CORRESPONDENCE

Exposure to asphalt or bitumen fume and renal disease

Editor,—The correspondence from Dittmer and Armitage provides further support for a causal association between exposure to various hydrocarbons and the development of renal disease. Since 1912, some case reports,1 case-control studies,2 and cross-sectional3 studies together with animal experiments4 have provided compelling evidence for a causative role for hydrocarbon exposure in the development of both tubular and glomerular lesions.

We now report the case of a road worker exposed to asphalt and bitumen fumes who presented in 1990 at the age of 56 with nephrotic syndrome. He was then normotensive, had proteinuria with 24 hour urinary protein of 12.2 g, showed some clinical oedema, and his renal biopsy was consistent with a diagnosis of stage 2 membranous glomerulonephritis. Since the diagnosis of nephrotic syndrome was made, he has had persistently raised serum creatinine of 298 compared with his previously normal value of 85 µmol/l, and a marked deterioration in renal function. This followed several weeks of abdominal pain, and he then had haematuria without pyuria, serum creatinine of 208 compared with his previously normal value of 85 µmol/l, and a marked deterioration in his renal biopsy with 20 glomerular profiles per section and tubulointerstitial scarring occupying 40% of the biopsy.

Before developing renal disease, the patient had been employed as a road worker for more than 10 years, during which time he was repeatedly exposed to intermittent but high concentrations of asphalt or bitumen fumes. Since the diagnosis of nephrotic syndrome due to membranous glomerulonephritis, the patient stopped being exposed to asphalt and bitumen fumes. Subsequent assessments of proteinuria have shown a reduction of up to 50% from 12 to 5 g/day. However, he currently is hypertensive with serum creatinine 170 µmol/l, urea 10.4 mmol/l, serum albumin 30 mmol/l, and 24 hour urinary excretion of protein 5.0 g.

Searches of the scientific literature in 1990 and subsequently have not found any specific references to exposure to asphalt or bitumen and renal disease. We therefore investigated the issue further by means of (a) detailed fume analyses, and (b) a study of the renal health of road workers exposed to asphalt or bitumen.

It was clear from the fume analyses that exposures in this industry include a wide range of aromatic and aliphatic hydrocarbons. Time weighted average exposures ranged from 0.4 to 8.9 mg/m³ measured as total organic fume (not including inorganic particulates), but short term or peak fume exposures were as high as 300–900 mg/m³. During all his years exposed to these fumes, the patient had never been provided with or worn respiratory protective equipment.

The study of renal health included 92 people regularly exposed to asphalt or bitumen fumes as road workers, 38 hard rock quarry workers not occupationally exposed to hydrocarbons, and 43 office workers also not exposed to hydrocarbons. Each participant was given a questionnaire examining his work history, which included questions about occupational and recreational exposures and medical history including renal disease. Urine and blood samples were collected for urinary chemistry, blood biochemistry, and microscopic analyses. Any person with an abnormal finding on blood or urine analyses were retested and examined by a nephrologist to assess the presence or otherwise of renal disease.

The criteria which determined an abnormal test result were as follows: (a) persistently raised serum creatinine >120 µmol/l; (b) persistently raised serum urea >7.5 mmol/l; (c) persistent microscopic haematuria or pyuria; (d) 24 hour urinary protein >150 mg/day; or (e) corrected creatinine clearance <90 ml/min.

Results

The presence of renal disease was determined as pre-existing or idiopathic according to the following criteria. Pre-existing renal disease: (a) family history or history of renal disease; (b) abnormal renal ultrasound. Idiopathic renal disease: (a) no known cause for abnormalities; (b) abnormal creatinine, urea, and creatinine clearance; (c) abnormal proteinuria; or (d) abnormal urinalysis—haematuria or pyuria.

The findings of the study are summarised in tables 1–3.

We concluded from this study that: (a) workers regularly exposed to asphalt or bitumen fumes were far more likely to have evidence of early stage renal disease than those working in a quarry or office; (b) workers regularly exposed to asphalt or bitumen fumes were far more likely to have at least one abnormal renal function test than those working in a quarry or office; and (c) the renal dysfunction was non-specific, but the overall findings were consistent with previous findings—such as those from the similar study done by Yaqoob et al.

We think that chronic glomerulonephritis and chronic tubulointerstitial nephritis are renal diseases which may result from exposure to hydrocarbons—as those experienced from asphalt or bitumen fumes generated during road making.

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GAVIN CARNEY
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Table 1 Age and blood pressure

<table>
<thead>
<tr>
<th>No exposure</th>
<th>Office</th>
<th>Quarry</th>
<th>Exposure to bitumen or asphalt</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>People (n)</td>
<td>43</td>
<td>38</td>
<td>92</td>
<td>173</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>39</td>
<td>32</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>BP (mean systolic)</td>
<td>133</td>
<td>131</td>
<td>133</td>
<td>133</td>
</tr>
<tr>
<td>BP (mean diastolic)</td>
<td>86</td>
<td>83</td>
<td>83</td>
<td>84</td>
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</table>

Table 2 Renal disease

<table>
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<th>No exposure</th>
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<th>Exposure to bitumen or asphalt</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of people</td>
<td>43</td>
<td>38</td>
<td>92</td>
<td>173</td>
</tr>
<tr>
<td>Pre-existing renal disease (n (%)) NS</td>
<td>4 (9.3)</td>
<td>2 (5.3)</td>
<td>1 (1.1)</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>Idiopathic renal disease (%)**</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>12 (13.0)</td>
<td>12 (6.9)</td>
</tr>
</tbody>
</table>

**p<0.01.

Table 3 Renal function

<table>
<thead>
<tr>
<th>No exposure</th>
<th>Office</th>
<th>Quarry</th>
<th>Exposure to bitumen or asphalt</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>People (n)</td>
<td>43</td>
<td>38</td>
<td>92</td>
<td>173</td>
</tr>
<tr>
<td>Haematuria</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Raised creatinine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>At least one abnormality (n (%))**</td>
<td>4 (9.3)</td>
<td>2 (5.3)</td>
<td>24 (26.1)</td>
<td>30 (17.3)</td>
</tr>
</tbody>
</table>

**p<0.01.
epoxy resin fumes. If there was evidence of significant renal damage then it may also be wise to counsel the patient to avoid further contact with the substance. Indeed in our case, the patient found that his general health improved dramatically when direct contact with the material ceased. The issues of general industrial health and possible compensation or litigation also need to be considered.

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Cancer risk in the rubber industry: a review of recent epidemiological evidence

EDITOR,—Although the comprehensive review of the rubber industry reported by Kogevinas et al only considers papers published after 1982, several of these studies relate to groups of workers from much earlier eras—for example, 1910 for the German study, 1946 for the British Rubber Manufacturers Association (BRMA) study, and Veys studies. 1 By considering the findings of these earlier rubber workers along with studies of more recent groups of workers we are getting a picture of 80 years of cancer experience in the industry, which is not the same as the situation that exists today.

It should also be borne in mind that the very large cohort studies—such as the 34 000 workers examined in the Veys study—have very much greater statistical power than those of the smaller studies, in which confounding factors and the role of chance are more difficult to evaluate. This does not seem to have been fully taken into account and indeed Kogevinas et al tell us that they have not “paid much attention to statistical significance”. This is disappointing as it is the omission of a full meta-analysis of the studies, which if it had been carried out, would have added considerable weight to their conclusions.

In general, the review would seem to endorse and reflect the evaluation by the International Agency for Research on Cancer (IARC) of the industry in the 1987 monograph, supplement 7, of a moderate increase in risk of cancer at several different organ sites which are not consistently found in epidemiological evidence for a full analysis to be carried out or whether it would be appropriate to delay this until more data are available. Kogevinas et al have given an interesting and important overview of health hazards observed in rubber workers employed during the past 80 years and I agree with him that this is more relevant, modern, and comprehensive than the past 80 years and I agree with him that this is more relevant, modern, and comprehensive epidemiological evidence if we are to obtain a true picture of the situation today.

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Authors’ reply—We thank Straughan for his comments. We agree that some of the studies we reviewed provided a picture of 80 years of cancer experience in the industry, which is not the situation existing today (in industrialised countries). We tried to identify and report separately results for studies examining risk in the first employment periods. These studies did not clearly indicate the absence of an excess risk of cancer. Unfortunately the number of subjects and cancer deaths or cases in these studies is small and does not allow definitive conclusions to be drawn yet.

Considerable heterogeneity exists between and within countries in exposure circumstances in the rubber industry. What we did in our review was to give a picture of excesses of risks in this industry. This overall picture does not apply to all countries, nor to all periods. However, an overall picture may highlight conditions that are not easily recognized at a local level. One example is the identification of an increased risk for laryngeal cancer, which had not been previously reported although it seemed consistent between centres. We refer the reader to the reply written by Straughan (and others), that the British studies do not indicate an excess risk for bladder cancer after the discontinuation of use of β-naphthylamine. What is usually meant by an excess risk, is that there was no significant excess risk, which is correct. What can be distinguished, however, looking at the overall picture (see figure 1 of our review) is a small but consistent excess risk for bladder cancer even in studies conducted in relatively late periods. There is a lack of detailed exposure information in most studies but it is probable that β-naphthylamine was not used in these late periods. We agree with Straughan that it is difficult to exclude the possibility that the observed small excess risk is due to a late effect of early exposures.

The findings of the large BRMA study are, indeed, more relevant, modern, and comprehensive than those of studies in the Nordic or other countries, but they are not necessarily either more or less confounded than those of other studies. We understand Straughan’s plea for a full meta-analysis in which large studies are not given the same weight as small studies. The variability of exposures over time, geography, and process argue against performing a meta-analysis which presumes homogeneity of exposure.

It is commendable that the BRMA has been and continues to be actively involved in examining risk of cancer among workers in the rubber industry. We hope that the new study initiated by the BRMA will do justice to the concluding sentence of our paper: “The preventive measures taken in the rubber industry in recent years may decrease risks, but this has not been documented yet in epidemiological studies”.

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Inhalation of ammonium nitrate fuel oil explosive (ANFO): and possible concomitant exposure

Editor,—Donoghue\(^1\) reports on respiratory symptoms and rhonchi in a miner after exposure to ammonium nitrate fuel oil explosive (ANFO). As diesel fuel is the most commonly used fuel in ANFO the vapour he refers to might be components of diesel fuel. He excludes concomitant exposure to nitrogen dioxide because the inhalation occurred before any explosion took place. Although diesel powered machines are commonly used in underground work he does not discuss possible exposure to diesel exhaust. I have measured up to 15 ppm nitrogen dioxide during construction of a tunnel where the only known source was diesel exhaust. Exposure to such high concentration may contribute to respiratory symptoms and rhonchi. Therefore nitrogen dioxide should not be excluded as a concomitant causative factor. In a study of the contribution of gases from diesel exhaust and from the blasting cloud during excavation of a mine, 0.3–3 ppm nitrogen dioxide was measured during the blasting. Inhalation of enzyme dusts during exposure to diesel exhaust, tunnel dust exposure and possible exposure to diesel exhaust following an explosion are all possible and may be concomitant factors. Diesel exhaust, tunnel dust and explosives are all possible sources of inorganic gases from diesel exhaust and from the blasting cloud during excavation of a tunnel. The association between handling one or other material and the development of symptoms was clear cut, and because of the short period of handling, with intervals of at least a month between these periods, there was time for symptoms to regress between exposures.

I had already validated a skin prick test for papain sensitivity,\(^1\) and was able to use the same test to make a similar diagnosis and to find a similar association to that reported by Hendrick.\(^2\) Positive prick test findings seemed to confirm the specificity and likely mechanism of the atypical asthmatic symptoms from each enzyme.

Had I had any reasonable doubt as to causality I would not have published the warning. Happily, subsequent reports, including the excellent one by Aitkin \(\text{et al.}^4\), of which Hendrick is a coauthor, which included inhalation challenge tests with fungal u-amyrase,\(^1\) have endorsed my conclusions and added further knowledge.

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Occupational asthma due to amylase

Editor,—In a letter to you,\(^1\) Hendrick points out my inadvertently overlooked report in The Lancet on allergy to u-amylase and papain,\(^2\) and makes generous reference to my other work on enzymes.

For clarification, I should point out that the evidence, supported by the findings with amylase, that sensitisation and consequent symptoms may occur from proteases independently of proteolytic activity, must not obscure the fact that proteolytic mechanisms may cause other clinical and subclinical effects. As well as skin irritation, non-sensitised people may experience epistaxis or haemoptysis, whereas rhinorrhoea or asthma are more likely to be due to allergy. Proteolytic effects may be apparent in the lungs, including proteolytic effects varies between different proteases, and susceptibility to such effects varies between people.\(^3\) I think I have experienced such effects myself,\(^4\) and possible long term consequences have been described.

Although he concurs with the use of skin prick tests as an index of sensitisation, Kendrick expresses reservations about my evidence of causality in respect of chest symptoms from u-amylase. This is understandable if I relied solely on his condensation of an already condensed report. Although my report derived from a comprehensive ongoing investigation, I had hoped I had summarised sufficient information to make my point.

His reservations seem to derive from the fact that papain and u-amylase had also been handled in the workplace, and that some of those sensitised to u-amylase were also sensitised to papain.

At this factory papain and u-amylase were handled in pure form, seldom, and at different times and places. The association between handling one or other material and the development of symptoms was clear cut, and because of the short period of handling, with intervals of at least a month between these periods, there was time for symptoms to regress between exposures.

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of epidemiological associations, and reliance on personal memory will not provide the detailed data which allow chromosomal abnormalities to be grouped in a meaningful way when exploring possible environmental influences. The study of Roman et al. illustrates the need to confirm diagnoses reported in questionnaires, if possible, and to obtain any additional information that may assist in the scientific evaluation of epidemiological results.

BOOK REVIEWS

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As indicated by the title, this book is the eighth in a series of proceedings on inhaled particles. These international symposia, held in 1980, 1965, 1970, 1975, 1980, 1985, 1991, and 1996 at various venues in the United Kingdom, were all sponsored by the British Occupational Hygiene Society (BOHS). Since the 1975 meeting, the proceedings were also issued simultaneously as special issues of the BOHS journal Annals of Occupational Hygiene. These symposia and their proceedings have served as landmarks documenting the state of the art in knowledge and techniques concerning human exposures to airborne particles, their deposition and clearance within the respiratory tract, and their health effects. The broadening depth and scope of the symposia to now include radioactive, outdoor and indoor particulate matter have put a great strain on the organisers and especially on the editors. Additional pressure was resulted from the fact that the two previous proceedings did not appear until three years after the meetings. Thus, the publication of this volume only one year after the symposium is a significant accomplishment and a tribute to the dedication of its new editors. A price for this accomplishment was the restriction of the 127 papers to four to six pages each, and the elimination of external peer reviews. The reviews and editing were done by the editors alone. Also, for the first time, there were no abstracts included in the papers and the questions from the audience, and authors’ responses, that were notable features of the earlier volumes, were not included.

The quality of the papers and editing remain at a high level, and this volume should be a valuable addition to the bookshelf of all scientists, health professionals, and public health authorities who are seriously interested in the health effects of airborne particles. It is also acknowledged that the price is high enough to limit its readership.
This book, one of a series of reviews produced by the Institute for Environment and Health, provides a useful summary of the current understanding of the risks associated with both asbestos and more importantly, and less well-known, man-made mineral fibres. It provides useful insight into the production and use of fibre, and summarises the scientific literature on fibre concentrations to be found in the general and domestic environment and makes estimates of the exposures that members of the United Kingdom population might expect over a lifetime. In parenthesis the sort of figures provided show nicely how protagonists in the polarised fibre debate can use figures to strengthen their case. For example, our background exposure to fibres in the environment average between 0.000001 and 0.0001 fibres per ml, a figure that might not reassure the reader of the fibre's reassurance. However, calculating up a total lifetime exposure over 70 years can give a figure as high as almost 30 million fibres in total which to the unsophisticated sounds rather a lot. Those, however, who really understand the lung-anatomy and physiology can take comfort from the fact that we have some 300 million alveoli for these fibres to be shared out among even assuming that most of them are deposited (which they are not!).

The book summarises the known health effects of asbestos and the, as yet, incomplete but reassuring literature on the epidemiology of workers exposed to other fibres. It also discusses the experimental animal and in vitro evidence with respect to man-made fibres. There is useful discussion of fibre deposition, clearance, and solubility leading to conclusions which in my view are wholly sensible. For asbestos, the authors argue against a general policy of removal and for management in situ unless the material is releasing unacceptable amounts of dust. For man-made mineral fibres they express caution about the production of fine diameter fibres but point out that almost all the material used commercially is not respirable and that there is no reason to suppose that current levels of exposure pose any risk to the public.

All in all this is a remarkably informative book containing much information on mineral fibres that is not readily available elsewhere. The debate about the harmfulness of fibres needs to shift back to the protection of exposed workers and away from theoretical risks to the general population.

ANTHONY SEATON


“Every 10 seconds, another person dies as a result of tobacco use”. This is the stark introductory sentence to this reference book compiled by the World Health Organisation as a source of standardised baseline information on tobacco production, trade, consumption, health effects, and control in WHO member states. The book is divided into two parts: the first, comprising 60 pages, attempts to summarise the global situation in the late 1980s and early 1990s. The second and larger part presents a series of “country profiles” for each of the member states, typically of one or two pages. These list the latest available information on demographic and general health indicators, tobacco production, trade and industry, tobacco consumption, and smoking prevalence by age and sex, and national tobacco control policies and programmes.

Designed as a reference text, this is not a book to be read from cover to cover. Its strength is the near comprehensive coverage of national statistics on tobacco production and use, which are usefully summarised in part one. These may suffice for readers with an epidemiological background, among whom the adverse health effects of smoking are taken for granted. For a more general readership, however, a notable weakness of this book is the paucity of information on health consequences of tobacco use. The relevant chapter in the first part runs to only five pages, including four tables, and is supported by only two references, one of which is yet to be published. Although published in 1997 it is cited as a series of recent articles in the Lancet.

The discussion of health effects is extremely focused on mortality, mainly from broad groups of causes, such as total mortality, cancer deaths and heart disease. There is no mention of the disability and loss of productivity related to cardiovascular and respiratory diseases, nor of the consequences of environmental tobacco smoke. Where the health effects are assessed for individual countries in part two, figures are provided mainly for developed countries and relate principally to estimates of tobacco related death and disease.

This volume provides a powerful reminder, if such is needed, that tobacco use is a global phenomenon, with one third of adults now smoking, and two thirds of those residing in developing countries. The premise underlying the report is that widespread tobacco consumption and public health are mutually incompatible, but readers seeking a comprehensive collation and consideration of the epidemiological evidence might find this book very useful. It is a baseline for a global programme of surveillance of smoking habits and tobacco control and it is hoped that the WHO will compile a similarly comprehensive account of the effects of tobacco use on health in many countries, particularly in the developing world. A valuable addition to future editions would be evidence from countries with well developed tobacco control policies of the extent to which lowering smoking prevalence reduces death and disability. This might encourage much needed policy initiatives in many other countries where tobacco control has yet to achieve prominence on the public health agenda.

DAVID P STRACHAN


This monograph gives full details of a study conducted to test the Gardner hypothesis—namely, that childhood leukaemia and non-Hodgkin's lymphoma result from the father's
exposures to ionising irradiation before conception. This study has also been published as a paper in the BMJ, but this volume goes into far greater detail than is available elsewhere. This is very much a book for the concerned specialist reader who wants the technical background to the BMJ article.

This study is essentially a record linkage exercise. The exposed fathers (and mothers) were defined as having records with the National Registry for Radiation Workers (NRRW) held by the NRPB. This is a database of over 120,000 people and it was linked with the national register of childhood tumours, a database of over 50,000 children with all types of cancers. Two other data sources on childhood cancers were also included.

For the three sources of data on childhood tumours, controls were found in various ways to ascertain if these children had a father in the NRRW. The parental estimated doses were created from the NRRW. In all a total of 200 fathers and mothers were linked to children with cancer. Eighty two children with leukaemia or lymphoma were linked to fathers’ records at the NRRW, as were 79 control fathers. The corresponding numbers for mothers were 15 and three.

The cases in the original Gardner paper were excluded and the results for fathers showed that case fathers had a 1.77 significant excess risk over control fathers for having a child with leukaemia or lymphoma. However, the risk was associated with the lowest dosages and there were no dose responses in any of the comparisons. In this sense the Gardner hypothesis is refuted!

Furthermore, the risk in mothers was also significantly and greater in magnitude than the fathers. However, the small numbers make this result unreliable and difficult to use to extrapolate risk.

The explanation of the association found in these NRRW members exposed to low doses is not known. It could be chance, it could also be due to misuse of film badges by those in high risk industries. This explanation is unlikely in that the cancers were distributed widely across industries in the United Kingdom and were not confined, by any means, to the nuclear reprocessing or related industries. It may be due to other exposures associated with the wider radiation industries where many other hazardous substances exist as well as ionising irradiation. Finally, it could be some other, more subtle aspect, of wearing a film badge. The authors speculate that this might be associated with the mobility of the parents, thereby linking these results with the Kinlen hypothesis which is based on ideas of infectivity associated with population mixing. They do not produce evidence to suggest that film badge wearers are more mobile than other professions but the differences in behaviour may be more complex.

Further light might be shed on this association when the nuclear industry family study (NIFS) is analysed shortly. This study will answer some criticisms of the present study. For example, it is known that there are differences in behaviour of people within the nuclear industry and those outside it. The NIFS uses internal comparisons and so such differences can be accounted for.

Despite the lack of any explanation of this observation attention is now bound to be focused on other preconceptional and periconceptual exposures in both sexes and their possible links with childhood malignancies.

R A CARTWRIGHT