

Cold Air Challenge and Platinum Skin Reactivity in Platinum Refinery Workers

Bronchial Reactivity Precedes Skin Prick Response

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An investigation of a platinum refinery operation consisted of an administered questionnaire, spirometry, skin prick testing with platinum salts and common aeroallergens, serum total IgE, radioallergosorbent test for platinum salts, and measurement of nonspecific airway hyperresponsiveness by cold air challenge testing. Among 136 employees examined, there were 107 current and 29 medically terminated workers; 23 (17 percent) subjects had a positive platinum salts prick skin test and 19 (14 percent) displayed a positive cold air challenge. RAST binding for platinum salts IgE antibodies showed a high level of agreement with platinum skin prick test results. A proportion (63 percent) of the population (74 current and 12 terminated workers) underwent repeat platinum skin testing one year later. Among current workers, there was conversion of the platinum skin test from negative to a positive test in five

employees, with three conversions occurring in workers who showed only a positive cold air challenge test the year before. Platinum skin sensitivity, asthma symptoms, and nonspecific airway hyperresponsiveness persisted for years after termination of exposure in some medically terminated workers presumably because of a delay in removal from work of employees who became sensitized to platinum salts. It is suggested that proper surveillance for occupational asthma involves the use of several testing procedures. Prompt removal from work of individuals found to become sensitized to platinum salts is important in this industry.

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RAST = radioallergosorbent test; TWA = time weighted averages

Epidemiologic investigations of asthma from occupational exposures have traditionally utilized such tools as standardized questionnaires and spirometry. More recently, studies have evaluated airway hyperresponsiveness using a variety of inhalation challenge techniques.¹⁻⁷ The present investigation addresses the effectiveness of testing for nonspecific airways hyperresponsiveness using a cold air challenge method in a population exposed to an agent capable of causing occupational asthma. The investigation

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represents the largest study of platinum refinery workers in the United States and was conducted as a collaborative effort by the University of Cincinnati Medical Center, the National Institute for Occupational Safety and Health (NIOSH), and the New Jersey State Department of Health.

METHODS AND MATERIALS

Industrial Process

The plant had been in operation for about 13 years and reclaimed platinum and other precious metals from scrap metals and consumed catalysts from a variety of industries. Briefly, the process involved first burning the scraps to remove carbon and combustibles; then, milling and sifting to form a fine powder; next, dissolving the powder in hydrochloric and nitric acid, followed by separation and concentration; and finally, precipitation to yield ammonium hexachloroplatinate [(NH₄)₂ Pt (Cl)₆] or "yellow salt." The salt was then calcined into a platinum sponge, dissolved, and further refined into pure metallic platinum.

Worker Population

A total of 136 workers were enrolled in the investigation in 1981. One hundred and seven were current workers, which represented 87 percent of a possible 123 persons in the available work force. The absence of 16 subjects in the study was due mainly to unavailability or absence from work during the time of the investigation. An additional 29 of 36 terminated employees living in proximity to the plant were contacted and also participated in the

study. Review of company medical records indicated that these workers were terminated from work because of suspected platinum salts sensitization. In a follow-up study conducted one year later, a proportion of the original study group (63 percent) was reinvestigated in a limited manner. In this latter study, 74 of the 107 current and 12 of the 29 terminated employees underwent repeat platinum skin tests.

Environmental Measurements

Industrial hygiene surveys were conducted by the company and over 75 air samples were made. Time weighted averages for platinum salt dusts and geometric means of the TWA values were determined, and the results were available for review.

Questionnaire

Informed consent was obtained from all participants and the research protocol was reviewed and approved by the University of Cincinnati and NIOSH's Committees on Human Research. A modified American Thoracic Society questionnaire was administered by trained interviewers.⁹ The questionnaire included questions pertaining to eye, nasal, and chest symptoms. A positive response to various questions were categorized into clinical designations: asthma was considered to be present if the worker reported wheezing, and in addition, reported at least two of three other symptoms, including cough, breathlessness, and/or chest tightness. Other clinical designations were: rhinitis: itchy and/or runny nose while at work; and, chronic bronchitis, persistent cough and/or sputum for at least two years' duration.

Skin Testing

Platinum: A standardized procedure for prick skin testing was conducted using disodium hexachloroplatinate ($[\text{Na}_2] \text{PtCl}_6$) and ammonium hexachloroplatinate ($[\text{NH}_4]_2 \text{Pt}[\text{Cl}_6]$).¹⁰ The prick testing involved first cleansing the volar surface of the forearm and placing 0.5 ml of freshly prepared aliquots of the test solutions on the skin. A 26 gauge hypodermic needle was inserted into the epidermis through the drop of solution and gently pricked in an upward direction. The platinum salts were dissolved in Coca solution and tested in a tenfold titration (10^{-9} to 10^{-3} g/ml). Histamine dihydrochloride solution (0.1 percent) was used as a positive and the negative control was the diluent solution. A control group of 45 employees at the University of Cincinnati, with no known previous platinum salts exposure, were tested for skin test reactivity to the platinum salts allergens. Additionally, preliminary skin test assays of all $(\text{NH}_4)_2 \text{PtCl}_6$ solutions did not reveal evidence of a nonspecific irritant response.

Aeroallergens: Subjects were also tested with three common aeroallergens: ragweed, timothy, and dust at dilutions of 1:20, 1:20 and 1:10 (w/v), respectively. A reaction developing in at least one of the three allergens was considered a positive test.

Serum IGE: Total serum IgE was measured using a commercial radioimmunosorbent assay. Normal human serum values in our laboratory by this method are 60 ± 45 U/ml (mean \pm SE). For this investigation, we considered an elevated value to be >150 U/ml.¹¹

Radioallergosorbent Test: RAST for platinum specific antibodies was performed on sera from 20 of 23 workers with positive platinum prick skin test, 92 of 114 workers with negative platinum skin tests, and eight unexposed control volunteers. RAST measurement required a modification of a procedure using malic dehydrogenase because of an inability to eliminate the problem of high nonspecific background binding when platinum-HSA solid phase substrates were incubated with normal control sera.^{11,12}

Platinum protein conjugates were prepared with malic dehydrogenase which results in the formation of a stable platinum-protein complex.^{11,13} The RAST technique was performed as previously described.¹⁴

Cold Air Challenge Testing

Our mobile cold air challenge apparatus was specially built and is a modification of the one reported by Deal and associates.¹⁵ Briefly, the subject breathed through a mouthpiece connected to a refrigeration apparatus which provided an inspired air temperature of -40°C . The expired air was directed through a one-way valve and into a 7-L reservoir bag which was steadily evacuated by a vacuum pump. The minute ventilation was controlled to a rate of approximately 60-65 L by instructing the subject to constantly keep the reservoir bag full by matching its rate of emptying. Carbon dioxide was added to the inspired air to allow eucapnic hyperventilation. A baseline spirogram was obtained using a dry rolling spirometer. Subjects with FEV_1/FVC values of <60 percent or severe cardiovascular disease were excluded. No one fell into this category. A FEV_1/FVC value of less than <70 percent was considered to indicate "airway obstruction." Next, the cold air challenge test was performed. It consisted of, first, 2 minutes of tidal breathing of the cold air to acclimate the subject; then 4 minutes of coached hyperventilation at 60 to 65 L/min ventilation rate; finally, spirometry was repeated at 2 and 4 minutes after cessation of hyperventilation. We considered a "positive test" to be a fall in FEV_1 of 9 percent or greater at either the 2- or 4-minute posthyperventilation measurement. We arrived at this value by the analysis of the testing of 43 "normal" workers without respiratory symptoms, normal physical examination and pulmonary function tests, no work-related change in FEV_1 , negative platinum skin testing, absence of a past medical history of asthma or allergy and negative aeroallergen prick skin tests to three allergens. The mean (\pm SEM) percent change in FEV_1 after cold air challenge in this subpopulation was -3.43 ± 2.80 percent, with a range of $+2.50$ to -12.13 percent. The "positive test" of a 9 percent fall or greater in FEV_1 presented an approximate value falling outside two standard errors from the mean of the change. This value of >9 percent is similar to values reported by other investigators.¹⁶ After completing the cold air challenge testing and examining the raw data, we concluded that nine of the 136 tests were inadequate for various technical reasons and these were excluded from analysis.

Analysis of the Data

We utilized the Statistical Analysis System and BMDP computer packages for statistical analyses. The subjects were grouped into various categories according to the results of the skin and cold air challenge testing, as well as other testing categories. We used chi-square analyses and Fischer's exact test to test associations.¹⁷ The Mantel-Haenzel method was used to test for associations and calculate odds ratios poststratification.¹⁷ This method was also used for examining associations between symptoms after stratifying for smoking status. We also employed Student *t*-tests to compare groups.¹⁷ Scheffe's method was used to compare results of RAST testing.¹⁷ A modified Woolf method provided calculations of relative risks estimates with 95 percent confidence intervals for associations after stratifying for smoking status.¹⁷

RESULTS

Environmental Exposures

Elevated platinum salt air measurements were noted in the refinery, recovery, and warehouse areas, and often exceeded the OSHA governmental standard of $2 \mu\text{g}/\text{m}^3$. It was estimated that within a four-month period of measurements, values exceeded the OSHA standard between 50 and 75 percent of the time. Besides platinum salts, a number of respiratory irritants were recognized including nitrogen dioxide,

Table 1—Demographic Data on Population Studied

Demographics	Current Workers	Terminated Workers
Number studied		
Total	107	29
Men	99	28
Women	8	1
Mean age, yr	33.7	36.5
Current/ex-smokers, %	65	97
Mean duration of employment, mo	70.8	61.2
Duration since stop working		
Mean, mo	...	60
Range, mo	...	7.2-107

ammonia, hydrogen sulfide, chlorine gas, sulfur dioxide, and hydrogen chloride.

Worker Demographics

Table 1 displays demographics of the 107 current and 29 former workers, who consisted mainly of male cigarette smokers in their 30s with an average duration of employment of 70.8 and 61.2 months, respectively. When tested, the former workers had been terminated from employment on average for about five years, ranging from seven months to 107 months.

Skin Prick Test for Platinum

Table 2 provides the results of the skin prick sensitivity to platinum salts, using the allergens in concentration ranging between 10^{-9} and 10^{-3} g/ml. The results show the lowest titer of either salt (Na_2Pt_6 or $(\text{NH}_4)_2\text{PtCl}_6$) at which a reaction occurred. There was an overall prevalence rate of positive platinum salts skin reactivity of 17 percent in the total population. There were 15 (14 percent) current and eight (28 percent) terminated workers who demonstrated a positive skin prick test reaction, with most of the reactions occurring at concentrations ranging between 10^{-6} and 10^{-3} g/ml. The terminated workers, however, showed reactions mainly at the lower concentrations of 10^{-9} to 10^{-6} g/ml. In the control group consisting of 45 nonexposed individuals, there was only one positive reaction which occurred at the highest concentration of 10^{-3} g/ml. This reaction occurred in a biologic scientist who had worked extensively with platinum salts in past research.

RAST and Total IGE

Total IgE levels were elevated in some individuals of both groups of workers, especially terminated workers. The total IgE concentration was above 150 U/ml in 40 individuals (29 percent), 25 (23 percent) current and 15 (52 percent) terminated workers. Among 23 individuals with a positive platinum skin test, IgE concentration ≥ 150 U/ml was observed in 13 (56 percent) employees compared to 27 of 114 (24 percent)

Table 2—Skin Prick Test Sensitivity to Platinum Salts

	Work Status		
	Current	Terminated	Control Subjects
Number tested	107	29	45
Number positive	15	8	1
% Positive	14	28	2*
Number positive at each concentration, g/ml			
10^3	2	0	1
10^4	2	0	0
10^5	4	0	0
10^6	4	6	0
10^7	2	0	0
10^8	1	0	0
10^9	0	0	0

* $p < 0.03$.

of those with a negative test ($p = 0.002$). Five of 15 current, and eight of eight terminated workers with positive platinum skin tests showed serum total IgE concentrations exceeding 150 U/ml. The mean (\pm SEM) serum IgE concentration was 150 ± 34 for current workers with negative platinum skin tests which was similar to the level of 152 ± 42 noted among skin test positive individuals. However, among terminated workers with a positive platinum prick skin test, the mean IgE value was 620 ± 160 ($p < 0.01$).

The level of agreement between RAST and platinum skin reactivity was striking. There was a higher platinum-MDH specific RAST binding in sera of workers with a positive platinum skin test compared to individuals with a negative skin test. The values were 7.0 ± 1.4 percent vs 4.3 ± 0.7 percent, respectively ($p < 0.001$). The value for the eight normal control volunteers was 4.2 ± 0.8 percent. By using a value of two standard errors above the mean as an "abnormal" test value, a RAST binding of 5.8 percent or greater was observed in 20 of 22 platinum skin test positive subject in which the test was measured. In contrast, only eight of 94 (8.5 percent) platinum skin test negative workers had "abnormal" RAST test values ($p < 0.01$).

Medical Symptoms, Spirometry and Aeroallergens

There was a high prevalence of symptoms recorded for the two worker groups: rhinitis was noted in 46 (44 percent) current and ten (34 percent) terminated workers. Asthma was reported in 28 (29 percent) and 12 (48 percent); and chronic bronchitis in 30 (29 percent) and 15 (52 percent), respectively. Six current (6 percent) and five terminated (18 percent) workers showed evidence of airways obstruction with FEV_1/FVC percent < 70 percent. A positive aeroallergen reaction was noted in 37 (35 percent) and eight (28 percent) of current and terminated worker groups, respectively.

Table 3—Test Results According to Whether the Platinum Skin and Cold Air Challenge Tests Are Positive

Reported symptom or test result	Positive Platinum Skin Test		Positive Cold Air Challenge	
	Prevalence PORmh*		Prevalence PORmh*	
	number (%)	95% confid	number (%)	95% confid
Rhinitis symptoms	16 (70)	4.0 (1.6-10.4)	7 (37)	0.8 (0.3-2.1)
Asthma symptoms	15 (65)	6.1 (2.4-15.6)	13 (68)	6.1 (2.2-17.2)
Chronic bronchitis	13 (57)	3.3 (1.3-8.0)	11 (58)	3.3 (1.2-8.9)
Airway obstruction	6 (26)	3.7 (1.2-11.1)	6 (31)	5.0 (1.6-15.9)
Elevated IgE	13 (56)	4.1 (1.6-10.2)	10 (53)	4.9 (1.7-13.6)
Positive aeroallergens	10 (43)	1.7 (0.7-4.3)	8 (42)	1.7 (0.6-4.4)
Positive cold air challenge	9 (39)	6.5 (2.3-18.4)
Positive platinum skin test	9 (47)	5.9 (2.1-16.6)

*Prevalence odds ratio by Mantel-Haenzel method.

Cold Air Challenge and Platinum Skin Testing

A positive cold air challenge was found in 19 persons (14 percent); 11 (11 percent) current and eight (30 percent) terminated workers (Table 3). Positive platinum salts skin reactivity was identified in nine of 19 (47 percent) cold air challenge positive workers and 14 of 108 (13 percent) with this test negative ($p < 0.001$). The sensitivity of the cold air challenge test alone for identifying persons with asthma symptoms is 68 percent and specificity is 77 percent, while for the platinum skin test alone it is 35 percent and 69 percent, respectively. When both positive platinum skin test and positive cold air challenge test are used together for identifying workers with asthma symptoms, the sensitivity increases to 78 percent and specificity is 64 percent.

There were 23 workers (17 percent), 15 (14 percent) current and eight (28 percent) terminated workers with a positive platinum skin test. As shown in Table 3, compared to workers with a negative test, employees with a positive platinum skin test were characterized by rhinitis ($p < 0.003$), asthma ($p < 0.001$), bronchitis ($p < 0.01$), obstructive airways disease ($p < 0.05$), elevated IgE levels ($p < 0.01$), and positive cold air challenge ($p < 0.001$). A positive cold air challenge was observed in nine of 23 (39 percent) of the subjects with a positive platinum skin test compared to ten of 114 (9 percent) with a negative test ($p < 0.001$). Skin reactivity to aeroallergens was more common in both

the positive platinum skin test and cold air challenge groups compared to the aeroallergen negative group, but the differences were not statistically significant. The prevalence of aeroallergen skin test reactivity in the platinum positive skin test alone was 36 percent; positive cold air challenge alone, 50 percent; both tests positive, 33 percent; and, both tests negative, 33 percent.

Table 4 reports medical symptoms and test results in the various categories depending on the status of the skin test or cold air challenge. Subjects with positive skin test or cold air challenge alone were characterized by a high prevalence of asthma symptoms and elevated serum IgE levels. Individuals with both tests being negative had much lower prevalence of such findings. The skin test positive groups tended to display more rhinitis symptoms while bronchitis was prominent in the group with both tests positive. In contrast, respiratory and rhinitis symptoms, airways obstruction, and elevated IgE were not prevalent in the group with both tests negative. A strong association between cigarette smoking and the presence of a positive platinum skin test ($p < 0.003$) was noted.

Repeat Platinum Skin Tests

One year later, in 1982, the skin tests were repeated in 74 of 107 (69 percent) current workers and 12 of 29 (41 percent) terminated workers. Some of the former subjects no longer worked for the company or were

Table 4—Findings According to Results of Platinum Skin Test and/or Cold Air Challenge

Findings	Total N = 107	Positive Platinum N = 14	Alone Cold Air N = 10	Both Tests Positive N = 9	Both Tests Negative N = 92
Rhinitis	56	11	2	5	38
Asthma	40	8	6	7	19
Bronchitis	45	4	2	9	30
Airway Obstruction	11	2	3	3	3
Increased IgE	40	9	6	4	21
Positive Aeroallergens	43	5	5	3	30
Smoker or exsmoker	97	13	9	7	68

Table 5—Results of 12 Month Follow-up Skin Prick Tests for Platinum Salts Reactivity Among 107 Current Workers

Results of Tests	Total 107 Workers, 1981	Retesting 74 Workers, 1982	Positive Test 12 Workers, 1982
Positive cold air challenge	6	3	3*
Positive platinum skin test	10	7	7
Positive both tests	5	0	0
Negative both tests	86	64	2*

*Skin test conversion.

unavailable for various reasons. There was no change in the skin test findings among the terminated employees: five of 12 continued to show positive skin tests, while seven continued to show negative tests. Table 5 summarizes the results of repeat platinum skin tests among current workers. Among the 67 current workers with initially negative skin tests and continued platinum salts exposure over the one-year period, five conversions of the platinum skin test from a negative to a positive result were observed. We found a strong association between a positive cold air challenge test at baseline measurement in 1981 and subsequent conversion to a positive platinum skin test one year later. Of the four workers in the follow-up study with positive cold air challenge and negative skin test, three conversions occurred. In comparison, only two of 63 workers with negative cold air and negative skin test so converted. Seven other current workers had skin tests previously testing positive and the test remained that way on retesting. In both groups, there were no losses of skin reactivity observed, nor reversions from a positive to negative test.

DISCUSSION

Repeated exposure to platinum salts can produce allergic sensitization with both upper and lower respiratory tract symptoms, a syndrome formerly referred to as "platinosis."^{11,18-25} The allergic potential of platinum salts is so great that in some studies as many as 60 to 100 percent of exposed persons developed allergy.²⁵ While asthma has been reported in workers exposed to the halide salts of platinum in the platinum refinery industry, the prevalence of asthma in this industry has been reported to be decreasing in the United Kingdom.²³ The reason given for this reduction in prevalence of asthma is because of the policy in England of removing employees from exposure once a positive platinum skin test is identified by surveillance testing.²³ Furthermore, it has generally been concluded that asthma in terminated platinum refinery workers does not persist once work exposure has ceased.²³

Our findings are contrary to this conclusion. In the present investigation, terminated workers, with no

apparent continued platinum salts exposure for an average of five years, reported asthma symptoms in 48 percent; showed evidence of airways obstruction in 18 percent; maintained a positive platinum salts prick skin test in 28 percent; had elevated IgE levels in 52 percent; and displayed a positive cold air challenge in 30 percent. These findings suggest that allergic sensitization with asthma symptoms and the presence of nonspecific airway hyperresponsiveness in affected workers may continue for years after leaving the industry and is consistent with the findings for other types of occupational asthma.²⁶⁻³²

The most likely explanation for the different prognostic outcomes of United States workers compared to those in the United Kingdom is the delay in identifying sensitized workers and early removal from work.³² Because no formal testing program was operative in the United States plant compared to the British plant, early identification and removal from exposure of sensitized workers was not possible. While priority should be given to reducing exposures by environmental controls, it is equally important to initiate surveillance programs for identifying sensitized workers and promptly removing them from the workplace exposure.

There are studies reporting the unreliability of using a respiratory questionnaire and measuring for nonspecific airways hyperresponsiveness for identifying asthmatic subjects.^{1,2,4,32} A low predictive value of testing for nonspecific airways hyperresponsiveness in epidemiologic investigations of occupational asthma was pointed out by Enarson et al³ who reported a positive methacholine challenge in 20 percent of subjects without respiratory symptoms. Additionally, Weiler et al³³ observed that nonspecific bronchial hyperresponsiveness was common in young adults and that methacholine challenge testing lacked specificity. Challenge methods for evaluating nonspecific airway hyperresponsiveness may be influenced by numerous factors including suggestion,³⁴ deep inspiration,³⁵ pretest pulmonary function status,³⁶ as well as a number of infectious, environmental and clinical factors.³⁷⁻⁴³ Cigarette smoking (past or current) was common in this worker population, and is likely to be an important factor in the pathogenesis of some of the positive cold air challenge tests we observed.⁴⁴ While the cold air challenge procedure has been used successfully in other epidemiologic investigations, its sensitivity, compared to using pharmacologic agents such as methacholine, for testing may be questioned.^{7,45-47}

Since we did not perform bronchial inhalation challenge testing with platinum salts, we cannot reach a definitive conclusion, at this time, as to the effectiveness of the cold air challenge test as a surveillance tool for occupational asthma due to platinum salts. It is clear there is a high prevalence of asthma in

previously studied platinum salts-exposed populations²⁵ and in the terminated workers we examined. The cold air challenge was better in identifying subjects with asthma symptoms. The sensitivity of the cold air challenge for selecting the workers reporting asthma symptoms was 68 percent (specificity, 77 percent) compared to the platinum skin test which was 35 percent (specificity, 69 percent). The two tests together had a sensitivity of 78 percent. Eighty five workers reported no asthma symptoms: eight were skin-test positive, and 77 were skin-test negative. Two of eight (25 percent) skin-test positive asymptomatic workers compared to seven of 77 (9 percent) platinum skin-test negative asymptomatic workers showed positive cold air challenge tests. These numbers are small and not statistically significant, but may suggest that cold air challenge testing is useful in evaluating asymptomatic workers with positive platinum skin tests.

While the cold air challenge testing is superior to platinum skin testing for identifying platinum refinery workers with asthma symptoms and possible occupational asthma, we must be cautious with our final conclusion. Other factors such as atopy and cigarette smoking may produce airway hyperresponsiveness.³² Among ten individuals with a positive cold air challenge but negative platinum skin test, 90 percent were either current or former cigarette smokers, a substantial percentage reported upper (20 percent) and lower (60 percent) respiratory symptomatology or showed aeroallergen positive skin tests (50 percent) and many displayed elevated levels of IgE serum concentrations (60 percent). The platinum salts skin test, when used alone, is the "gold standard" for determining platinum allergy; the sensitivity of the cold air challenge for revealing platinum allergy is low (39 percent). The 14 subjects who showed only a positive platinum skin test demonstrated airways obstruction (14 percent), asthma symptoms (57 percent), and rhinitis (79 percent), findings very similar to nine subjects with both platinum skin test and cold air challenge positive. An elevated total IgE level was found in all platinum salt-exposed groups. We suspect that the elevated serum total IgE is not wholly the result of an increased concentration of specific IgE antibodies to platinum salts because there is evidence to show that an elevated total IgE may actually be a nonspecific response to platinum exposure.¹¹ The relative contributions and interactions of cigarette smoking, atopy, and allergic sensitization are important considerations.^{32,48,49} A recent study documents the strong association between platinum allergy and cigarette smoking.⁵⁰

Of particular interest is our finding of platinum skin test conversion from a negative to a positive test in five individuals, three of whom demonstrated a positive cold air challenge test the previous year. This

observation suggests that perhaps testing for nonspecific airways hyperresponsiveness is appropriate in surveillance investigations when utilized as part of serial testing procedures and that bronchial hyperresponsiveness may precede evidence of cutaneous sensitization in some workers. It is unfortunate we were not able to repeat cold air challenge testing in the same subjects on whom we performed repeat skin testing, since this added information might have allowed us to gain better understanding of the relationship between skin and airways reactivity.

The cold air challenge, when used in conjunction with the platinum skin test and a respiratory questionnaire, seems to offer a relatively good screening protocol for identifying workers with occupational asthma from platinum salts. Our investigation suggests that it is advantageous to use several surveillance techniques for identifying potential occupational asthmatic subjects and in this manner may prevent long term respiratory disability.

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