

Effectiveness of a medical surveillance program for the prevention of occupational asthma caused by platinum salts: A nested case-control study

Rolf Merget, MD,^a Carmen Caspari, MD,^a Alexandra Dierkes-Globisch, MD,^a
Rupprecht Kulzer, MD,^b Rolf Breitstadt, MD,^b Annegret Kniffka, MD,^b Paul Degens, PhD,^c
and Gerhard Schultze-Werninghaus, MD^a *Bochum and Frankfurt, Germany*

Background: Exposure reduction has proven to be effective in the prevention of occupational asthma. Few data are available on the effectiveness of secondary prevention programs, including medical examinations and removal of workers from exposure sources after detecting symptoms or signs indicative of a beginning disease.

Objective: We sought to assess the effectiveness of a medical surveillance program in workers with exposure to platinum salts.

Methods: A nested case-control study was performed in 14 workers of a catalyst production plant whose skin prick test (SPT) responses to platinum salt converted from negative to positive during a 5-year prospective cohort study with yearly medical examinations and 42 matched control subjects from the plant who did not experience SPT response conversion. With the exception of 2 subjects, the workers showing SPT response conversion were removed completely from exposure sources and followed for up to 42 months.

Results: Work-related new symptoms were reported by 9 of the 14 subjects, and new symptoms without relation to work were reported by 3 subjects at the time of SPT response conversion. Symptoms were not accompanied by a change in FEV₁ or bronchial responsiveness to histamine. Symptoms resolved after transferral, but occasional shortness of breath or wheeze persisted in 4 subjects. SPT reactions decreased or became negative in all workers after complete removal but remained unchanged in a craftsman with ongoing occasional exposure to contaminated materials.

Conclusion: Although no randomized intervention was performed, this study proves the effectiveness of a medical surveillance program for the prevention of occupational asthma caused by platinum salts. (*J Allergy Clin Immunol* 2001;107:707-12.)

Key words: Platinum, allergy, asthma, occupational, prevention

Abbreviations used

OA: Occupational asthma
SPT: Skin prick test

Symptoms, lung function impairment, or bronchial hyperresponsiveness persist in a considerable number of subjects with occupational asthma (OA) after removal from exposure sources.¹ Although primary prevention has been shown to reduce the incidence of OA,^{2,3} the high prevalence and incidence rates of OA in many industries indicate failure of primary prevention. Medical surveillance programs as part of secondary prevention measures may be an additional tool to improve the prognosis of OA. These programs aim at detecting signs of disease at an early stage to prevent or improve OA by an intervention, mostly removal from exposure sources. Such examinations are hypothesized to be effective because more severe disease was demonstrated in workers who continued working for longer periods in spite of symptoms.⁴⁻⁷ Although a beneficial effect of early transferral from exposure sources is plausible, the effectiveness of such programs has not been studied prospectively.

We chose a catalyst production plant with known previous cases of OA caused by platinum salts. Compared with precious metal refineries, the production process is more uniform in catalyst production plants, and exposure to irritants or spills with massive release of the allergen is probably not a relevant confounder.

METHODS

A total of 159 catalyst production workers, 50 craftsmen and 66 control subjects, were enrolled in a 5-year prospective cohort study.⁸ The present study was designed as a nested case-control study describing the course of symptoms, sensitization, total IgE, FEV₁, and bronchial hyperresponsiveness of subjects with conversion of skin prick test (SPT) responses to platinum salt from negative to positive during the study period ($n = 14$) and control subjects without SPT conversion matched after completion of the study for age (± 3 years), sex, smoking status, and job title ($n = 42$). Examinations were performed 6 and 12 months after the first investigation and thereafter in yearly intervals. If a person was not available because of illness or vacation, the examination took place after

From ^athe Department of Internal Medicine, Division of Pneumology, Allergology and Sleep Medicine, University Hospital Bergmannsheil, Bochum; ^bDegussa-Hüls AG, Medical Department, Frankfurt; and ^cResearch Institute for Occupational Medicine, Bochum.

Received for publication May 10, 2000; revised December 11, 2000; accepted for publication December 14, 2000.

Reprint requests: Rolf Merget, MD, BGFA, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany.

Copyright © 2001 by Mosby, Inc

0091-6749/2001 \$35.00 + 0 1/86/113564

doi:10.1067/mai.2001.113564

TABLE I. Symptoms in SPT response converters reported at each examination

Subject No.	Symptoms					OET before conversion (mo)	Symptoms to transferral (mo)	Conversion to transferral (mo)
	Before conversion	At conversion	After conversion					
			6 mo	12 mo	>12 mo			
1	None	Shortness of breath,* cough,* runny nose,* itching eyes,* recurrent skin rash*	None	ND	ND	50	5	2 before conversion [†]
2 [‡]	None	Shortness of breath,* cough,* runny nose,* sneezing,* itching skin*	Runny nose*	Runny nose*	18 and 30 mo: runny nose*	33	7	3 before conversion [†]
3	None	Cough,* runny nose,* itching eyes*	None	None	24 mo: none	6	2	1
4	None	Sneezing,* recurrent skin rash*	None	ND	24 mo: none	37	12	2
5	Persistent cough	Shortness of breath,* cough,* sneezing,* runny nose,* itching eyes*	Persistent cough, occasional shortness of breath	ND	ND	21	12	2
6	Runny nose, itching eyes after contact with cat	Runny nose, itching eyes after contact with cat and during summer	Occasional shortness of breath; runny nose and itching eyes after contact with cat and during summer	ND	18 and 24 mo: occasional shortness of breath; runny nose and itching eyes after contact with cat and during summer	38	1	1
7	None	Runny nose*	Wheeze, runny nose	Wheeze and cough	ND	33	10	5
8	Persistent runny nose and sneezing	Persistent runny nose, sneezing, and furunculosis on both arms	Persistent runny nose, sneezing, and furunculosis	Persistent runny nose, sneezing, and furunculosis	24 mo: persistent runny nose and sneezing and intermittent furunculosis	96	3	3
9	Intermittent bronchitis	Shortness of breath, persistent cough	ND	ND	ND	28	? [§]	2
10	None	Sneezing,* itching eyes*	ND	None	24 mo: none	32	13	4
11	None	Itching skin*	Itching skin	None	ND	31	5	4
12	None	Contact urticaria*	ND	ND	18 and 30 mo: occasional shortness of breath	45	11	4
13	Persistent runny nose	Persistent runny nose	Persistent runny nose	ND	ND	67	—	4
14	Intermittent bronchitis	Intermittent bronchitis	ND	Intermittent bronchitis	ND	48	—	3

Note that only subjects No. 5 and 14 showed bronchial hyperresponsiveness to histamine at the final examination; in subject No. 5 it was present also at the initial examination.

OET, Occupational exposure time (from employment until transferral or final examination; ND, not done).

*Symptoms with relation to work.

‡Subjects No. 1 and 2 had been transferred before SPT response conversion was documented by the study team. In both cases the plant physician had documented a wheal diameter of 10 mm with platinum salt, and subjects were transferred immediately afterward.

§Subject No. 2 was a craftsman without complete removal.

§Subject No. 9 did not remember the date of symptom occurrence.

||Subjects No. 13 and 14 did not report new symptoms.

TABLE II. Anamnestic data and results of the initial examination of later SPT response converters and control subjects

	Converters (n = 14)	Control subjects (n = 42)	P value	OR (95% CI)
Age (y)	33 (29-36)	33 (31-34)	—	—
Smoking				
Smokers	11 (78.6%)	33 (78.6%)	—	1.0 (0.2-5.0)
Pack-years	13 (9-17)	13 (10-16)	1.0	—
Atopy				
History of hay fever	1 (7.1%)	5 (11.9%)	—	0.5 (0.01-5.0)
Positive SPT and EAST results				
Grass	1 (7.1%)	3 (7.1%)	—	—
Birch	0	2 (4.8%)	—	—
Cat		0	1 (2.4%)	—
House dust mite	1 (7.1%)	6 (14.3%)	—	—
Any	2 (14.3%)	9 (21.4%)	—	0.6 (0.06-3.3)
Occupational exposure time (mo)	9 (0-18)	12 (6-17)	.13	—
Wheal diameter with platinum salt (mm)	0	0	—	—
Total IgE (U/mL)	83 (47-146)	39 (27-56)	.08	—
FEV ₁ (% predicted)	105 (97-113)	98 (94-101)	.06	—
Bronchial hyperresponsiveness				
Slope dose-response curve (%·mg ⁻¹)	4.0 (2.2-7.2)	2.7 (1.8-3.9)	.28	—
PD ₁₅ <1 mg of histamine	2 (14.3%)	4 (9.5%)	—	1.7 (0.1-10.0)

OR, Odds ratio.

another 6 months. After SPT response conversion, the examination intervals were chosen as at the beginning of the study. All subjects were removed as soon as possible after SPT response conversion, irrespective of symptoms. Two workers complained of work-related symptoms and were transferred immediately after SPT response conversion was documented by the plant's physician (before the half-yearly examinations by our team, Table I). The mean observation period until SPT response conversion was 30 months (95% CI, 24-37), and the observation period afterward was 19 months (95% CI, 12-25). The mean total period was 49 months (95% CI, 41-56) for SPT response converters and 38 months (95% CI, 32-44) for control subjects.

One SPT response converter was not available for follow-up examinations. One craftsman reported ongoing work-related runny nose after occasional contact with contaminated materials. Thus 12 of the SPT response converters, all operators, were completely removed from exposure sources and had at least one follow-up examination. Only 9 of the 12 subjects underwent histamine testing at follow-up examinations.

Technical details of the methods, including exposure assessment, were described recently.⁸ Briefly, symptoms were assessed by means of a questionnaire and physician interview. Afterward, SPTs with hexachloroplatinic acid (10⁻² mol/L; Sigma, Munich, Germany) were performed. A positive SPT reaction was assumed if the wheal diameter was 4 mm or larger. Total serum IgE levels, FEV₁, and bronchial responsiveness to histamine were assessed according to standard procedures at all visits.⁸ To get a quantitative value of bronchial responsiveness to histamine for subjects without a significant FEV₁ decrease, responsiveness was expressed by the slope of a line extending from the origin of the dose-response curve to the last data point.⁹

Mean values are arithmetic or geometric (IgE and slope of histamine testing) means with 95% CIs. Parameters in Table II were compared with the Wilcoxon Mann-Whitney test for ordinal data or the Fisher exact test for binomial data. The Wilcoxon signed-rank test was used for the comparison of data at 2 different time points (occasions). Odds ratios and 95% CIs (see legend of Table III) were calculated by using StatXact software (Cytel Software Corp, Cambridge, Mass). A *P* value of less than .05 was considered significant.

RESULTS

Although maximal soluble platinum values in high exposure areas were above the current threshold limit value of 2 µg/m³, they were 90 pg/m³ (980 pg/m³ total platinum) in areas considered free from exposure to platinum.⁸ Thus removal resulted in an approximately 10,000-fold exposure reduction, with airborne platinum values being only marginally higher than reported values in the environment.¹⁰

Personal data, symptoms, and results of the initial survey did not differ between patients and control subjects (Tables II and III).

New symptoms were reported by 12 (85.7%) of the 14 SPT response converters, but only 9 (64.3%) subjects complained about work-related new symptoms (Tables I and III). Work-related runny nose or sneezing was the most prominent new symptom in converters, and work-related shortness of breath or wheeze was the least frequent symptom. Interestingly, one subject with preexisting ocular and nasal symptoms after contact to cats reported seasonal hay fever (SPT response conversion was documented in June; subject No. 6). Another converter demonstrated furunculosis on both arms, whereas preexisting rhinoconjunctivitis was unchanged (subject No. 8). Work-related symptoms did not occur in subjects after transferal to areas without any platinum salt exposure.

The prognosis of new symptoms in converters was excellent for all symptoms, with the exception of shortness of breath and wheezing. Four subjects reported persistent mild asthmatic symptoms without relation to work after SPT response conversion (subjects No. 5, 6, 7, and 12). Among them was one person who did not report any work-related complaints at the time of SPT response conversion (subject No. 6) and another 2 subjects (No. 7 and 12) with runny nose and contact urticaria at conver-

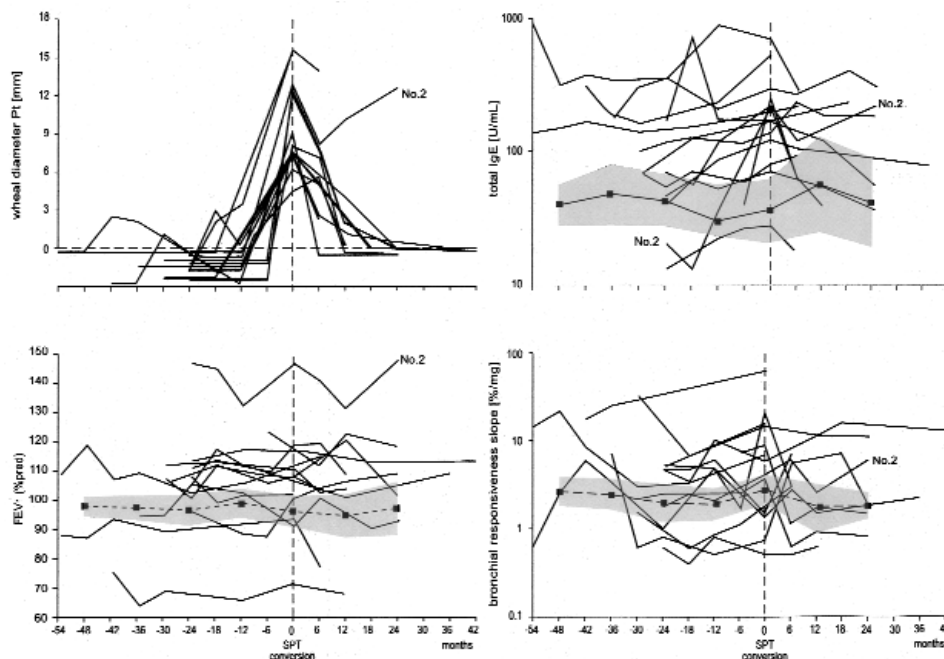


FIG 1. FEV₁, SPT responses with platinum salt, bronchial hyperresponsiveness (expressed as the slope of the dose-response curve), and total IgE levels in SPT response converters. For each person, the date of SPT response conversion is taken as common origin (time 0). Shaded areas represent the mean values and 95% CIs of the control subjects at each examination. Subject No. 2 reported recurrent platinum exposure from contaminated materials. Bronchial hyperresponsiveness corresponds to a slope of about 15%-mg⁻¹ or greater.

sion who reported asthma symptoms later. Of the 4 workers who had symptoms of asthma at conversion, only one stayed symptomatic on follow-up (note that information is missing for one subject).

Work-related symptoms were also reported by a small number of control subjects. This occurred both at the initial and at the final survey (Table III). Overall symptoms at the final survey were not different between cases and control subjects, but shortness of breath without relation to work was more prevalent among cases (33.3% vs 7.1%; odds ratio, 6.5; 95% CI, 0.9-51.0; Table III). SPT responses became negative or decreased in all SPT response converters after transferral, with the exception of the craftsman who reported ongoing occasional contact to contaminated materials from the catalyst production (Fig 1). Total IgE levels of SPT response converters increased from 83 kU/L (95% CI, 46-149) at the initial examination to 168 kU/L (95% CI, 110-258) at the time of SPT response conversion ($P \leq .001$) and decreased after transferral to 109 kU/L (95% CI, 59-201; $P \leq .01$). Twelve of 14 SPT response converters showed an increase in IgE level at the time of SPT response conversion. FEV₁ and bronchial hyperresponsiveness did not show a significant change during the study period in SPT response converters (Fig 1). In control subjects total IgE levels, FEV₁, and bronchial hyperresponsiveness did not change during the study (shaded area in Fig 1). Total IgE levels at the final survey were higher in converters than in control subjects (118 U/mL [95% CI, 65-213] vs 65 U/mL [95% CI, 42-103]; $P = .023$), but FEV₁ and

bronchial hyperresponsiveness did not differ between groups. No difference was found in either group for any parameter (except asthma symptoms in SPT response converters) between the initial and final examination, although control subjects tended to report more symptoms at the final survey (Table III).

DISCUSSION

There is convincing evidence from a South African longitudinal study (in which workers with sensitization to platinum were not removed from contact with the substance until they demonstrated symptoms of asthma) that those without symptoms but with a positive SPT response to platinum salts will inevitably have symptoms of asthma at follow-up.¹¹ In addition, exposed workers with work-related symptoms being referred to our department for diagnosis (thus later in the course of the disease) demonstrated bronchial hyperresponsiveness that was not reversible after exposure cessation in almost all subjects.^{12,13} In this study a medical surveillance program including workers exposed to platinum salts prevented chronic symptoms of asthma (with few exceptions). Persistent deterioration of objective parameters, such as bronchial responsiveness to histamine or lung function impairment as a result of occupational exposure, could not be demonstrated. Thus it can be concluded that the intervention was effective, although a randomized intervention was not performed because of ethical reasons and the small number of converters.

TABLE III. Symptoms in SPT response converters at the initial examination, at SPT response conversion, and at the final examination

Symptoms	Converters (n = 14)			Control subjects (n = 42)		OR (95% CI), converters vs controls*	
	Initial	Conversion	Final†	Initial	Final	Initial	Final
Without relation to work							
Shortness of breath or wheeze	0	1 (7.1%)	4 (33.3%)	2 (4.8%)	3 (7.1%)	0 (0-16.3)	6.5 (0.9-51.0)
Runny nose or sneezing	3 (21.4%)	3 (21.4%)	3 (25.0%)	7 (16.7%)	9 (21.4%)	1.4 (0.2-7.3)	1.2 (0.2-6.4)
Burning or itching eyes	1 (7.1%)	1 (7.1%)	1 (8.3%)	5 (11.9%)	6 (14.3%)	0.6 (0.01-5.9)	0.6 (0.01-5.4)
Skin rash, itching	0	0	0	1 (2.4%)	3 (7.1%)	0 (0-117.0)	0 (0-8.7)
Any	3 (21.4%)	4 (28.6%)	7 (58.3%)	9 (21.4%)	14 (33.3%)	1.0 (0.1-5.0)	2.8 (0.6-13.2)
With relation to work							
Shortness of breath or wheeze	0	3 (21.4%)	0	0	1 (2.4%)	—	0 (0-136.5)
Runny nose or sneezing	0	6 (42.9%)‡	0	1 (2.4%)	3 (7.1%)	0 (0-117.0)	0 (0-8.7)
Burning or itching eyes	0	4 (28.6%)	0	0	2 (4.8%)	—	0 (0-19.1)
Skin rash, itching	0	5 (35.7%)‡	0	2 (4.8%)	3 (7.1%)	0 (0-16.3)	0 (0-8.7)
Any	0	9 (64.3%)‡	0	3 (7.1%)	5 (11.9%)	0 (0-7.4)	0 (0-3.9)
With or without relation to work							
Shortness of breath or wheeze	0	4 (28.6%)	4 (33.3%)	2 (4.8%)	4 (9.5%)	0 (0-16.3)	4.8 (0.7-30.6)
Runny nose or sneezing	3 (21.4%)	9 (64.3%)	3 (25.0%)	9 (21.4%)	12 (28.6%)	1.0 (0.1-5.0)	0.8 (0.1-4.2)
Burning or itching eyes	1 (7.1%)	5 (35.7%)	1 (8.3%)	5 (11.9%)	8 (19.0%)	0.6 (0.01-5.9)	0.4 (0.01-3.5)
Skin rash, itching	0	5 (35.7%)‡	0	3 (7.1%)	6 (14.3%)	0 (0-7.4)	0 (0-3.0)
Any	3 (21.4%)	13 (92.9%)‡	7 (58.3%)	10 (23.8%)	19 (45.2%)	0.9 (0.1-4.3)	1.7 (0.4-7.9)

Note that cough, bronchitis, and furunculosis were not considered in this Table. If a parameter changed at the time of SPT response conversion (or final survey) with respect to the initial survey, this is indicated by a double dagger (‡; $P < .05$).

OR, Odds ratio.

*The initial examination of later SPT response converters was compared with the initial examination of the control subjects, as was the final examination of SPT response converters with the final examination of controls. The time of SPT response conversion was not considered in these calculations.

†Only the 12 subjects with complete removal and follow-up examinations were considered.

Yearly examination intervals were sufficient in most subjects to prevent persistent symptoms. This may be due to a high standard of control measures in the catalyst production plant compared with precious metal refineries. Because subjects with persistent symptoms in the present study experienced somewhat longer symptomatic exposure periods than those without symptoms after transferral (mean, 8.5 vs 6.7 months), shorter examination intervals may be recommended. Persistent asthmatic symptoms in 4 subjects were mild and did not require medication. Because symptoms may also have developed during the period between conversion and transferral, there is no reason to doubt that asthmatic symptoms that were not reported at conversion but occurred on follow-up examinations were due to platinum salt sensitization. Some subjects with symptoms of asthma at conversion lost these after transferral. Because of the small number of converters in this study, it remains unclear whether asthma symptoms have a worse prognosis than symptoms of rhinitis, conjunctivitis, or contact urticaria, which disappeared in almost all cases.

This study clearly demonstrates that the assessment of both symptoms and sensitization are more sensitive tools in beginning platinum salt allergy than histamine testing or spirometry. Interestingly, sensitization as assessed by SPT seemed even more sensitive than symptoms. However, there were only 2 SPT response converters without new symptoms at the time when SPT response conversion was detected, and we cannot exclude underreporting of symptoms.

If one takes SPT response conversion as the gold stan-

dard for beginning disease, specificity of work-related symptoms may be considered acceptable because only a small number of control subjects reported work-related symptoms. The trend for more work-related symptoms at the final examination in control subjects may be interpreted as better self-observation because this was also demonstrated for symptoms without relation to work.

Skin sensitization to platinum salt decreased or disappeared rapidly after cessation of exposure. To our knowledge, this has not been shown previously either for platinum salt sensitization or for other occupational allergens. The rapid decrease in sensitization in all SPT response converters after complete removal from exposure within a few months contrasts with a more delayed decrease in subjects with platinum salt-induced asthma with longer lasting exposure after the onset of symptoms.^{12,13} Thus our results indicate that there is probably a correlation between the duration of exposure after the onset of symptoms and the period needed without exposure to lose sensitization.

One SPT response converter, a craftsman with persisting sensitization to platinum salt after removal from exposure, had ongoing low exposure to contaminated materials. This observation supports the concept that sensitization is boosted by occasional contact to small amounts of the allergen.

Although the results of the present study may possibly not be transferrable to OA caused by other allergens or to other settings with different exposure degrees, they sup-

port the postulate that medical surveillance programs be instituted in workplaces at high risk of OA.¹⁴

We thank the workforce of Degussa Rheinfelden for participation and Mrs I. Santo (Rheinfelden), Mrs B. Aulbach (Frankfurt), and Mrs B. Schaerling (Bochum) for their excellent technical assistance.

REFERENCES

1. Chan-Yeung M. Evaluation of impairment/disability in patients with occupational asthma. *Am Rev Respir Dis* 1987;135:950-1.
2. Bernstein DI, Korbee L, Stauder T, et al. The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. *J Allergy Clin Immunol* 1993;92:387-96.
3. Vedal S, Chan-Yeung M, Enarson D, et al. Symptoms and pulmonary function in western red cedar workers related to duration of employment and dust exposure. *Arch Environ Health* 1986;41:179-83.
4. Hudson P, Cartier A, Pineau L, et al. Follow-up of occupational asthma caused by crab and various agents. *J Allergy Clin Immunol* 1985;76:682-8.
5. Chan-Yeung M, Lam S, Koerner S. Clinical features and natural history of occupational asthma due to western red cedar (*Thuja plicata*). *Am J Med* 1982;72:411-5.
6. Pisati G, Baraffuni A, Zedda S. Toluene diisocyanate induced asthma: outcome according to persistence or cessation of exposure. *Br J Ind Med* 1993;50:60-4.
7. Tarlo SM, Banks D, Liss G, Broder I. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. *Occup Environ Med* 1997;54:756-61.
8. Merget R, Kulzer R, Dierkes-Globisch A, et al. Exposure-effect relationship of platinum salt allergy in a catalyst production plant—conclusions from a five-year prospective cohort study. *J Allergy Clin Immunol* 2000;105:364-70.
9. O'Connor G, Sparrow D, Taylor D, Segal M, Weiss S. Analysis of dose response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis* 1987;136:1412-7.
10. Alt F, Bambauer A, Hoppstock K, Mergler B, Tölg G. Platinum traces in airborne particulate matter. Determination of whole content, particle size distribution and soluble platinum. *Fresenius J Anal Chem* 1993;346:693-6.
11. Calverley AE, Rees D, Dowdeswell RJ, Linnett PJ, Kielkowski D. Platinum salt sensitivity in refinery workers: incidence and effects of smoking exposure. *Occup Environ Med* 1995;52:661-6.
12. Merget R, Schulte A, Gebler A, et al. Outcome of occupational asthma due to platinum salts after transferral to low exposure areas. *Int Arch Occup Environ Health* 1999;72:33-9.
13. Merget R, Reineke M, Rückmann A, Bergmann EM, Schultze-Werninghaus G. Nonspecific and specific bronchial responsiveness in occupational asthma due to platinum salts after allergen avoidance. *Am J Respir Crit Care Med* 1994;150:1146-9.
14. Bernstein DI, Liss GI. Surveillance and prevention. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. *Asthma in the workplace*. 2nd ed. New York: Marcel Dekker Inc; 1999.

Bound volumes available to subscribers

Bound volumes of *The Journal of Allergy and Clinical Immunology* are available to subscribers (only) for the 2001 issues from the Publisher, at a cost of \$107.00 for domestic, and \$128.00 for international subscribers for Vol. 107 (January-June) and Vol. 108 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby, Subscription Customer Service, 6277 Sea Harbor Dr, Orlando, FL 32887; phone (800) 654-2452 or (407) 345-4000.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.