contribution to gas exchange by the abnormal lung. However, with exercise, one would expect ventilation-perfusion matching to worsen. The unaffected lung will receive an increase in perfusion appropriate or high relative to the rise in ventilation as all of the right-sided cardiac output goes through the single pulmonary artery. The affected lung will also receive an increase in ventilation, but it is doubtful that perfusion will increase appropriately since it is supplied by the left-sided circulation and most of the augmented left-sided cardiac output goes to the exercising muscles. The net result of this would be an inappropriate reduction or rise in $V_{O_2}/V_{T}$ as was seen in our patient.

In summary, a patient with UAPA and dyspnea on exertion was studied. In the absence of associated cardiac disease or pulmonary hypertension, exercise limitation appeared to be due to increasing percent dead space ventilation.

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Occupational Asthma in a Pesticides Manufacturing Worker*

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A 34-year-old male chemical manufacturing worker had new onset of work-related asthma after several years of exposure to the fungicide, captafol. On specific bronchial challenge testing, he demonstrated a marked and persistent fall in FEV₁. Cessation of exposure resulted in improved symptoms and pulmonary function. The delay in symptoms after several years of workplace exposure and the dual reaction demonstrated on specific bronchial challenge testing suggest sensitization to some component of technical-grade captafol, but an IgE response was not detected.

(Chest 1993; 103:295-96)

Captafol (Difolatan) is a chlorinated thiocarboximide fungicide extensively used in the United States until the Environmental Protection Agency designated it as a "probable human carcinogen," and the sole US manufacturer cancelled its registration in 1987. Its manufacture and distribution in the United States was prohibited after May 1988, but use of existing stocks is allowed. Active suppliers of captafol include companies based in the United States, India, Italy, Taiwan, Brazil, the Netherlands, Germany, Canada, and Singapore.

There have been numerous reports of skin rashes associated with captafol manufacture and use and several authors have reported positive patch testing that they interpreted to represent allergic contact dermatitis. Captafol's respiratory effects are less well studied. Two unpublished epidemiologic studies in the US manufacturing plant where this patient worked both showed a significant prevalence of work-related respiratory tract symptoms. Eight cases of captafol-associated wheezing have also been reported.

The captafol manufactured at this plant consists of respirable particles, 1.5 to 5.0 μm in diameter. The technical-grade product consists of 97 percent captafol, 0.5 percent dye, <0.5 percent solvents, and several captafol metabolites. Two of captafol's precursors, tetrahydrophthalic acid and maleic anhydride, have been documented to cause occupational asthma via immunologic mechanisms.

CASE REPORT

A 34-year-old male chemical manufacturing worker was examined at the Occupational Health Clinic at San Francisco General Hospital because of recurrent attacks of chest tightness, wheezing, and shortness of breath for the prior three years. He was a nonsmoker with no personal history of asthma, hay fever, hives, or eczema.

Twelve years before presentation, the patient started work without respiratory protection in the captafol bag room where there was visible dust in the air. (Three personal air samples in the bag room in 1986 exceeded the current threshold limit value of 0.1 mg/m³ set by the American Conference of Governmental Industrial Hygienists.) Within two years, he developed sneezing and rhinitis at work. He was then transferred to the captafol production line, during which time a facial splash of a precursor called 1,1,2,2-tetrachloroethylsulfenyl chloride (TES) caused pleuritic chest pain followed by several weeks of morning sputum production.

Three years prior to presentation, the patient noted burning eyes, rhinitis, and rash on his wrists between his coveralls and his gloves precipitated by entering the bagroom. Three to 4 h after leaving the area, he would notice chest tightness followed by wheezing awakening him from sleep. During a two-week vacation, his chest symptoms disappeared, but recently they had began to recur upon exercise.

Physical examination at presentation to the clinic revealed clear lungs and no skin rash. Pulmonary function testing included an FEV₁ of 3.62 L (100 percent of predicted), with an FVC of 4.70 L (98 percent of predicted), and an FEV₁/FVC ratio of 0.76. His forced expiratory flow-volume curve demonstrated decreased flow rates at low lung volumes. The concentration of methacholine that produced a 100 percent increase in airway resistance (SRaw) from baseline (PC100) was 0.7 mg methacholine per milliliter. (A value of 4 mg/ml is the lower limit of normal for PC100 in the laboratory where the test was performed.) After returning to intermittent
CAPTAFOl exposure at work, measurements of serial peak expiratory flow performed during intermittent captafol exposure showed diurnal variability exceeding 20 percent, but a work-related pattern was not clearly established. Given that his symptom history strongly suggested a work-related cause, and our suspicion that captafol could be a respiratory tract sensitizer, specific bronchial provocation testing was undertaken to clarify the cause of the patient’s asthma.

The specific captafol challenge protocol was approved by the Committee on Human Research of the University of California, San Francisco. The patient was admitted to the San Francisco General Hospital Clinical Research Center the day prior to the challenge, and written informed consent was obtained. Results of the two-day challenge are displayed in Figure 1. On day 1, baseline spirometry, SRaw, and methacholine responsiveness were measured. Serial spirometry was then performed up to 11 h after exposure to dust generated when the patient poured 500 mg of lactose from one beaker to another for 15 min. While measurements of captafol concentration in the patient’s breathing zone were not conducted, the pouring generated a visible cloud of dust.

On day 2, the patient’s baseline pulmonary function parameters were unchanged. He was then exposed to 200 mg of a 1:1 lactose-captafol (Difolatan) technical-grade mixture using the same method of pouring from one container to another. Serial spirometry was performed up to 11 h and showed a decrement in FEV1, reaching a nadir of 2.31 L (64 percent of baseline FEV1) 30 min after the challenge. The patient awoke 16 h postcaptafol challenge with shortness of breath, coughing, and chest tightness, relieved by using an albuterol inhaler before spirometry could be performed.

After the inhalation challenge, the patient ceased regular exposure to captafol. On follow-up two years later, he reports occasional bouts of chest tightness precipitated by environmental tobacco exposure, saw dust, or dirt. He occasionally requires the use of an inhaled bronchodilator. Repeated pulmonary function testing showed that his FEV1 had increased 0.3 L to 3.92, and his FVC had increased 0.31 L to 4.92, giving an FEV1/FVC ratio of 0.80. His forced expiratory volume curve again showed decreased flow rates at low lung volumes. His PC20 had increased to 1.3 mg of methacholine per milliliter. Allergy skin testing showed positive reactions to several common environmental allergens. Serum showed no evidence of IgE cross reactivity to common acid anhydride occupational allergens, including maleic anhydride, a captafol precursor, but specific reactivity to captafol was not assessed (L. L. Bernstein, M.D., University of Cincinnati, written communication, June 1988).

**DISCUSSION**

The patient’s intermittent chest symptoms, variable airways obstruction, temporal exacerbations with exposure to captafol dust at work, and improvement in symptoms and pulmonary function with the cessation of exposure fulfill the National Institute for Occupational Safety and Health (NIOSH) surveillance case definition for work-related asthma. The positive response to specific bronchial provocation testing strongly suggests that technical-grade captafol is responsible for this patient’s symptoms.

The delay of several years of exposure before the development of respiratory tract symptoms may represent sensitization, a phenomenon well described for other types of occupational asthma. The pattern of marked FEV1 decline in the hospital persisting 11 h after exposure (and his history of wheezing at home at night after work) suggest a dual reaction with both an immediate and a late component, also seen in occupational asthma due to sensitizers.

Captafol’s apparent ability to cause sensitization and bronchoconstriction (in addition to its carcinogenicity) necessitate more stringent regulatory action. Unless use is prohibited, workers should be informed of the risks, and medical surveillance should be provided. Structurally related (and widely used in the United States today), folpet and captan are also skin sensitizers, and should be suspect causes of asthma as well.

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Occupational Asthma in Pesticide Manufacturing (Royce et al)