

is the persisting and increasing edema over weeks or months without the subsidence of swelling seen in common angioedema with other causes.

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Baker's asthma caused by *Saccharomyces cerevisiae* in dry powder form

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Bakers' asthma is a well-defined disease. It can be caused by various antigens: flours and bran, yeast, baking additives, saprophytic molds, and storage mites.¹⁻³ It is well known that hypersensitivity to flour represents a significant proportion of occupational allergies.^{4,5} However, in recent years many more substances used in baked goods and pastry have been reported as causes of allergy.

In 1713 Ramazzini, in *De Morbis Artificum Diatriba*, stated that work environments and products were factors responsible for disease. We believe it is important to be familiar with the workplace and existing dust products and the procedures for handling such products to be able to establish a correct etiologic diagnosis.

We report a case of bakers' asthma caused by an antigen that is always present in the baking industry but does not easily affect the airways and rarely sensitizes workers.

CASE REPORT

A 48-year-old man who was a nonsmoker came to our attention with repeated episodes of hydorrhea, sneezing, nasal obstruction, wheezing, spasmodic cough, and dyspnea. The symptoms would always appear 1 to 2

Abbreviations used

PEFR: Peak expiratory flow rate
SC: *Saccharomyces cerevisiae*

hours after starting work. They first appeared a year ago on weekdays and improved on Sundays (the patient's rest day). The symptoms were initially mild but became progressively worse until continuous medical treatment was required. During short holiday periods he was free of symptoms and did not need bronchodilators. Results of an allergy test were negative, and the patient was diagnosed as having rhinitis and intrinsic asthma. Treatment was started with budesonide and salbutamol, but the symptoms were not fully controlled.

The bakery is approximately 90 m², well-ventilated, and not near the patient's home. There are two other workers, besides the patient, who remain free of symptoms. No changes have been implemented in the last few years. Contamination by molds and mites not used in the skin tests was ruled out by an optical microscopy study of different dust samples.⁶ The bread ingredients are as follows: water, salt, wheat flour and bran, dry powder dehydrated yeast, and baking additives containing exogenous enzymes (amylases, glucoamylase, and lipoxigenase), antioxidant agents (potassium bromate, azodicarbonamide, ascorbic acid, and soybean flour), and emulsifiers (soybean lecithin). When the flour, yeast, and additives are mixed, a dusty environment is created, which decreases once cold water is added and kneading is started.

Three years ago as a result of storage problems, the conventional yeast (nondehydrated, 70% to 75% humidity and requiring a temperature of 4°C for proper

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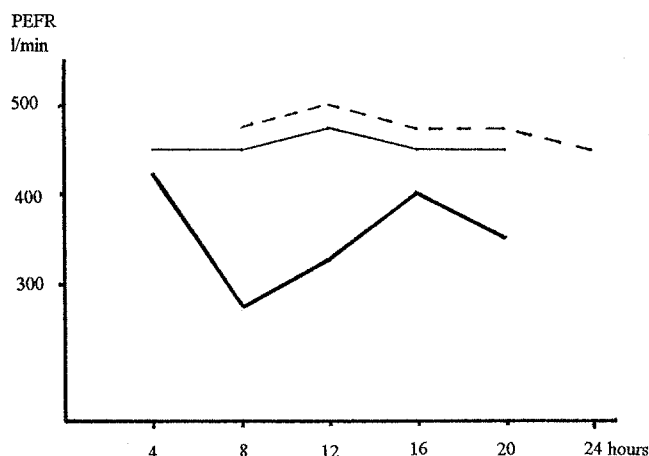


FIG. 1. Bronchial response patterns during PEFR monitoring: (—) working with dry yeast, (---) working with wet yeast, (....) on vacation.

storage) was replaced with dehydrated yeast (dry powder, 8% humidity and storable at ambient temperature).

METHODS

We used dehydrated yeast in dry powder form, conventional wet yeast, and a commercial mixture of baking additives. For the preparation of the crude extracts, proteins were extracted by incubation of dry yeast, wet yeast, and baking additives in phosphate-buffered saline (pH 7.3) at 1:10 wt/vol. The resulting suspensions were stirred for 6 hours at 4° C and then centrifuged. The supernatants were passed through Whatman 2 filter paper (Whatman Inc., Clifton, N.J.) and then through a 0.22 μ m Millipore filter (Millipore Corp., Bedford, Mass.) for sterilization. Five 10-fold dilutions (1:1, 1:10, 1:100, 1:1000, and 1:10,000) were made for the skin prick tests and to enable selection of a safe initial dose for the specific bronchial provocation test.

Skin prick tests were performed on the volar side of the forearm with a prick lancetter (DHS; Bayer, Leverkusen Germany) and with the extracts described previously. A battery of inhalant allergens including *Dermatophagoides species*, storage mites, molds (*Alternaria*, *Cladosporium*, *Aspergillus*, *Fusarium*, and *Rhizopus species*), pollens from our geographic area (*Artemisia vulgaris*, *Chenopodium album*, *Salsola kali*, *Olea europea*, *Parietaria judaica*, *Plantago lanceolata*, and grasses), wheat, barley and soybean flours (Abello S.A., Madrid, Spain), and α -amylase (Ifidisa-Aristegui, Bilbao, Spain) were tested. Histamine phosphate, 10 mg/ml, and phosphate-buffered saline were used as positive and negative controls. A positive response was defined as a wheal with a mean diameter greater than 5 mm in the presence of a negative response to the diluent. Four exposed asymptomatic bakers and eight nonexposed asthmatic patients were tested to determine that yeast and baking additive extracts are not irritating. Specific IgE was measured by enzyme immunoassay (CAP system, Pharmacia Diagnostics, Uppsala, Sweden).

Baseline peak expiratory flow rate (PEFR) measurements were obtained with a mini Wright peak flow meter (Ferraris Medical, Inc., Holland, N.Y.). The patient was asked to monitor his own PEFR every 4 hours for 1 week during work time and again for 1 week when on holiday. He was to do this three times on each occasion, and the readings were to be within 5% of each other. He was also asked to record his symptoms and therapeutic requirements during this time. After 7 days away from the bakery, the patient had another PEFR monitoring performed at work, but with the dry powder yeast substituted for conventional wet yeast. The bronchial response was considered positive when the PEFR was greater than or equal to 25%. The patient had not received any drug therapy in the month before the test.

The nonspecific bronchial provocation test was performed with methacholine to determine the presence of bronchial hyperreactivity. Methacholine was administered with a Devilbiss 646 nebulizer (Devilbiss Healthcare, Inc., Somerset, Pa.) according to the method described by M. Chatham. The specific bronchial provocation test was performed with a *Saccharomyces cerevisiae* (SC) extract to confirm or rule out that the bronchial manifestation was due to sensitization to this allergen. This was done when the patient was not at the bakery while he was free of symptoms and not receiving any medication that could affect the results. The extract was administered with a Devilbiss 646 nebulizer at a flow rate of 0.28 ml/min and inhaled by tidal breathing for 2 minutes. We started the test with a 10^{-4} diluted dry yeast extract, which in the skin test produced a negative result. Forced vital capacity and FEV₁ were measured at 5, 10, 15, 20, 30, and 60 minutes and hourly thereafter for the next 12 hours. A week later, we performed another bronchial provocation test with a baking additive extract, starting with a 10^{-3} dilution. A positive response was defined as a decrease in FEV₁ greater than or equal to 20%.

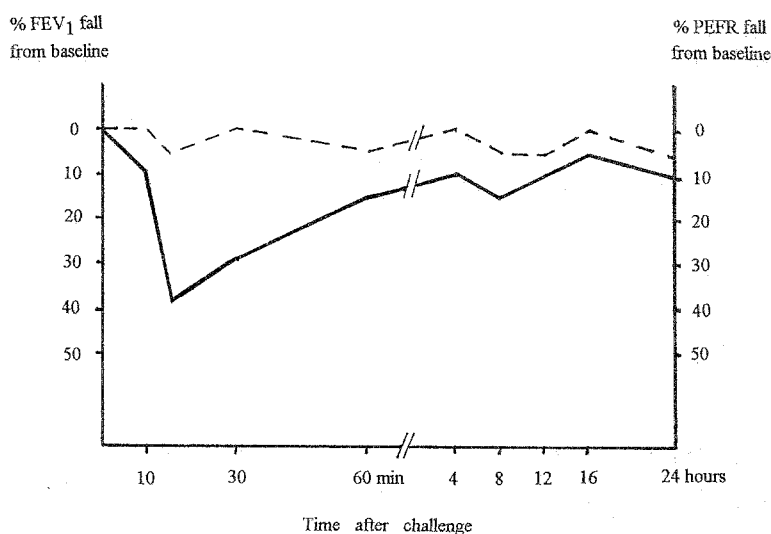


FIG. 2. Bronchial response after challenge with (----) baking additives and (—) SC extract 10^{-3} wt/vol.

RESULTS

With optical microscopy we found no other contaminants that might be responsible for symptoms. The patient had negative skin test results for the battery of pneumoallergens and the baking additive extract. The skin test result was negative with 10^{-4} and 10^{-3} dilutions of the SC extract; with a 10^{-2} dilution it was positive for both extracts (dry and wet), with wheals of 7 mm and 9 mm, respectively.

Significant CAP binding to SC was demonstrated with 7.8 PRU/ml. The rest of the antigens tested did not show specific IgE.

The baseline PEFR values were within normal limits ($>80\%$ of the theoretic values). On the patient's workdays the PEFR measurements showed significant decreases from baseline values ($>25\%$), and variability was more than 20%. During the time he was away from work, PEFR values did not fall more than 20%, and variability was less than 10%. When the patient began using conventional wet yeast, PEFR values did not decrease significantly, and variability was less than 10% (Fig. 1).

The methacholine challenge revealed bronchial hyperresponsiveness with a PD_{20} FEV₁ value of 12 accumulative breath units. No response was observed to the bronchial provocation test with baking additives. Inhalation of the 10^{-4} dilution of SC showed no significant changes in FEV₁ (a 6% decrease); inhalation of the 10^{-3} dilution produced a 38% drop in FEV₁, with the patient experiencing shortness of breath and wheezing. No late reactions were noted (Fig. 2).

After being diagnosed with occupational asthma caused by sensitization to SC, the patient began to use conventional wet yeast and carried on normal work activity without symptoms. Exercise-induced asthma persisted for a few months. He does not currently require treatment, and pulmonary function is within normal limits.

DISCUSSION

Various antigenic substances that have been reported as causes of rhinitis or occupational asthma can be found in a bakery; some of them can cause sensitization both in the home and at work. At first, considerable importance was assigned to flour proteins as sensitizing agents of the airways, with differences found between these and the proteins that cause food allergy. In recent years, baking additives have been considered an important cause of bakers' asthma,⁷⁻¹⁰ including fermentation accelerators (enzymes), antioxidant and whitening agents (soybean flour, potassium bromate), and emulsifiers (soybean lecithin). The enzymes obtained from *Aspergillus oryzae* (α -amylase, β -amylase, and glucoamylase)¹¹ and soybean flour (lipoxygenase)^{12,13} are currently regarded as powerful allergens. We must not forget that these enzymes are active in wheat grain, barley, and SC yeast,¹¹ which suggests that the allergy in our patient could be due to the endogenous α -amylase in wheat. However, the qualitative and quantitative structure of these enzymes is different from that of the enzymes from *Aspergillus oryzae*; furthermore, only α -amylase from the soluble fraction of wheat grain has been reported to be allergenic.¹⁴ The skin

prick test results were negative for flours and baking additives, and the bronchial provocation test results were negative for baking additives. This leads us to regard other SC proteins (e.g., enolase, peroxidase, ascorbat oxidase) as important allergenic agents,¹⁵ some of which (enolase) have been implicated in the presence of cross-reactivity to *Candida* species.

The use of SC as a ferment dates to 2500 BC during the time of the Roman Empire. It has been used, practically unchanged, until the present. However, it is uncommon to find publications on sensitization to this yeast. This enzyme is always used in a cold-water solution, which is why it is difficult for a dusty environment to be formed. In contrast, flours and baking additives always form dusty environments. As a result of technical progress, yeast can now be preserved in dehydrated form and does not require special storage conditions. When SC yeast is used in powder form, as is the case with our patient, a dusty environment is created; therefore, we do not find it uncommon for exposed workers to be sensitized.

We know that occupational asthma in bakers is nothing new; however, the rare sensitization to such a common antigen in a bakery is indeed exceptional. It is important to be familiar with the workplace and with the procedures and materials used in order to establish a correct etiologic diagnosis.

In conclusion, our results suggest that occupational asthma caused by SC is uncommon in bakers despite the frequent use of this yeast. We believe it is important to be familiar with the work activity and substances to which the worker is exposed in order to establish an etiologic diagnosis of occupational asthma. It would therefore be useful to include an SC antigen when testing bakers with respiratory symptoms who are not sensitized to wheat grain components or enzyme additives.

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