Isocyanate-induced asthma in an automobile spray painter

D.W. COCKCROFT,* MD, FRCP[C]; J.T. MINK,† B SC

Toluene diisocyanate and related chemicals induce asthma by specific sensitization.[1-5] The mechanism for this is not yet clear. Hexamethylene diisocyanate is a hardening agent used in an acrylic enamel spray paint for cars that has recently been introduced. We report a case in which asthma and an increase in nonspecific bronchial reactivity to inhaled histamine were induced by this substance in a spray painter in an automotive body shop.

Case report

A 44-year-old man employed in an automotive body shop as a spray painter for the previous 28 years presented to a respiratory clinic complaining of an increasing cough productive of small amounts of sputum and shortness of breath for 6 to 12 months. He denied wheezing, chest pain, hemoptysis, chest tightness, nasal symptoms and eye symptoms. The respiratory symptoms were worse at night than during the day. However, he related their occurrence to exposure to an acrylic enamel spray paint containing hexamethylene diisocyanate, a type of paint that had been in use at the shop for the past 2 years. He had always worn a heavy-duty mask while spraying and was the only individual in the shop doing spray-painting. There was no history of past chest or atopic disease, and he had not smoked for 5 years. The only other medical problem in his past was mild hypertension, which had easily been controlled with weight reduction.

The man's blood pressure was 140 110 mm Hg, pulse rate 80 beats/min and respiratory rate 16/min. Results of the physical examination were normal, as were the results of the following investigations: determination of the hemoglobin concentration, leukocyte count and differential, erythrocyte sedimentation rate, serum electrolyte concentrations, SMA-12 biochemical analysis, serum protein electrophoresis, sputum culture, chest roentgenography and electrocardiography. A sputum specimen contained eosinophils. Pulmonary function studies revealed very mild fixed airflow obstruction; the only value that deviated from the normal prediction was the maximum mid-expiratory flow, which was 70% of the predicted value both before and after inhalation of salbutamol. Prick skin tests with 25 common allergens were all negative. A histamine inhalation test, performed to measure the level of nonspecific bronchial reactivity, gave normal results.

Special investigations

Methods: An occupational-type exposure test was performed in the laboratory as described by Pepys.[6] On day 1, the control day, the patient was exposed to the spray paint with no hardener, diluted 50% with thinner; it was sprayed with a DeVilbiss JGA-502 spray gun (DeVilbiss Company, Somerset, Pennsylvania) in an enclosed room (150 × 180 × 240 cm) for 5 minutes, during which time 325 ml was nebulized. On day 2 the patient was exposed to the paint with hardener containing 11.5% hexamethylene diisocyanate by weight added in a concentration of 1:10 by volume prior to 50% dilution with thinner; thus, the concentration of isocyanate in the spray was 0.6%. The paint was sprayed for only 2 minutes (130 ml was nebulized), as this was all that the patient could tolerate, and exposure was continued for a further 5 minutes. The forced expiratory volume in 1 second (FEV_1), maximum midexpiratory flow and vital capacity were determined with a 9-l water spirometer before exposure and after exposure at 10-minute intervals for the first hour, 30-minute intervals for the second hour and hourly for the next 4 hours.

Histamine inhalation tests were performed as described by Cockcroft and colleagues.[7] Progressively doubled concentrations of histamine acid phosphate from 0.03 to 8.0 mg/ml were delivered by a Wright nebulizer (airflow 7 l/min; output 0.130 ml/min; Aerosol Products [Colchester] Ltd., London, England) at 5-minute intervals; after each inhalation the patient breathed quietly for 2 minutes. The FEV_1 was measured 30 and 90 seconds after each inhalation, and the test was continued until the FEV_1 was reduced by 20% or more or until the maximum concentration of histamine had been administered. The results were expressed as the provocation concentration of histamine producing a 20% reduction in FEV_1 (PC_{20}) calculated or extrapolated from the histamine dose–response curve. Histamine inhalation tests were performed six times at the same time of day — at the initial visit, 6 hours after control exposure, and 6 hours, 30 hours, 54 hours and 6 days after the isocyanate challenge.

From midnight the day before the control exposure until the special investigations were completed the patient was away from work.

Results: The day prior to day 1 the patient had been heavily exposed to the isocyanate-containing spray paint during a 16-hour work shift and had experienced shortness of breath and cough throughout the night. However, when he arrived at the laboratory for the control exposure the FEV_1 was unchanged from previous visits and he was asymptomatic.

The FEV_1 on days 1 and 2 are shown in Fig. 1. There was less than a 10% change in the FEV_1 in the 6 hours following the control inhalation. Following the isocyanate exposure there was an 18% reduction in the FEV_1 at 10 minutes, then spontaneous improvement followed

From the pulmonary medicine service, department of medicine, University Hospital, Saskatoon

*Assistant professor, department of medicine, University of Saskatchewan
†Research technician

Reprint requests to: Dr. D.W. Cockcroft, Pulmonary medicine service, Department of medicine, University Hospital, Saskatoon, Sask. S7N 0X0

by a late asthmatic response with a maximum FEV_1 reduction of 41% at 3 hours.

Changes in the FEV_1 before each histamine test and in the histamine PC_{20} are shown in Fig. 2. The control PC_{20}, determined 1 month before the exposure test, on a Monday 72 hours remote from exposure to hexamethylene diisocyanate, was normal (9.4 mg/ml). On day 1 (16 hours after the end of the 16-hour occupational exposure to the paint) there was a 15-fold reduction in the PC_{20} (to 0.63 mg/ml), and on day 2, 6 hours after the 7-minute exposure to isocyanate in the laboratory, there was a further 8-fold reduction in the PC_{20} (to 0.078 mg/ml). The PC_{20} returned to normal (19.0 mg/ml) by day 8.

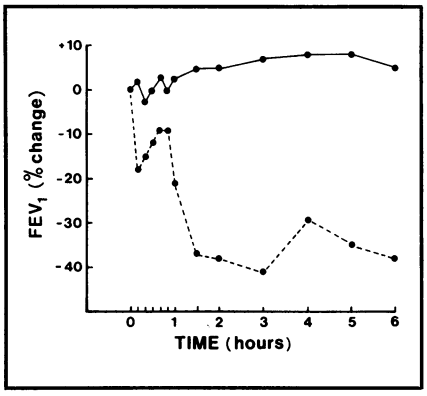

FIG. 1—Changes in forced expiratory volume in 1 second (FEV_1) following control and hexamethylene diisocyanate exposure, represented by interrupted and solid lines respectively.

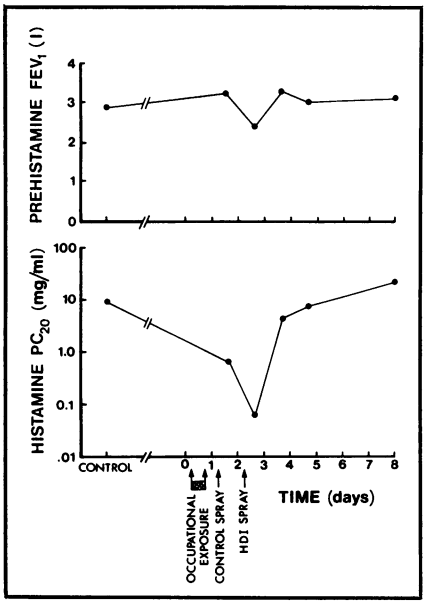

FIG. 2—Changes in FEV_1 before each histamine inhalation test and in provocation concentration of histamine producing a 20% reduction in FEV_1 (PC_{20}). HDI = hexamethylene diisocyanate.

Discussion

This patient demonstrated specific sensitization to hexamethylene diisocyanate. Brief exposure to paint containing this substance in a concentration of 0.6% produced a profound and sustained late asthmatic response. This type of response occurs frequently following exposure to toluene diisocyanate in the laboratory. Isocyanate exposure in sensitive individuals can produce an early asthmatic response with recovery in the first 1 to 2 hours, a late asthmatic response that begins within the first 1 to 3 hours and may persist up to 24 hours, or a dual asthmatic response (both early and late).[8,9]

Nonspecific bronchial hyperreactivity to inhaled chemicals such as histamine and methacholine is a characteristic feature of most persons with asthma.[7,10,11] Nonspecific bronchial hyperreactivity is also generally seen in persons with asthma due to toluene diisocyanate sensitivity.[12,13] In fact, the presence of pre-existing nonspecific bronchial hyperreactivity has been suggested as an important risk factor for the development of asthma due to toluene diisocyanate. Our patient demonstrated a normal response to inhaled histamine when away from work. Sixteen hours after a 16-hour occupational exposure the bronchial responsiveness to inhaled histamine had increased so that the concentration of histamine required to provoke a 20% fall in the FEV_1 was 15-fold less than that required when there had been no recent exposure. At this time the patient was asymptomatic and the FEV_1, maximum midexpiratory flow and vital capacity were similar to those at the initial visit. Six hours after the isocyanate challenge in the laboratory the bronchial reactivity to inhaled histamine had increased further, so that the PC_{20} was reduced a further eightfold. At that time, however, the FEV_1 was reduced by about 30%. The reduced airway calibre may have been a factor in the increased response to histamine at this time, for some have suggested that reduced airway calibre is an important determinant of bronchial responsiveness to inhaled histamine.[14] Others, however, have shown that even moderate fluctuations in airway calibre fail to affect the response to inhaled histamine or methacholine.[15,16] For 6 days following the isocyanate challenge the patient was away from work and not exposed to the paint. During this time the histamine PC_{20} returned to normal, increasing by a factor of 200. These results demonstrate that, at least in certain individuals, exposure to isocyanate can not only induce a specific asthmatic response but also result in increased nonspecific bronchial reactivity. This suggests that nonspecific bronchial hyperreactivity may be acquired as a result of isocyanate sensitivity rather than be a pre-existing determinant for the development of isocyanate-induced asthma.

Similar increases in nonspecific bronchial reactivity to inhaled histamine occur in sensitized individuals following exposure to allergens,[17,18] dimethylethanolamine[19] and western red cedar.[20] The mechanism for this is unclear. The common feature of persons demonstrating increased nonspecific bronchial reactivity following exposure to allergens, isocyanate, ethanolamine or red cedar appears to be the occurrence of a late asthmatic response. Persons with allergen-induced isolated early asthmatic responses have not shown any change in histamine sensitivity,[18] nor has such a change been seen following an isolated early asthmatic response induced by red cedar (unpublished data). Small changes in bronchial reactivity to inhaled histamine have been observed in healthy individuals following viral upper respiratory tract infections[21] and following ozone exposure;[22] these have been postulated to be the result of inflammation and damage of the bronchial mucosa leading to exposure and sensitization of epithelial irritant receptors, which could result in an increased vagal reflex following the inhalation of histamine.[21,22]

Hexamethylene diisocyanate belongs to a group of chemicals referred to as copolymerizing agents, which, although differing widely in chemical structure, have a similar

chemical function. They act as catalysts in a number of chemical processes to harden liquid or semiliquid materials. There are at least four types of copolymerizing chemicals: isocyanates, acid anhydrides, ethanolamines and complex amines. Asthma caused by specific sensitization to chemicals of all four types has been reported. As well as isocyanates, the responsible chemicals have included phthalic anhydride,[23,24] trimellitic anhydride,[24,25] dimethylethanolamine,[19] aminoethylethanolamine,[26,27] and a number of complex amines such as paraphenylenediamine, ethylenediamine and hexamethylene tetramine.[28-30] These chemicals are encountered in paints, lacquers, glues, soldering fluxes, plastics and synthetic rubber.

The mechanism of this specific type of sensitivity is unclear. The specificity of the responses as well as the patterns of early, late and dual asthmatic responses are similar to those of allergen-induced asthma and suggest an immunologic mechanism. However, immunologic investigations in asthma induced by isocyanates[2,9,12,13,31] and ethanolamine[19] have produced conflicting results. Some studies show that conjugates of toluene diisocyanate and human serum albumin stimulate lymphocytes from sensitized individuals.[2,31] However, IgE antibodies have rarely been demonstrable.[13,19,31] In contrast, immunologic investigations in asthma induced by phthalic anhydride[23] and trimellitic anhydride[25] have demonstrated specific IgE antibodies directed against conjugates of these chemicals and human serum albumin.

With the increasing use of isocyanates and related chemicals in industry, asthma induced by sensitization to these chemicals is likely to become an increasing problem. This case has demonstrated a new source of occupational exposure to isocyanates, namely spray paint used for automobiles. This syndrome should be considered in employees of automotive body shops presenting with bronchial asthma.

We thank Mrs. R. Tennent for technical assistance, Miss K. Storey for typing the manuscript and Dr. D.J. Cotton for his helpful comments.

This work was supported by the Saskatchewan Anti-Tuberculosis League.

References

1. BRUGSCH HG, ELKINS HB: Toluene di-isocyanate (TDI) toxicity. *N Engl J Med* 268: 353, 1963
2. BRUCKNER HC, AVERY SB, STETSON DM, et al: Clinical and immunologic appraisal of workers exposed to diisocyanates. *Arch Environ Health* 16: 619, 1968
3. PETERS JM, MURPHY RLH, PAGNOTTO LD, et al: Acute respiratory effects in workers exposed to low levels of toluene diisocyanate (TDI). Ibid, p 642
4. Isocyanates in industry (E). *Lancet* 1: 1375, 1970
5. PETERS JM, MURPHY RLH: Pulmonary toxicity of isocyanates. *Ann Intern Med* 73: 654, 1970
6. PEPYS J: Inhalation challenge tests in asthma. *N Engl J Med* 293: 758, 1975
7. COCKCROFT DW, KILLIAN DN, MELLON JJA, et al: Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 7: 235, 1977
8. PEPYS J, PICKERING CAC, BRESLIN ABX, et al: Asthma due to inhaled chemical agents, tolylene di-isocyanate. *Clin Allergy* 2: 225, 1972
9. BUTCHER BT, SALVAGGIO JE, WEILL H, et al: Toluene diisocyanate (TDI) pulmonary disease: immunologic and inhalation challenge studies. *J Allergy Clin Immunol* 58: 89, 1976
10. LAITINEN LAI: Histamine and metacholine challenge in the testing of bronchial reactivity. *Scand J Respir Dis* suppl 86: 1, 1974
11. OREHEK J, GAYRARD P: Les tests de provocation bronchique non-spécifiques dans l'asthme. *Bull Eur Physiopathol Respir* 12: 565, 1976
12. BUTCHER BT, SALVAGGIO JE, O'NEIL CE, et al: Toluene diisocyanate pulmonary disease — immunopharmacologic and Mecholyl challenge studies. *J Allergy Clin Immunol* 59: 223, 1977
13. BUTCHER BT, JONES RN, O'NEIL CE, et al: Longitudinal study of workers employed in the manufacture of toluene-diisocyanate. *Am Rev Respir Dis* 116: 411, 1977
14. BENSON MK: Bronchial hyperreactivity. *Br J Dis Chest* 69: 227, 1975
15. RUBINFELD AR, PAIN MCF: Relationship between bronchial reactivity, airway caliber, and severity of asthma. *Am Rev Respir Dis* 115: 381, 1977
16. FISH JE, KELLY JF, PETERMAN VI: Bronchoconstrictor aerosol responses in asymptomatic asthma: effect of prechallenge pulmonary function (abstr). *J Allergy Clin Immunol* 61: 140, 1978
17. ALTOUNYAN REC: Changes in histamine and atropine responsiveness as a guide to diagnosis and evaluation of therapy in obstructive airways disease, in *Disodium Cromoglycate in Allergic Airways Disease*, PEPYS J, FRANKLAND AW (eds), Butterworths, London, 1970, p 47
18. COCKCROFT DW, RUFFIN RE, DOLOVICH J, et al: Allergen-induced increase in non-allergic bronchial reactivity. *Clin Allergy* 7: 503, 1977
19. VALLIERES M, COCKCROFT DW, TAYLOR DM, et al: Dimethyl ethanolamine-induced asthma. *Am Rev Respir Dis* 115: 867, 1977
20. COCKCROFT DW, COTTON DJ, MINK JT: Non-specific bronchial hyperreactivity after exposure to western red cedar: a case report. *Am Rev Respir Dis* 119: 505, 1979
21. EMPEY DW, LAITINEN LA, JACOBS L, et al: Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 113: 131, 1976
22. GOLDEN JA, NADEL JA, BOUSHEY HA: Bronchial hyperirritability in healthy subjects after exposure to ozone. *Am Rev Respir Dis* 118: 287, 1978
23. MACCIA CA, BERNSTEIN IL, EMMETT EA, et al: *In vitro* demonstration of specific IgE in phthalic anhydride hypersensitivity. *Am Rev Respir Dis* 113: 701, 1976
24. FAWCETT IW, NEWMAN TAYLOR AJ, PEPYS J: Asthma due to inhaled chemical agents — epoxy resin systems containing phthalic acid anhydride, trimellitic acid anhydride, and triethylene tetramine. *Clin Allergy* 7: 1, 1977
25. ZEISS CR, PATTERSON R, PRUZANSKY JJ, et al: Trimellitic anhydride-induced airway syndromes: clinical and immunologic studies. *J Allergy Clin Immunol* 60: 96, 1977
26. STERLING GM: Asthma due to aluminium soldering flux. *Thorax* 22: 533, 1967
27. PEPYS J, PICKERING CA: Asthma due to inhaled chemical fumes — amino-ethyl ethanolamine in aluminium soldering flux. *Clin Allergy* 2: 197, 1972
28. SILBERMAN DE, SORRELL AH: Allergy in fur workers with special reference to paraphenylenediamine. *J Allergy* 30: 11, 1959
29. GELFAND HH: Respiratory allergy due to chemical compounds encountered in the rubber, lacquer, shellac, and beauty culture industries. *J Allergy* 34: 374, 1963
30. POPA V, TECULESCU D, STANESCU D, et al: Bronchial asthma and asthmatic bronchitis determined by simple chemicals. *Dis Chest* 56: 395, 1969
31. AVERY SB, STETSON DM, PAN PM, et al: Immunological investigation of individuals with toluene diisocyanate asthma. *Clin Exp Immunol* 4: 585, 1969