The Presence of Urinary Cellular Sediment and Albuminuria in Newspaper Pressworkers Exposed to Solvents

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To investigate the relationship between exposure to organic solvents and the presence of increased urinary cellular sediment, we conducted a cross-sectional study of 215 newspaper pressroom workers who were exposed to solvent and lubricant mixtures. Thirty-two compositors were surveyed as referents. Industrial hygiene measurements showed low-level airborne exposures to organic solvents (primarily naphthas) and minimal airborne exposure to glycol ethers. There was a high prevalence of solvent-related dermatitis indicating there was significant dermal exposure to these substances. Pressworkers were exposed to solvent mixtures that were associated with dose-related increases in leukocyturia alone or in urinary cellular sediment (erythrocyturia and/or leukocyturia). The presence of urinary cellular sediment was associated with increasing frequency of use of five particular organic solvent mixtures. These results suggest that the increase in urinary cellular sediment may be due, at least in part, to the effects of solvents on the kidney. Consistent with this hypothesis, 16% of pressmen and no compositors were found to have primarily low-grade albuminuria detectable by dipstick. Workers with urinary cellular sediment were significantly more likely to have detectable albuminuria. Albuminuria was more likely to occur with increased frequency of use of four particular solvent mixtures. The presence of urinary cellular sediment was less likely to occur with occasional use of analgesics suggesting a possible etiologic role for acute or chronic urinary tract inflammation.

Occupational exposure to organic solvents has been found to be associated with an increased excretion of erythrocytes and leukocytes in urine.[1] Researchers generally attribute this finding to the possible role of organic solvent exposure in renal disease. Animal studies have demonstrated a dose-dependent effect of certain industrial solvents with renal tubular injury.[2,3] However, the role of organic solvents in the development of occupational renal disease remains controversial,[4] and epidemiological results have been conflicting.

Investigators to date have not considered the possibility that increases in erythrocytes and leukocytes in urine associated with workplace solvent exposure may also result from lower urinary tract lesions. Inflammation of the lower urinary tract is associated with the presence of increased erythrocyte[5] and leukocyte[6,7] sediment in the urine. Solvent exposure has not, however, yet been linked to inflammation of the lower urinary tract. Such a link could, perhaps, have important clinical implications in occupational medicine. For example, several epidemiologic studies have suggested that epithelial inflammation may be an important risk factor for bladder cancer.[8-10]

We investigated the occurrence of subjective reports of six cases of "red urine" among newspaper pressroom workers in a large newspaper publishing facility. Three of the workers had gross hematuria documented by a urologist. In one of the cases of gross hematuria, a

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urologist found visible inflammation of the bladder mucosa under cystoscopic examination. There was one case of a squamous cell carcinoma in the trigone area of the bladder. Squamous cell carcinomas of the urinary tract are rare and may be associated with occupational exposures.[11] We sought, therefore, to determine whether there was a relationship between the presence of urinary cellular sediment and workplace solvent exposures.

Methods

Study Population

The entire eligible study population consisted of 284 full-time newspaper pressworkers and 262 compositors from a large newspaper located in the northeastern United States. Newspapers are printed at two plants, a main printing facility and a satellite plant. At the time of this survey, 203 pressworkers worked at the main printing facility that also houses the administrative and composition offices (plant 1), and 81 were employed at plant 2. All pressworkers were given the opportunity to participate in the study and were encouraged to do so by union and management personnel. A descriptive pamphlet was developed by the investigators and mailed to the pressworkers prior to the start of the study to provide an understanding of what was involved and how the study findings would be used.

Job and Process Descriptions

Plant 1 has been in operation since 1955, and plant 2 has been in operation since 1983. Approximately 500,000 newspapers are printed weekdays and over 750,000 are printed for the Sunday edition. Before 1977, plant 1 used the letterpress (raised surface) printing process that included the handling of lead plates. Workers were exposed to inks and ink mist thrown off by inking rollers. Cleanup involved the use of solvents, such as kerosene. The letterpress operation was phased out in 1976, and plant 1 was converted to the di-lithographic process. With the advent of di-lithographic operations, use of lead plates ceased. Di-lithographic printing involved the use of a plate treated chemically so that ink adhered only to the print image. Although generation of ink fly from high-speed litho presses was reportedly minimal, workers were exposed to a wider variety of solvents than in the letterpress operation. Di-lithographic operations were gradually phased out of plant 1 between 1979 and 1987 and replaced by the offset process. Plant 2 opened in December 1983 as an offset operation.

In the offset process (also a lithographic operation) a plate cylinder is wet by a fountain solution, then inked by an ink roller. The print image repels the solution and retains the ink for transfer to a blanket cylinder. The blanket cylinder then offsets the image to continuous printing stock.

Exposures among pressroom workers vary depending on the job performed. Workers progress through a series of positions on the working press that provide them with a full understanding of its operation. Entry level positions include the paperhandler who feeds paper to the press and the platehandler who delivers and removes plates. Paperhandlers have less contact with the press machinery than do other pressroom workers. Apprentice job responsibilities include oiling and greasing the press, splicing new paper rolls to old, and paper folding and alignment. Pressworkers run the presses and set the ink adjustment. The floor supervisors check the quality of the newspaper and may perform any of the other operators' tasks as necessary. All apprentice and pressworker positions become involved in "plating up" the press (putting plates on printing cylinders). Job duties also vary by shift. Typically, the day crew "make ready" the presses by performing cleanup and maintenance as well as changing blankets and rollers, and the night crew operates the presses for newspaper production. By contrast, the compositors are responsible for composing the printed page and do not have contact with inks or lubricants but rarely with cleaning solvents.

Environmental Evaluation

The work environment was assessed by plant walkthrough surveys, informal discussions with workers, observation of work practices during both production and maintenance shifts, and measurement of personal breathing zone and general area air concentrations of organic solvents (primarily naphthas) and several glycol ethers. All substances used during the printing process or during maintenance and cleaning activities were identified, and material safety data sheets (MSDS) reviewed for each. Further analysis of several process solutions and cleaning solvents was performed using gas chromatography with mass spectrometry detection (GC-MSD) to further characterize the samples and identify components not specified on the MSDS.

A preliminary analysis of the major printing solutions (fountain solutions, blanket wash) and cleaning agents (Cleansall, kerosene, All-Purpose Cleaner, Solvent Type 1) indicated these organic solvents contain a blend of naphthas, and for some solutions, small amounts of glycol ethers. A list of products used in newspaper printing and their major constituents is presented in Table 1. Naphtha is a general term that refers to a nonuniform blend of petroleum hydrocarbons containing aliphatic and aromatic components, with the predominant hydrocarbon species and aromatic content varying among individual products.

Gas chromatographic analysis of representative bulk air samples obtained in the pressroom resulted in complex chromatograms containing primarily C_9 to C_{14} aliphatic hydrocarbons, with small amounts of C_9 to C_{10} aromatics, toluene and xylene. Based on this preliminary information, full shift personal breathing zone and general area air samples to assess organic solvent exposure were quantitated for total naphthas as it was not feasible to quantitate individual peaks present in each chroma-

TABLE 1
Products Used in Newspaper Printing

Product	Constituents
Cleansall	Naphtha
	Limonene
	Pine oil
	Surfactants
All-Purpose Cleaner	Glycol ethers
Plate Cleaner	Glycol ethers
Kerosene	C_9-C_{16} hydrocarbons
Solvent Type 1	Naphtha and mineral spirits blend
Isopropyl alcohol	Isopropyl alcohol
Mobil Oil® 600 W. Cylinder	Oils
Newsprint paper	Cellulose paper
Newsprint inks	Mineral oil
	Carbon black
	Pigments
	Varnishes
	Binding agents
Fountain solutions	Glycol ethers
Blanket wash	Aliphatic hydrocarbons
	Butyl carbitol

togram. Air samples were collected on activated charcoal tubes, using calibrated SKC Model 222 personal sampling pumps operating at flowrates of 50 or 100 cc/min. The charcoal tube samples were desorbed with carbon disulfide and analyzed by gas chromatography with flame ionization detection (GC-FID). Total naphthas were determined using as standards either Stoddard solvent (which had a chromatogram similar to representative bulk air samples) or dodecane.

Because the presence of naphthas interfered with the analysis of glycol ethers by gas chromatography with flame ionization detection, the technique of multidimensional gas chromatography was used to minimize interferences and maximize selectivity. Air samples were collected on activated charcoal tubes using calibrated SKC Model 222 personal sampling pumps operating at flowrates of 50 to 100 cm^3/min. The charcoal tube samples were desorbed with 5% methanol in methylene chloride as outlined in National Institute for Occupational Health and Safety Method 1403.[12] Quantitation of the individual glycol ether compounds was done using multidimensional gas chromatography/mass spectrometry (E. Kennedy, personal communication, 1990).

Questionnaire

A comprehensive health questionnaire was developed and mailed to all pressworker and compositor participants. Collection of data on job process and job description was intended to help provide an exposure assessment based on the employee's self-reported work history. Exposure questions included both recent and long-term use of solvents and other substances at work, at home, or as part of a hobby. In particular, information was obtained about the frequency of use of seven solvents, cleaners, and lubricants that were known to have been used at the time of the present study at plants 1 and 2 (Table 1). The seven solvents were specifically included as a result of preliminary industrial hygiene evaluation and assessment of the workplace. This survey indicated these materials were most prevalent, most intensively used, and/or most commonly cited by workers as potential causes of problems. The medical history assessed the health status of genitourinary and other organ systems. Information concerning medications, habits, and hobbies also was collected. A trained interviewer reviewed the questionnaire for completeness.

Blood and Urine Evaluation

Blood tests for creatinine and blood urea nitrogen were performed. Urine samples were also obtained. Ten mL of the urine was poured off from a urine sample, and a visual dipstick urinalysis for sugar, albumin, occult blood, nitrites, leukocytes, bile, and urobilinogen was performed. The reported sensitivity of the dipstick urinalysis to urine albumin was 15 to 30 mg/dL. The reported sensitivity to erythrocyturia and leukocyturia were 0.015 to 0.062 mg/dL and 20 leukocytes/mL, respectively. If the dipstick urinalysis was positive for the presence of erythrocytes or leukocytes (trace or above), then the 10-mL tube was spun at 3000 rpm for 5 minutes and was decanted except for 0.25 mL. One drop was placed on a microscope slide and a 22×22 mm coverslip put on the slide. Ten to 15 high-power fields were examined. The dipstick urinalysis and microscope procedures were performed within 3 hours after obtaining the urine samples. Trained laboratory technicians and physicians performed the tests without knowledge of exposure or questionnaire data.

Statistical Analysis

Significance of means of the descriptive statistics for pressroom workers and compositors were performed by use of two-tailed *t*-tests for unpaired data. The frequency distributions of total pressroom workers and participating pressroom workers were calculated and compared. Chi-square tests were used to compare the creatinine and blood urea nitrogen values and the urological symptoms reported in the questionnaire by pressroom workers and compositors. The frequencies of the presence of leukocytes and erythrocytes detected by either dipstick or microscopic examinations were compared using Fisher's exact test.

The frequencies of use of seven common solvents, cleaners, and lubricants by the total cohort in comparison to the presence of erythrocytes alone, leukocytes alone, and erythrocytes and/or leukocytes (urinary cellular sediment) were determined. The frequency of use was categorized as "none," "occasional" ($<$ once per week), and "frequent" ($\geq$ once per week). The presence of cellular sediment was based on positive tests either by dipstick or microscopic examination. Mantel-Haenszel χ^2 tests for trend were performed. Correlation coefficient analyses and logistic regression models were used to determine the relationships between the presence of erythrocytes alone, leukocytes alone, and urinary

cellular sediment and exposure to the seven types of common solvents and lubricants used in the pressroom. Seven potentially confounding variables were also included in these analyses. The total cohort was divided into four exposure groups: use of 0 to 1, 2 to 3, 4 to 5, or 6 to 7 types of the seven solvent and lubricant mixtures. Other variables included were age, current smoking status, ounces of alcohol consumed per week, current analgesic use, recent marijuana use, performance of maintenance work, diabetes, and hypertension. Logistic regression models were constructed for the total cohort and for pressmen alone (internal analysis). The internal analysis did not include compositors or paperhandlers because of the limited solvent exposures of these two groups. Additional logistic regression was performed to test for interactions between age, exposure, and analgesic use.

The relationships between presence of erythrocytes alone, leukocytes alone, and urinary cellular sediment and frequency of use of each of the 7 solvent and lubricant mixtures were determined. Workers were divided among three exposure groups: "none," "occasional" (< once per week), and "frequent" (≥ once per week). A Mantel-Haenszel χ^2 test was performed to test for significance of trends.

For the purposes of this study, albuminuria was defined as a trace or greater response on dipstick examination. The frequencies of the presence of albuminuria were determined for comparisons between pressmen and compositors and subjects with and without erythrocyturia and leukocyturia. Fisher's exact tests were performed to determine statistical significance. A logistic regression model was then constructed to assess the relationship between the presence of albuminuria and the use of increasing number of types of solvent and lubricant mixtures. The total cohort was again divided into four exposure groups and the variables were the same used in the logistic regression models for erythrocyturia, leukocyturia, and urinary cellular sediment. Finally, the presence of albuminuria and the frequency of use of seven solvent and lubricant mixtures was determined. Increasing use was categorized according to "none," "occasional" (< one time per week), and "frequent" (≥ one time per week). Mantel-Haenszel χ^2 tests were performed to test for significance of trends.

Results

Two hundred fifteen pressroom workers (76% of the total eligible) chose to participate. In addition, 34 compositors (13% of the total eligible) agreed to participate in the study as referents. Of the 249 workers who chose to participate in the survey, one pressroom worker did not return a questionnaire and was subsequently removed from the study. In addition, two nonwhite pressroom workers and one woman compositor were removed from the analysis. As a result, 245 white male workers were analyzed. Table 2 provides descriptive characteristics of the total cohort. The compositors, who served as the reference group, were on average 10 years older than the pressroom workers and had spent more years in their trade. The pressroom workers and the compositors had similar education levels. The participating pressroom workers were representative of the total pressroom workers in age and years in trade as illustrated in Figures 1 and 2.

Results from the industrial hygiene evaluation conducted at the two printing plants are shown in Table 3. Concentrations of total naphthas in 54 personal breathing zone air samples obtained on pressroom workers ranged from 0.5 to 105 mg/m^3. The mean concentration

TABLE 2
Characteristics of Pressroom Workers and Compositors

	Pressroom Workers	Compositors
n	212	33
Age	44.6 ± 13.2*	54.2 ± 6.8
Years in trade	24.9 ± 13.1	31.4 ± 7.0
Work weeks per year	45.3 ± 6.1	46.4 ± 6.6
Work hours per week	46.0 ± 8.6	37.8 ± 4.0
Education†	1.4 ± 0.9	1.4 ± 0.7
English speaking	212 (100%)	33 (100%)
Past disability	98 (46%)	8 (24%)
Exposure to processes:		
Letterpress	152 (77%)	0 (0%)
Dilitho	196 (94%)	0 (0%)
Offset	201 (97%)	0 (0%)
Work at plant 1	150 (71%)	33 (100%)
Work at plant 2	62 (29%)	0 (0%)
Serum creatinine	1.2 ± 0.2	1.2 ± 0.2
Serum BUN	16.7 ± 4.2	17.2 ± 4.6
BUN/creatinine ratio	13.9 ± 3.5	14.6 ± 3.9
Occult blood by dipstick	21 (10%)	1 (3.0%)
≥1 Erythrocytes/hpf‡	19 (9%)	1 (3.0%)
1 Erythrocyte/hpf	10 (5%)	0 (0%)
≥3 Erythrocytes/hpf	9 (4%)	1 (3.0%)
Leukocytes by dipstick	5 (2%)	0 (0%)
≥1 Leukocytes/hpf‡	24 (11%)	0 (0%)
1 Leukocyte/hpf	13 (6%)	0 (0%)
Urinary cellular sediment‡	37 (18%)	1 (3.0%)
Albumin by dipstick	33 (16%)	0 (0%)

* Mean ± SD.
† 1 = finished high school; 2 = 1–2 years of college.
‡ Urinalysis obtained on 208 of 212 pressworkers.

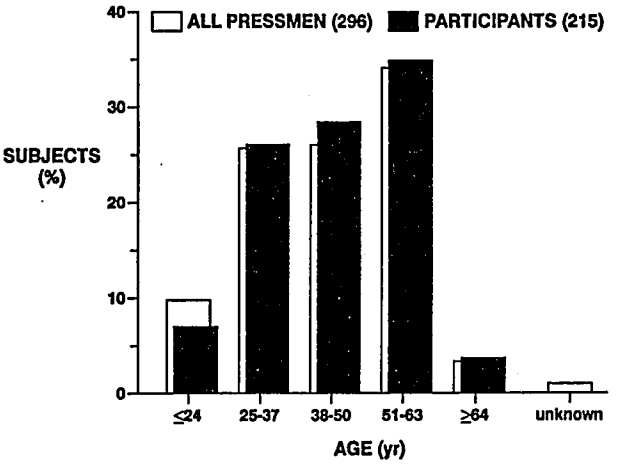

Fig. 1. Age distribution of pressroom workers participating in the study closely matched that of total cohort of pressmen working at the two plants.

of total naphthas in personal air samples obtained during the newspaper production shift was 3.4 mg/m^3, and during the maintenance and cleaning shift was 25.2 mg/m^3. Total naphtha concentrations were highest during the maintenance shift, as expected, because of the increased use of various cleaning solvents and the types of activities performed by these workers. By contrast, pressroom workers spend a considerable portion of their time during the production shift in an enclosed "quiet room" that recently had been reinstalled. In addition, there was limited contact with cleaning solvents (kerosene, blanket wash, All-Purpose Cleaner) during the production shift.

Personal exposures to total naphthas were well below the applicable environmental evaluation criteria established by the Occupational Safety and Health Administration,[13] the American Conference of Governmental Industrial Hygienists,[14] and the National Institute for Occupational Safety and Health.[15]

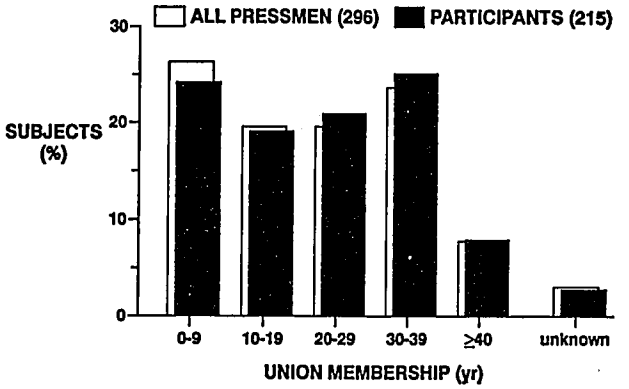

Fig. 2. Lifetime exposure to pressroom conditions, as measured by years of union membership. Distribution for pressmen participating in the study was similar to that of total cohort of pressmen working at the two plants.

TABLE 3
Concentration of Organic Solvents and Glycol Ethers in Personal Breathing Zone Air Samples Obtained on Pressroom Employees

Substance	Shift	No. of Samples	Concentration (mg/m^3)	
			Range	Mean
Total napthas*	Newspaper production	35	0.5 to 67.5	3.4
	Maintenance	19	7.0 to 105	25.2
Glycol ethers†	Newspaper production	2	ND‡ (<0.3)	
	Maintenance	3	ND (<0.8) to 2.6	

* Representative air samples contained primarily C_9 to C_{14} aliphatic hydrocarbons with small amounts of C_9 to C_{10} aromatics, toluene and xylene. The OSHA PEL and ACGIH TLV for stoddard solvent and VM&P Naphthas are 525 mg/m^3 and 1350 mg/m^3, respectively, as 8-hour time-weighted averages (TWA). The NIOSH REL for petroleum distillates (which include naphtha blends having an aromatic content less than 20%) is 350 mg/m^3 as a TWA for up to a 10-hour workshift.

† Analysis included determination of butyl cellosolve, butoxypropanol, diethylene glycol monomethyl ether, dipropylene glycol monomethyl ether, and butoxyethoxyethanol. The OSHA PEL and ACGIH TLV for dipropylene glycol methyl ether is 600 mg/m^3 as an 8-hour TWA. The current ACGIH TLV for butyl cellosolve is 120 mg/m^3 as an 8-hour TWA.

‡ ND = none detected. Only one personal air sample contained detectable levels of any of the glycol ethers at 2.6 mg/m^3 butyl cellosolve.

Of the five personal air samples quantitated for five specific glycol ethers (butyl cellosolve, butoxypropanol, diethylene glycol monobutyl ether, dipropylene glycol monomethyl ether, and butoxyethoxyethanol), only one sample contained a detectable level of any of the glycol ethers. This sample, obtained on a worker performing maintenance and cleaning activities, had a concentration of 2.6 mg/m^3 butyl cellosolve. Although the number of personal air samples was small, results from the analysis of 12 area air samples obtained in areas expected to have the greatest potential glycol ether concentrations, were also quite low. Area air concentrations of individual glycol ethers or glycol ethers combined were less than 4 mg/m^3, with the exception of one area air sample collected during the maintenance shift that had a concentration of 13 mg/m^3 butyl cellosolve. All personal breathing zone and general area air samples for glycol ethers were below the existing environmental evaluation criteria for butyl cellosolve and dipropylene glycol methyl ether. Environmental evaluation criteria have not been established for the other glycol ethers analyzed during this survey.

Although the airborne concentrations of naphthas and glycol ethers were all quite low, there was considerable potential for dermal exposure to solvents. Absorption following skin contact could occur with these substances, and for glycol ethers in particular, skin absorption may be a more important route of exposure than inhalation.[16] At the time of this study there was a high prevalence of solvent-related dermatitis in these workers.[17]

Urinary Cellular Sediment

Urine samples were obtained from 212 pressworkers and 32 compositors (Table 2). No gross hematuria was present in any sample. More pressroom workers (10% [21]) than compositors (3.0% [1]) had occult blood detected by dipstick, but this difference was not statistically significant ($P = 0.33$). Under microscopic examination performed on subjects with positive dipstick tests for blood or leukocytes, 9.0% (19) of pressroom workers (range 0 to 9) and 3.0% (1) of compositors had 1 or more erythrocytes per high-power field (hpf). While 4.8% (10) of pressroom workers had 1 erythrocyte/hpf, there were no compositors with this amount. Of the remainder who had erythrocytes detected by microscopic examination, 4.3% (9) of pressroom workers and 3.0% (1) of compositors had ≥3 erythrocytes/hpf (the one compositor had 3 erythrocytes/hpf). Leukocytes were detected by dipstick in 2.4% (5) of pressroom workers and in no compositors. One or more leukocytes/hpf were detected in 11.5% (24) of pressworkers (range 0 to 8) and in no compositors. This difference was statistically significant ($P < 0.05$). Only one leukocyte/hpf was detected in 6.3% (13) of pressworkers. In total, 17.8% (37) of pressroom workers and 3.0% (1) of compositors had urinary cellular sediment detected by dipstick or microscopic examination. This difference was also statistically significant ($P < 0.05$).

The self-reported history of urinary symptoms and

disease is shown in Table 4. Participants were asked to report any symptoms or physician-diagnosed disease that had ever occurred. The compositors generally reported a higher prevalence of urinary diseases and symptoms than did pressroom workers. One case of bladder cancer was reported by a pressroom worker who had a squamous cell carcinoma in the bladder trigone area. The compositors reported more cases of physician-diagnosed kidney and bladder infection, prostate obstruction, kidney stones, and kidney failure, but the differences were not statistically significant. Similarly, the compositors more frequently reported symptoms of difficulty starting urination and dysuria. A slightly higher percentage of compositors (12.1%) reported a history of red or pink urine compared with pressroom workers (9.9%).

The seven common solvents and lubricants presently used in plants 1 and 2 include Cleansall, kerosene, All-Purpose Cleaner, Plate Cleaner, Solvent Type 1, isopropyl alcohol, and Mobil 600 W. Cylinder Oil.® Table 1 lists products commonly used at this facility and the main constituents of these substances. To determine the possible relationship between the presence of urinary cellular sediment and exposure to these seven materials, the exposure to both the number of these materials and the frequency of use of each material was analyzed.

The relationship between the presence of urinary cellular sediment and the number of the seven materials used was examined (Figure 3). For erythrocytes alone, the distribution among the four exposure groups was 3.8% (2), 7.7% (4), 12.5% (8), and 15.8% (12), respectively ($P = 0.02$). For leukocytes alone, the distribution among the four exposures were 0.0% (0), 11.5% (6), 9.4% (6), and 15.8% (12), respectively ($P = 0.008$). For urinary cellular sediment, the distribution among the four exposure groups was 3.8% (2), 13.5% (7), 15.6% (10), and 25.0% (19), respectively ($P = 0.001$).

A logistic regression model was constructed to examine the relationship between the prevalence of erythrocytes in urine with exposure to an increasing number of the seven materials while adjusting for potential confounders including age, cigarette smoking, alcohol intake, analgesic use, marijuana smoking, and maintenance and cleaning work (Table 5). Analgesic use included intake of aspirin, acetaminophen, or nonsteroidal anti-inflammatory medicines. The frequency of analgesic use was categorized as "none," "occasional" (once

TABLE 4
Urinary Diseases and Symptoms Reported

Diseases or Symptoms	Pressroom Workers	Compositors
n	212	33
Kidney infection	11 (5%)	5 (15%)
Bladder infection	16 (8%)	3 (9%)
Prostate obstruction	5 (2%)	3 (9%)
Kidney stones	12 (6%)	3 (9%)
Kidney failure	0 (0%)	0 (0%)
Bladder cancer	1 (1%)	0 (0%)
Difficulty starting urination	15 (7%)	3 (9%)
Red or pink urine	21 (10%)	4 (12%)
Pain with urination	10 (9%)	3 (9%)

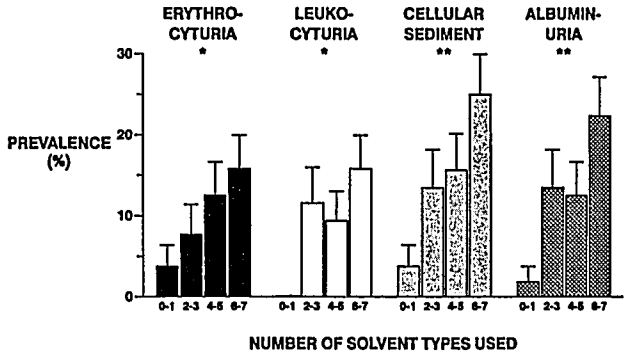

Fig. 3. Association between prevalence of urinary findings and use of several different solvents by 245 male pressroom workers and compositors. Asterisks indicate statistically significant trend as indicated by Mantel-Haenszel χ^2: (*) $P < 0.05$, (**) $P < 0.005$.

or more per month), or "frequent" (every day or every other day). A correlation analysis was performed and showed no redundancy of terms. In the total cohort, increasing exposure to the seven selected materials was associated with increasing likelihood of erythrocytes in urine ($P < 0.005$). The variable of increasing exposure to the seven solvent and lubricant mixtures was also statistically significant with an adjusted odds ratio of 1.87 (95% confidence interval [CI] = 1.21, 2.91; $P < 0.05$). Among pressmen alone (with compositors and paperhandlers omitted), only analgesic use was significant with an adjusted odds ratio of 0.34 (95% CI = 0.12, 0.96; $P < 0.05$).

A similar logistic regression analysis of the prevalence of leukocytes in urine also was performed. A correlation analysis again showed no redundancy of terms, and, in the total cohort, exposure to an increasing number of the seven substances ($P < 0.002$) and age ($P < 0.05$) were significantly associated with leukocytes. Among pressmen alone, only age was significantly associated with the presence of leukocytes ($P < 0.05$). Exposure to an increasing number of seven solvent and lubricant mixtures was statistically significant with an increasing prevalence of leukocytes in urine ($P < 0.002$) after adjustments for various potential confounders.

A logistic regression model was also constructed to examine the relationship between the presence of urinary cellular sediment with the increasing exposure to the seven selected substances while adjusting for six potential confounders. A correlation analysis of the independent variables again showed no redundancy, and in the total cohort, the exposure to increasing number of the seven substances (odds ratio [OR] = 2.18; 95% CI = 1.47, 3.24; $P < 0.0001$), age (OR = 1.04; 95% CI = 1.01, 1.08; $P < 0.01$), and analgesic use (OR = 0.33; 95% CI = 0.14, 0.81; $P < 0.01$) were significantly associated with presence of urinary sediment. Among pressworkers only, the same three variables remained significant. Interactions between age, analgesic use, and exposure were insignificant.

The relationships of the presence of erythrocyturia alone, leukocyturia alone, and urinary cellular sediment with the frequency of use of each of the seven selected substances were examined. For erythrocyturia alone,

TABLE 5
Adjusted Odds Ratio for Urinary Findings in 240 Pressroom Workers and Compositors

Explanatory Variable*	Adjusted Odds Ratio†			
Solvent exposure	Erythrocyturia	Leukocyturia	Cellular Sediment	Albuminuria
	1.87 (1.21–2.91)	2.08 (1.30–3.35)	2.18 (1.47–3.24)	1.96 (1.31–2.95)
	$P < 0.005$	$P < 0.002$	$P < 0.0001$	$P < 0.002$
Analgesic use	0.34 (0.12–0.96)	0.48 (0.17–1.29)	0.33 (0.14–0.81)	0.47 (0.20–1.12)
	$P < 0.05$		$P < 0.01$	
Age (yr)	1.03 (1.00–1.07)	1.04 (1.00–1.07)	1.04 (1.01–1.08)	1.01 (0.98–1.04)

* The following variables were not significantly associated with urinary findings: alcohol consumption, cigarette smoking, marijuana smoking, hypertension, diabetes, exposure to lead, or performance of pressroom maintenance work.
† From multiple logistic regression model (Estimate; 95% Confidence Interval; p|OR = 1).

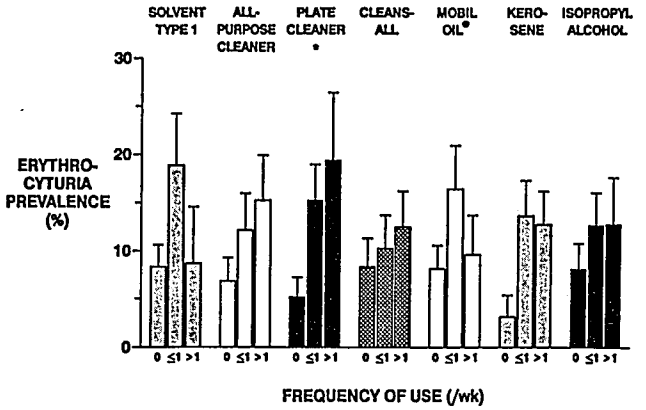

Fig. 4. Association between prevalence of erythrocyturia and frequency of use of various solvents by 245 male pressroom workers and compositors. (*) Statistically significant trend as indicated by Mantel-Haenszel χ^2, $P < 0.05$.

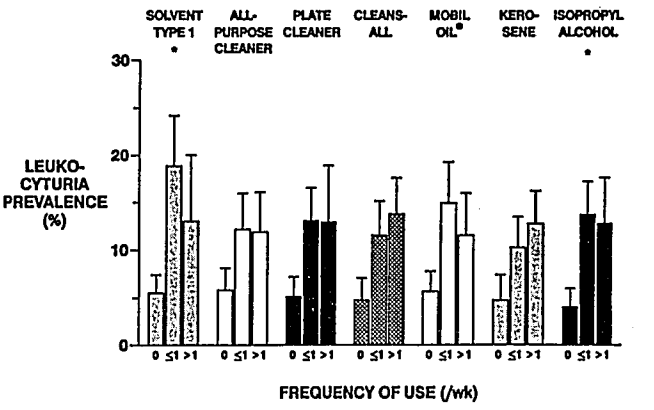

Fig. 5. Association between prevalence of leukocyturia and frequency of use of various solvents by 245 male pressroom workers and compositors. (*) Statistically significant trend as indicated by Mantel-Haenszel χ^2, $P < 0.05$.

only Plate Cleaner had a significant trend ($P = 0.006$). Exposures to kerosene ($P = 0.08$) and All-Purpose Cleaner ($P = 0.08$) approached significance (Figure 4). For leukocyturia alone, a significant trend was associated with increasing frequency of use for Cleansall ($P = 0.054$), Solvent Type 1 ($P = 0.026$), and isopropyl alcohol ($P = 0.042$) (Figure 5). Exposure to Plate Cleaner approached significance ($P = 0.063$). For urinary cellular sediment, significant trends were observed for frequency of use for five of the seven materials: Solvent Type 1 ($P = 0.017$), Plate Cleaner ($P = 0.005$), All-Purpose Cleaner ($P = 0.017$), kerosene ($P = 0.041$), and Cleansall ($P = 0.037$) (Figure 6). When logistic regression models were constructed to assess the effect of frequency of particular solvent use on the prevalence of urinary cellular sediment while adjusting for potential confounders, coefficients for three of the five compounds (Solvent Type 1, Plate Cleaner, and Cleansall) remained significant. Two solvents, All-Purpose Cleaner and kerosene, dropped out of the model (data not shown).

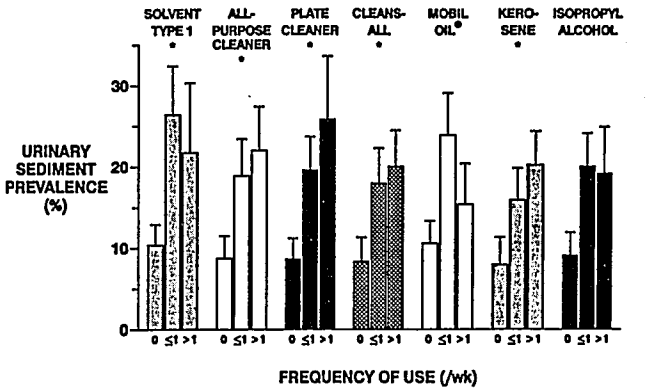

Fig. 6. Association between prevalence of urinary cellular sediment and frequency of use of various solvents by 245 male pressroom workers and compositors. (*) Statistically significant trend as indicated by Mantel-Haenszel χ^2, $P < 0.05$.

Albuminuria

We also evaluated the presence of albuminuria (trace or more albumin detected by dipstick) to determine if the increased cellular sediment in pressworkers was associated with a possible index of renal disease. No compositors had albuminuria by dipstick examination compared to 16% (33) of pressmen ($P = 0.01$). The distribution of dipstick findings for pressroom workers was: zero = 179; trace = 22; $1^+ = 6$; $2^+ = 4$; $3^+ = 1$. Albuminuria was present in 52.6% (20) of those workers with urinary cellular sediment compared to 6.6% (13) of workers who did not have urinary cellular sediment ($P < 0.0001$). Albuminuria was present in 70.8% (17) of those workers with leukocytes detected in their urine compared to 7.2% (16) of those who did not have

leukocytes in their urine ($P < 0.0001$). Albuminuria was present in 42.3% (11) of workers with erythrocytes in their urine compared with 10.0% (22) of workers without erythrocytes in their urine ($P < 0.0001$).

There was an increasing frequency of albuminuria associated with use of an increasing number of the seven selected solvent and lubricant mixtures (Figure 3). The distribution among the four exposure groups was 1.8% (1), 13.5% (7), 12.5% (8), and 22.4% (17). This trend was significant ($P = 0.002$). Logistic regression analysis showed that exposure to an increasing number of the seven selected solvents and lubricants had a significant association with the presence of albuminuria when the variables included were solvent exposure, analgesic use, and age (Table 5). Exposure to an increasing number of the selected substances had an odds ratio (OR) of 1.96 (1.31, 2.95) with $P < 0.01$. However, when the logistic regression analysis included age, current cigarette smoking, analgesic use, current number of ounces of alcohol consumed per week, marijuana use, diabetes, past lead exposure, and hypertension, exposure was less significantly associated with albuminuria (OR = 1.96; $P = 0.10$). The diagnosis of diabetes approached significance in terms of its relationship with albuminuria with an OR = 3.60 (0.89, 14.55) and $P = 0.07$.

The analysis also indicates a significant association between the presence of albuminuria and the increasing use of four particular solvent mixtures by pressworkers (Figure 7). Significant tests for trends were observed for Solvent Type 1 ($P = 0.002$), Plate Cleaner ($P = 0.03$), All-Purpose Cleaner ($P = 0.003$), and kerosene ($P = 0.03$). No significant trends were found for Cleansall ($P = 0.541$), isopropyl alcohol ($P = 0.509$), or Mobil Oil® ($P = 0.122$). Logistic regression models constructed to assess frequency of particular solvent use and the prevalence of albuminuria while adjusting for potential confounders (age, smoking, alcohol consumption, analgesic use) resulted in nonsignificant coefficients for the four solvents of interest (data not shown).

Discussion

Our study suggests that newspaper pressroom workers are exposed to substances that induce leukocyturia and erythrocyturia. The presence of erythrocyturia, leukocyturia, and urinary cellular sediment was more likely to occur with self-reported exposure to an increasing number of seven selected substances that included solvent mixtures and an oil (Figure 3). Furthermore, the presence of erythrocytes and leukocytes in urine was more likely to occur with increasing frequency of use of five solvent mistures: Solvent Type 1, Plate Cleaner, All-Purpose Cleaner, kerosene, and Cleansall (Figure 6).

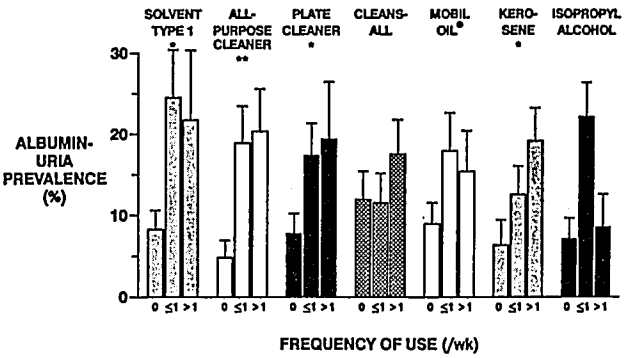

Fig. 7. Association between prevalence of albuminuria and frequency of use of various solvents by 245 male pressroom workers and compositors. Statistically significant trend as indicated by Mantel-Haenszel χ^2: (*) $P < 0.05$, (**) $P < 0.005$.

All the urinary findings in the workers studied could, individually, be considered "clinically within the normal range." Inasmuch as little is known of the course of occult disease of the kidneys and urinary tract, findings within the "normal" clinical range may represent markers of evolving disease. Furthermore, workers with overt renal disease are likely to be removed from work; this is often referred to as the "healthy worker effect." No gross hematuria was found among newspaper pressworkers or compositors. Only modest amounts of urinary erythrocytes (range 1 to 9) and leukocytes (range 1 to 8) were found in pressworkers.

Comparisons of this urinary cellular sediment with that of a referent group were made to facilitate detection of any significant exposure-induced departures from expected values. It has been shown that the rate of erythrocyte excretion must increase over 3 to 4 times the normal rate before 2 to 3 erythrocytes can be seen under the high-power field.[18] Another reason to be concerned about even modest increases of erythrocytes in the urine is that the degree of hematuria detected by dipstick has been reported to be unrelated to the seriousness of its underlying cause.[19-21] Comparison of the presence of urinary cellular sediment with a referent group was necessary because the techniques for detecting urinary cellular sediment are poorly defined and vary significantly between investigators.[22] As a consequence, there are widely varying estimates of the frequencies of urinary cellular sediment in the general population.

The newspaper pressroom workers had increased urinary cellular sediment in comparison with the referent group. We believe this increase was related to their occupational exposures rather than to the possibility that the referent group had less urinary cellular sediment than did the general population. Inasmuch as the volunteer rate of compositors was low (14%), there was no evidence the referent group was healthier with respect to urinary tract disease in comparison to those compositors who did not participate or to the general population. Self-selection by compositors for absence of urinary tract disease was less likely to occur because only subclinical, asymptomatic urinary tract effects were observed in this study. Indeed, the referent group had an equivalent or higher incidence of reported past hematuria or red urine and urinary tract symptoms than did the pressworkers (Table 4).

There is some evidence the results relating to the presence of urinary cellular sediment among the compositors are consistent with other comparable groups. The compositor group had one member (3.0%) who had

occult blood detected by dipstick. Other studies that used dipsticks to detect hematuria reported a prevalence of 1.9% to 3.5%.[23-25] One study, however, reported that 16% of adults undergoing multiphasic screening were dipstick positive for hematuria.[26] The reported prevalence of microscopic hematuria varies widely with estimates ranging from 0.20%[27] to over 30%.[28] In our study, fewer than 30 percent of the subjects had microscopic examination of their urine because only those subjects who had erythrocytes or leukocytes detected by urine dipsticks underwent microscopic examination. Moreover, our study included only men of working age and did not include women[29] and the aged[19] who are more likely to have hematuria related to menses, prostatism, and other causes.

The compositor group had no members who had leukocytes detected by dipstick or microscopic examination compared to pressmen who had 2.4% (5) detected by dipstick and 11.3% (24) detected by microscopic examination. It has been estimated that the prevalence of leukocytes detected by urine dipstick among men less than 60 years old is 0.3%.[30] We are unaware of published data relating to the distribution of leukocyturia detected by microscopic examination in healthy adult men. The referent group, therefore, had urinary cellular sediment findings that are consistent with other studies.

Our study also found relationships between the presence of microscopic erythrocyturia and leukocyturia and the type and degree of exposures to organic solvents. The logistic regression models indicate that the presence of either erythrocytes or leukocytes in urine is associated with the self-reported use of an increasing number of seven solvents and lubricants that were commonly used by pressworkers (Figure 3 and Table 5). Exposure to an increasing number of solvent and lubricant mixtures had an adjusted OR = 1.79 for erythrocytes and adjusted OR = 2.11 for leukocytes. This means that exposure to six to seven types of these substances increased the risk of finding erythrocyturia 5.7 times and of finding leukocyturia 9.4 times.

This association has at least three possible explanations. First, one or more of the solvents or lubricants may be causing the urinary cellular sediment to increase. Second, a mixture of two or more substances may be necessary to increase the urinary cellular sediment. Third, there may be a dose-response relationship between one or more of the substances and increases in urinary cellular sediment. Use of an increasing number of types of solvents may be a proxy for increasing exposure to solvents generally.

Analysis of questionnaire exposure data suggests a dose-response relationship exists between exposure to 5 solvent mixtures and the presence of urinary cellular sediment (Figure 6). The presence of urinary cellular sediment was more likely to occur with increasing frequency of use of Solvent Type 1, Plate Cleaner, All-Purpose Cleaner, kerosene, and Cleansall. This possible dose-response relationship does not appear to hold for isopropyl alcohol and Mobil Oil.®

Although the air sampling data obtained at this facility indicated the presence of low levels of organic solvents and glycol ethers in personal breathing zone air samples, the potential for dermal contact and subsequent skin absorption of these substances was observed. Repeated or prolonged contact to aliphatic hydrocarbons, mineral spirits, naphtha blends, and surfactants are irritating and may cause dermatitis.[31] Furthermore, these chemicals disrupt the skin barrier and make it easier for deeper penetration with subsequent absorption of chemicals through the affected area.[32] Skin examinations of these pressroom workers indicated that they were at significantly elevated risk of developing an occupationally related dermatitis.[17] Thus, it appears that a significant source of solvent exposure may have occurred through skin contact and subsequent absorption.

We tested for the presence of albuminuria to determine whether the increase in urinary cellular sediment may be due, at least in part, to the effects of solvents on the kidney. Only pressroom workers (16%) had albuminuria by dipstick evaluation. Workers with findings of urinary cellular sediment were more likely to have urine albumin detected compared with those who did not have sediment detected. Furthermore, there was a significant association between the presence of albuminuria and the increasing use of four particular solvent mixtures (Figure 7).

The above analysis may suggest a possible association between solvent exposure and the presence of albuminuria, but this relationship is not clearly established by our study. Although the presence of albuminuria was more likely to occur with exposure to increasing number of solvent and lubricant mixtures, it is not completely clear from the logistic regression model whether this may have been due to confounding. Exposure to an increasing number of seven solvent and lubricant mixtures had an adjusted OR = 1.96 ($P < 0.002$) when the variables included in the model were solvent exposure, analgesic use, and age. When the six additional variables (which were not significantly associated with the urinary findings) were added to the logistic regression model, the relationship between exposure and the presence of albuminuria was no longer significant. Furthermore, there was no difference between the pressmen and the referent group in terms of serum creatinine and BUN; however, these measures only show significant changes after 60% of renal function is lost.[33] Inasmuch as albumin excretion is a sensitive indicator of renal glomerular function,[34,35] we believe it is imperative that our findings be confirmed in other solvent-exposed groups and that occupational epidemiologists investigate the significance of physiologic excretion of albumin in solvent-exposed workers.

There has been much controversy in the last decade over the possible effect of organic solvents from occupational exposure on renal function. Occupational exposure to organic solvents has been suggested as an etiological factor in glomerulonephritis[36-39] and renal tubular disease,[40] but studies have yielded conflicting results.[41,42] Krusell et al[43] conducted a cross-sectional study of 43 printers occupationally exposed to organic solvents for 9 to 25 years who were compared with 43

age-matched controls and found no differences in β 2-microglobulin level or albumin excretion rates. The authors noted, however, that the study had the power to detect only a fourfold excess risk. Aspergren and others[44,45] studied 101 men exposed to organic solvents including styrene, xylene, and toluene. They found that men exposed to organic solvents excreted more cells in the urine than did the controls. No significant difference in β 2-microglobulin excretion could be demonstrated, but the exposed subjects excreted significantly larger quantities of albumin. The investigators did not find an association between urine cellular sediment or albumin excretion and the level of exposure. They concluded this result might be explained by their coarse subdivision into different exposure levels or the possible absence of a dose-response relationship at moderate exposures.

One recent study has found a dose-response relationship between lifetime occupational solvent exposure and erythrocyturia. Hotz and others[46] studied the relationship between a quantitative exposure "score" and kidney function tests in 148 workers exposed to organic solvents. The exposure score was based on an intensity factor and number of years of occupational exposure. They found that higher exposure scores were associated with increasing *N*-acetyl-β-D-glucosaminidase activity, erythrocyturia, and albuminuria, although the albuminuria trend was not statistically significant. No clear trend was found for leukocyturia.

The presence of erythrocytes or cellular sediment in urine was less likely to occur with moderate intake of analgesics (Table 5). Analgesics could have a protective effect by an anti-inflammatory action on the lower urinary tract. It should be noted that albuminuria was present in only about half of workers with urinary cellular sediment. Thus, only half the cases with urinary cellular sediment were associated with possible renal effects. Consistent with this explanation of the analgesic effect, one of the three cases of documented gross hematuria that initiated the study had visible inflammation of the bladder mucosa. Furthermore, analgesics would be expected to have either no effect on urinary cellular sediment or the opposite effect of increasing urinary cellular sediment if the effect were related to renal disease alone. Studies indicate that daily users of analgesics are at risk for chronic renal disease[47,48] and erythrocyturia.[49] Subjects in this study were, however, taking relatively low doses of analgesics. The maximum amount of analgesics taken was 1 or 2 tablets daily, with analgesic use defined as taking more than 1 tablet monthly. Thus, it is conceivable that low doses of analgesics taken by the pressworkers were too low to affect renal function but high enough to have an anti-inflammatory effect. While this is an attractive hypothesis, the current findings do not provide conclusive evidence that the protective effects of analgesic use are attributable to the anti-inflammatory action of these drugs on the lower urinary tract of workers exposed to solvents.

In summary, our study suggests that actively working newspaper pressmen are at a significantly elevated risk for development of increases in detectable urinary cellular sediment. The presence of urinary cellular sediment was more likely to occur with increasing frequency of use of certain solvent mixtures. This increase may be associated, at least in part, with solvent-related effects on the kidney. Further study is needed to determine the particular substances responsible for the observed increases in cellular sediment and albuminuria and to evaluate the effects of low doses of analgesics on these findings in workers chronically exposed to organic solvents.

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