CASE REPORT
A cluster of haematuria cases in a pesticide-manufacturing plant

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In a pesticide manufacturing and formulating facility, 10 employees out of 48 were shown to have haematuria on dipstick testing. They included seven of the 27 production workers, all of whom had worked in both of two particular areas prior to the commencement of the routine urine testing. Five of the seven production workers with haematuria underwent further investigations, and in all five the haematuria was glomerular in origin. Two underwent renal biopsy, which showed irregular attenuation of the glomerular basement membrane (GBM) but no abnormality by light microscopy. Immunofluorescence studies were negative. This case series of glomerular haematuria is not readily explained by chance, false positive dipstick testing, or a recognizable non-occupational cause. Thin GBM disease, which is a benign condition, appears the likely explanation. Thin GBM disease is usually an autosomal dominant condition, but clustering of these genotypes in this small population is improbable.

Key words: Thin GBM disease; haematuria; pesticides.

INTRODUCTION
Effects on the kidney are among the less common consequences of exposure to environmental chemicals, and those chemical agents found to be nephrotoxic tend to affect the proximal tubule rather than the glomerulus. We describe here a series of cases of haematuria in workers engaged in the formulation and packaging of agricultural chemicals.

INDEX CASES
Case 1. A 33-year-old male was seen in July 1994. He had had haematuria and heavy proteinuria detected on ward testing conducted by the company nurse. He had been diagnosed with hypertension in 1989, and was being treated with atenolol. He had been employed at the factory since 1988, successively in phenoxyacetic acid herbicide preparation, in ‘dust-packaging’, in formulating insecticides and fungicides in liquid form (I & F), and, after the haematuria and proteinuria were detected, in the office. On examination his blood pressure was 155/105. The urine contained 100-150mg/dl of protein but haematuria was not detected. There were no other abnormal clinical findings. Renal biopsy showed irregular attenuation of the glomerular basement membrane (GBM) but no abnormality by light microscopy. Immunofluorescence studies were negative. There was no recognized family history of renal disease.

Case 2. A 50-year-old female, also seen in July 1994, also had proteinuria and haematuria detected by the company nurse. She had been employed at the plant for five years, and had worked in the dust-packaging and I & F areas. Renal biopsy showed irregular attenuation of the glomerular basement membrane (GBM) but no abnormality by light microscopy. Immunofluorescence studies were negative.

THE WORKSITE
The factory produced a very large range of pesticides. However these did not include any mercurials or any
Figure 1. The area known as the 'dust-packaging area'.

Since the products handled included organophosphates and carbamates, production employees had undergone periodic blood testing for red blood cell cholinesterase and plasma cholinesterase activity. Twenty-five employee records were available, of which five were suggestive of anticholinesterase exposure at one time or another (25% or greater fall in plasma or red blood cell cholinesterase activity from baseline measurement, or red cell cholinesterase activity below the normal range of 31-49 units/g haemoglobin). These reports were anonymous, so that it was not known whether any of these five were amongst those with haematuria.

URINE TEST RESULTS OF ALL WORKFORCE

Following initial findings in 1993, all employees undertook regular dipstick-testing of urine. The results, summarized in Table 1, show a total of 10 of the 48 employees (21%) positive for haematuria. In the production area, seven of the 27 (26%) were positive. Most employees had several tests and, as shown in Table 2, and in those in whom haematuria was found, the finding was consistent in most cases.

ASSOCIATION OF HAEMATURIA WITH EXPOSURE

Of the seven production workers and one maintenance worker with haematuria, all had worked in the dust packaging area and in the I & F area prior to the

Table 1. Distribution of haematuria cases by work area

<table>
<thead>
<tr>
<th>Work area</th>
<th>Haematuria ever</th>
<th>Number employed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Production</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Maintenance</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stores</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Laboratory</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Unclassified</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2. Frequency of positive haematuria testing in workers who ever tested positive

<table>
<thead>
<tr>
<th>Work area</th>
<th>No. tests showing haematuria</th>
<th>No. tests performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Production</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Production</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Production</td>
<td>9</td>
<td>9</td>
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<td>Production</td>
<td>5</td>
<td>7</td>
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<td>Production</td>
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<td>Production</td>
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<td>9</td>
</tr>
<tr>
<td>Maintenance</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Laboratory</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

bipyridyls, e.g., paraquat, which are nephrotoxic. In the dust packaging area products in powder form were dispensed though an auger into plastic bags inside cartons. The product was weighed, and the package sealed. There was a well-functioning exhaust system, but some spillage on the floor and workbenches was apparent, and this cleaned up by vacuuming and wet mopping (Figure 1). The workers were issued with hoods fitted with an external air supply, although it was claimed that these were not used at all times, until the company became aware of the haematuria cases.

In the I & F plant, active ingredients — solid and liquid — were fed into vessels from the top. The solvents — vegetable oil, and aromatic and aliphatic hydrocarbons were added charged from the bottom of the vessel where there was little opportunity for splashing or frothing.

In the phenoxyacetic acid plant, since decommissioned, 2,4-D (2,4-dichlorophenoxyacetic acid) had been fed in flake form by means of a screw conveyor to the top of a water tank. There did not appear to be any exhaust extraction of solids. Dust measurements had showed total inspirable dust levels ranging from 18-50% of the current exposure standard of 10mg/m³. However it was not known how much of this dust was active product.
Duration of employment prior to 1993 in the dust packaging area of the seven production workers ranged from 1–6 years. Employment of these workers in the I&F area prior to 1993 ranged from 1.5–6 years. Only two workers had worked in the phenoxyacetic acid herbicide area.

OTHER INVESTIGATIONS

The renal biopsy tissue in index Cases 1 and 2 were reviewed (AS) for any unique features, or for any features in common. No specific abnormality was found to indicate a single mechanism for renal damage, or to suggest a nephrotoxic agent. The specimens showed irregular attenuation of the (GBM) by electron microscopy — an extremely common lesion and the most frequent finding in patients undergoing renal biopsy for minor abnormalities discovered by urine testing. No abnormality could be detected by light or immunofluorescence microscopy.

Five of the seven production workers with haematuria, including the two who had had renal biopsies, agreed to undergo further investigations (TM). All still had haematuria, and in all cases the haematuria was glomerular in origin (demonstrated by phase contrast microscopy). Only one, index Case 1, showed proteinuria. All five had renal function in the normal range except Case 1, whose serum creatinine was at the upper limit. Serum complement, serum immunoglobulins and ESRs were measured on four of the five patients, and were normal. The ultrasound appearance of the kidney was normal in all cases, and no other clinical cause of haematuria (e.g., history of stones) was evident. (One former employee was also examined. This was a man who had retired because of coronary artery disease in 1992, before the commencement of routine urine testing. In December 1993 a left renal adenocarcinoma was diagnosed, and was removed in January 1994. He had worked at the factory from 1988 to 1992. Subsequent examination of the non-malignant renal tissue around the tumour showed no histological abnormality, and his renal function was normal.)

DISCUSSION

In a recent review, Schroder quotes a report that microscopic haematuria has a prevalence of less than 1% in subjects below the age of 50 but rises to levels of between 2% and 18% after the age of 50. Approximately 10% of this workforce were aged more than 50 years, and the a priori probability of 10 such people having microscopic haematuria out of a population of 48 is remote in the extreme — about 33 in one billion.

Despite this extreme probability estimate, we cannot dismiss the possibility that the occurrence of haematuria in this group of employees is the result of chance alone. Statistical theory indicates that random events are not evenly scattered throughout the sampling space: rather, some clustering is to be expected. However, in this case there are two other important factors to take into consideration:

(i) The distribution of haematuria was highly clustered in the production workers, all of whom had been employed in the dust packaging and I & F areas;

(ii) All five employees who agreed to undergo further investigation were shown to have haematuria of glomerular origin.

The commonest causes of microscopic haematuria of glomerular origin are thin GBM disease and IgA nephropathy. IgA nephropathy progresses to renal failure in about 20% of those affected. Thin GBM disease, which is a benign condition, appears the likely explanation. Thin GBM disease is usually an autosomal dominant condition, but clustering of these genotypes in this small population is improbable. Exposure to hydrocarbons has been associated with this disorder, but most other environmental agents found to be nephrotoxic affect the proximal tubule rather than the glomerulus.

A literature search suggests that renal effects are not commonly seen from exposures to pesticides. Arsenic is reported as having caused acute renal failure. However the primary pathology usually affects the tubules; in any case, arsenic exposure was unlikely to have been significant and in some of the employees was probably nil. Bipyridyls (e.g., paraquat) are nephrotoxic herbicides but were not produced in this plant, and in any case typically affect the renal tubules rather than the glomeruli. Lindane has been described as causing nephropathy in rats. Again however the primary target appears to be the renal tubules. Lindane was present on the site, but may not have been handled in very large quantities, as the organochlorines have been falling into disuse in recent years. Anticholinesterase compounds such as organophosphates and carbamates have been reported to cause renal problems. However this is not a typical manifestation of exposure to such agents, and cholinesterase testing of this workforce indicated that exposures to these agents was unlikely to be the cause of this cluster. These employees have been potentially exposed to a large variety of substances, and although efforts had been made to provide adequate occupational hygiene standards in the plant, there is no doubt that these employees with haematuria would have had the opportunity for some airborne exposures to a number of different agents, some of which could conceivably have nephrotoxic effects which have so far been unrecognized.

Another possible explanation is that the dipstick testing for haematuria simply has a low specificity. A prevalence of haematuria of 31% has recently been reported in a printing company, and a follow-up of selected workers showed no abnormality. A comparable prevalence (25%) was found in a control group of workers, and the authors concluded that screening for
haematuria is not an appropriate part of an occupational health examination. To test this possibility we obtained data on the prevalence of haematuria in employees of another workplace where dipstick testing is performed annually. In this predominantly blue-collar male workforce, 94 workers were tested over a 12-month period. Only three tested positive. Two were males, of whom one was known to have had a long-standing inflammation of the prostatic urethra and the other was found on investigation to have prostatitis. The third case was a female whose urine was considered to contain blood from menstruation.

CONCLUSION

This case series of glomerular haematuria is not readily explained by chance, false positive dipstick testing, or a recognizable non-occupational cause. There was no exposure to any of the known environmental nephrotoxins, which in any case typically affect the tubules rather than the glomeruli. Nevertheless we have documented these cases in view of the common occupational exposures.

ACKNOWLEDGEMENTS

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REFERENCES