoms are likely to carry alkyl groups as these are needed to stabilise the diazo compound, for example:

\[
\begin{array}{c}
\text{CH}_3 \\
\end{array} - \begin{array}{c}
\text{C} \\
\text{H} \\
\text{B} \\
\text{H} \\
\end{array} - \begin{array}{c}
\text{N} \\
\text{H} \\
\end{array} \rightarrow \begin{array}{c}
\text{CH}_3 \\
\end{array} + \begin{array}{c}
\text{B} \\
\text{C} \\
\text{H} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{N} \\
\text{H} \\
\end{array}
\]

The close similarity between this and benzidine itself is obvious and although no data on its toxicity exist, it would be prudent to suspect a risk.

It seems probable from the foregoing that appreciable quantities of substances closely related to known bladder carcinogens may have been inadvertently produced in the light sensitive papers used in the diazo copying process and that anyone subsequently handling the papers on a regular basis without gloves could
Correspondence

have taken them up by absorption through the skin. Furthermore, the compounds were deliberately placed near to the surface of the paper to make the process more efficient, accentuating a potential hazard.

The diazo process as described was in fairly widespread use up to the mid-1970s (I understand that there are photographic applications today, but although there seems little danger of skin contact in them it would be as well to reconsider methods of waste disposal). As bladder cancers can take up to 20 years to develop many would have turned up after some delay, and indeed, it this explanation is correct, some have yet to surface. I make no claim of proof on the basis of this one case, but I suggest that current patients with bladder cancer should be surveyed for possible correlations, and also that an analysis be performed on some exposed papers for the suspected chemicals.

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Objective testing for vasospasm in the hand-arm vibration syndrome

Sir,—Regarding the article by Allen, Doherty, and McGrann (1992;49: 688-93), may I make the following comments: (1) We are unaware of any objective test that can distinguish hand-arm vibration syndrome of occupational origin from primary Raynaud's syndrome or any other secondary cause. Such a test is eagerly awaited not only for medicolegal reasons but in the management of true hand-arm vibration syndrome/vibration white finger. (2) Tests for vascular dysfunction do just that and do not give any information that the cause of dysfunction is related to vibration. (3) The authors describe the use of an investigative technique that showed a good correlation between a clinical white finger and a valid demonstration of digital vasospasm. But to describe this as objective testing for vasospasm in the hand-arm vibration syndrome is a non-sequitur that does not assist in the search to diagnose hand-arm vibration syndrome/vibration white finger of occupational origin on sound medical grounds.

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The Authors' reply

The investigative technique described was developed to detect the occurrence of digital vasospasm and grade its severity in an objective manner. This is helpful in the assessment of vasospastic disease whether it is primary or secondary in origin as diagnoses need no longer be based solely on the history given by the patient. Signs of cold induced vasospasm are often absent at the time of medical examination and so objective testing can help to clarify the situation.

The test procedure was first evaluated in patients with non-occupational vasospasm1 and it has never been suggested that it can differentiate between the various forms of Raynaud's syndrome, which are distinguished on clinical grounds and not investigative findings. In subjects diagnosed to have vibration white finger on clinical assessment, an objective test detecting vasospasm supports the clinical diagnosis and helps grade its severity. Such testing does therefore assist diagnosis of vibration white finger.


Pulmonary effects of exposure to fine fibreglass: irregular opacities and small airways obstruction

Sir,—I read with interest the article by Kilburn et al (1992;49:714-20). I first became aware of the results of Kilburn's investigation in 1989, when he reported his findings at the Second California thermal insulation conference. As a follow up to his report, Owens-Corning contacted General Electric, the operator of the plant. General Electric provided me with a copy of the industrial hygiene data that it had provided to Kilburn. From these data it seems that he has incorrectly reported the concentrations of fibreglass and asbestos that were present. For concentrations of fibreglass present in the plant, Kilburn states that: "when examined by light microscopy, they showed less than 0.1-0.4 fibres/ml with total dust concentrations of 0.13-0.47 mg/m3 measured gravimetrically."

In fact, the highest concentration of glass fibres reported in the 29 samples that were provided to him was 0.04 fibres/cc. Five of the data points were below detectable limits, which was pointed out to Kilburn. Fourteen of the measurements were 0.01 fibres/cc. The remaining data points were either 0.02 or 0.03 fibres/cc. In short, the data provided to Kilburn were at least a full order of magnitude below that reported in his paper.

Kilburn reported the historical data, from 1975, that was provided. Those measurements were less than 0.1 mg/m3 of respirable dust. He failed to mention, however, that at that concentration they were below the limit of detection of the sampling technique. He did not report at all the 1979 data, which also indicated that the glass fibres were below the limit of detection.

As to asbestos fibre concentrations, Kilburn states that: "no asbestos fibres were reported in the samples by phase contrast microscopy." That is true for the 1989 data with which he was provided. The data from 1974 and 1975 given to him, however, showed that there were low amounts of asbestos present in the plant. There were 14 measurements, 10 of which were below detectable levels. Three of the other four measurements of asbestos (0.2, 0.10, 0.25 fibres/ml) were an order of magnitude higher than the concentrations of fibre glass reported to Kilburn. Although they were all well below the permissible exposure limits in effect at that time, they would seem to be relevant to the analysis of the hypothesis proposed by Kilburn et al.

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A potential cause of bladder cancer.

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